Statistical Analysis Plan: J2T-MC-KGAK (Version 3)

A Phase 3, 16-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Impact of Lebrikizumab on Vaccine Responses in Adult Patients with Moderate-to- Severe Atopic Dermatitis

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1. Statistical Analysis Plan: J2T-MC-KGAK (DRM06-AD18): A Phase 3, 16-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Impact of Lebrikizumab on Vaccine Responses in Adult Patients with Moderate-to-Severe Atopic Dermatitis

Lebrikizumab (LY3650150)

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Protocol J2T-MC-KGAK
Phase 3

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved on 16 November 2020 prior to any unblinding on 16 November 2020.

SAP Version 2 was approved on 01 March 2022 prior to unblinding of Week 16 database lock (DBL). Revisions in SAP Version 2 included:

Section	Description of Change	Rationale
Section 4	Reworded the language of secondary objectives.	To be consistent with protocol language.
Section 4	Added exploratory section in Table KGAK.4.1.	To provide details about the exploratory analysis.
Section 6.1.1, Table KGAK.6.1	Added 2 analysis populations (mITT and Modified Safety Population). Removed "Unless otherwise specified, efficacy and health outcomes analyses will be conducted on this population" from the ITT population part. Removed "Safety analyses will be conducted on this population." from the Safety Population part. Reworded PPS population part.	See footnote of Table KGAK.6.1. To be consistent with protocol language and provide more details about how to record the additional significant protocol deviations that could possibly have impact on precise evaluation of the primary objective.
Section 6.1.1, Table KGAK.6.2	Added mITT and Modified Safety populations.	See footnote of Table KGAK.6.1.
Section 6.1.2	Baseline period of Pruritus NRS, Sleep-Loss, and Skin Pain NRS was changed from "7-day window on or prior to the baseline visit (Day 1)" to "7-day window prior to the baseline visit (Day 1)."	To exclude the observations collected at baseline visit (Day 1) such that all observations used to calculate baseline are collected before first dose.
Section 6.1.2	Added "There will be no adjustment for multiple comparisons."	Clarification.
Section 6.2	Amended to implement the definition of primary and supportive estimands following the ICH E9(R1) addendum. Added the missing data imputation methods relative to each estimand.	Following ICH E9(R1) addendum.
Section 6.3	Clarified no adjustment will be applied on age group because this study is adult only.	Clarification.

Section	Description of Change	Rationale
Section 6.4	Amended section to align with the definition of estimands. Clarified each missing data method. Clarified the imputation techniques for each endpoint. Specified the random seeds for each endpoint.	Clarification. Prespecify random seed.
Section 6.6	Changed analysis population for patient disposition summary table to mITT.	See footnote of Table KGAK.6.1.
Section 6.7.1	Changed analysis population for demographics and baseline characteristics to mITT from ITT. Removed age group. Removed height. Added "Other nonbiologic medication/treatment" under the "Atopic Dermatitis treatment used in the past" part. Added sleep loss category and skin pain NRS category.	See footnote of Table KGAK.6.1. KGAK is adult study. To be consistent with other lebrikizumab studies.
Section 6.7.2	Added *Adverse Event* eCRF as a source of Medical History records if start date is prior to the first study drug injection. Changed analysis population of medical history to mITT.	To reflect data collection mechanism. See footnote of Table KGAK.6.1.
Section 6.8	Changed analysis population of treatment compliance to Modified Safety Population. Added dosing diary as a source counting total number of injections administrated.	See footnote of Table KGAK.6.1. To reflect data collection mechanism.
Section 6.9	Changed analysis population of prior and concomitant medications to mITT population. Specified specific AD treatment that will be reported. Clarified "Rescue medication resulting in permanent discontinuation of study treatment during the Treatment Period is defined as any systemic treatment." Added subsection for flare.	See footnote of Table KGAK.6.1. Clarification. Adding flare to allow for related analysis.
Section 6.10, Table KGAK.6.4	Changed the weekly mean algorithm to prorated weekly mean for Pruritus NRS, Sleep-loss, and Skin Pain NRS. Added endpoints, 2-point improvement in Sleep-loss and 4-point improvement in Skin Pain NRS. Removed "Patients <= 17 years will complete pediatric versions for the duration of the study." in PROMIS part.	Make KGAK consistent with other lebrikizumab studies. KGAK is an adult-only study.

Section	Description of Change	Rationale
Section 6.10, Table KGAK.6.5	Added mITT as analysis population for 2 primary endpoints. Updated whole table to reflect statements in from Section 6.1 to Section 6.4.	To be consistent with protocol. To be consistent within this document.
Section 6.10.1	Clarified that the descriptive statistics for Meningococcal Group C serum hSBA titers will include the number and percentage of participants in each titer level.	Meningococcal Group C serum hSBA titer result is a categorical variable, so it should be treated differently from the antitetanus toxoid IgG antibody concentration result.
Section 6.10.2	Simplified this section by referring to Table KGAK.6.4 and Table KGAK 6.5.	To avoid duplicated statement.
Section 6.13	Added Modified Safety Population for safety evaluations.	See footnote of Table KGAK.6.1.
Section 6.13.1	Removed the by-patient listing of exposure. Clarified analysis population of exposure will be the Modified Safety Population. Clarified that drug interruption time period because of use of systemic rescue medication will not be removed from exposure calculation. Added dosing diary as a source counting total number of injections received.	Not necessary. To be consistent to PSAP. To reflect data collection mechanism.
Section 6.13.2	Changed analysis population in Table KGAK.6.6. Mentioned that "A listing of AEs of patients from Site 1883 and Site 1827 will be provided." Clarified the definition/scoop of AE in KGAK.	See footnote of Table KGAK.6.1. Clarification.
Section 6.13.3	Changed analysis population in Table KGAK.6.7.	See footnote of Table KGAK.6.1.
Section 6.13.4	Changed analysis population in Table KGAK.6.8.	See footnote of Table KGAK.6.1.
Section 6.13.5	Added "A participant is evaluable for TE-ADA if there is at least 1 nonmissing test result for ADA for both the baseline and the postbaseline visits." Changed analysis population of immunogenicity summary to Modified Safety Population.	To be consistent with protocol. See footnote of Table KGAK.6.1.
Section 6.13.6	Changed analysis population in tables within this section. Added several analysis related to AEs of special interest.	See footnote of Table KGAK.6.1. To be consistent to PSAP.

Section	Description of Change	Rationale
Section 6.14.1	Removed EASI 90, Pruritus NRS ≥4-points improvement, and Skin Pain ≥4-points improvement from efficacy subgroup analysis. Changed analysis population to mITT. Changed Fisher's exact test to Chi-square test. Combined small race groups into 1 group and only kept Asian, Black or African American, White, and Other. Removed ADA-related subgroup analysis.	Not necessary. See footnote of Table KGAK.6.1. Chi-square test has standard method to work with multiple imputation. To avoid too small subgroup and potential numerical problem.
Section 6.15.1	Added more clarifications.	Clarification.
Appendix 1	Added POEM and Skin Pain NRS. Changed weekly mean algorithm to prorated weekly mean. Changed from Assessment Date to Visit Date for postbaseline visits. Added algorithm for Week 1 weekly mean.	To allow weekly mean calculation for POEM and Skin Pain NRS. Make consistent with other lebrikizumab studies.
Appendix 2	Added this new appendix to define rescue medications.	Added per PSAP.
Appendix 3	Added this new appendix to provide more technical details about MCMC-MI.	Clarification.

Abbreviations: AD = atopic dermatitis; ADA = antidrug antibody; AE = adverse event; EASI = Eczema Area and Severity Index; EASI 90 = ≥90% reduction from baseline in EASI score; eCRF = electronic case report form; hSBA = human complement serum bactericidal assay; ICH = International Council for Harmonisation; IgG = immunoglobulin G; ITT = intent-to-treat; MCMC-MI = Markov chain Monte Carlo multiple imputation; mITT = modified intent-to-treat; NRS = numerical rating scale; POEM = Patient-Oriented Eczema Measure; PPS = per-protocol set; PROMIS = Patient-Reported Outcomes Measurement Information System; PSAP = program safety analysis plan; TE-ADA = treatment-emergent antidrug antibody.

SAP Version 3 was approved after Week 16 database lock (DBL) and before final DBL. Revisions in SAP Version 3 include:

Section	Description of Change	Rationale
Sections 4, 5.2, 6.10, 6.10.1	Replaced hSBA with rSBA.	At the time of Week 16 DBL, the MCV hSBA data collected and processed by Eurofins was considered invalid because the assay procedure was not successfully validated. Personnel who have access to the patient-level data have no access to the biospecimen for the MCV hSBA. For final analysis, Lilly has identified Nexelis as an alternate vendor for analyzing the MCV response using a fully validated rSBA to deliver results for the final DBL and for analysis.
Section 6.16	Added detailed description of MCV response data issue observed at Week 16 DBL. Added the solution of MCV response data issue and discussed the impact to Week 16 DBL and final DBL.	The same as above.

Abbreviations: DBL = database lock; hSBA = human complement serum bactericidal assay; MCV = Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine; rSBA = rabbit complement serum bactericidal assay.

4. Study Objectives

Table KGAK.4.1 shows the protocol-defined objectives and endpoints of the study. In addition, the analysis of some nonprotocol-defined endpoints is described in Section 6.10 to provide supportive evidence of efficacy.

Table KGAK.4.1. Protocol-Defined Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the seroresponses to the Tdap and MCV between lebrikizumab-treated and placebo-treated participants with moderate to severe AD	*The percentage of participants who:* 1. Develop a **booster response to tetanus toxoid** 4 weeks after the administration of the Tdap vaccine (Week 16) Booster response is defined as: o ≥4-fold increase in antitetanus IgG antibody concentration if the prevaccination level was >0.10 IU/mL and ≤2.7 IU/mL; OR o ≥2-fold increase in antitetanus IgG antibody concentration if the prevaccination level was >2.7 IU/mL; OR o ≥4-fold increase in antitetanus IgG antibody concentration and a postvaccination level ≥0.10 IU/mL if the prevaccination level was ≤0.10 IU/mL
	2. Have **positive antibody response to Meningococcus C antigen of the MCV** 4 weeks after the administration of the vaccine (Week 16) Positive antibody response to Meningococcus C antigen of the MCV is defined as: o postvaccination rSBA titer ≥4 times the LLOQ, if the prevaccination rSBA titer is less than the LLOQ; OR o postvaccination rSBA titer ≥4 times the prevaccination titer, if the prevaccination rSBA titer is greater than or equal to the LLOQ

Objectives	Endpoints
Secondary	
• To compare the efficacy of lebrikizumab with that of placebo in the treatment of patients with moderate-to-severe AD • To compare the patient-reported outcomes between lebrikizumab-treated and placebo-treated participants with moderate-to-severe AD	*Percentage of participants at Week 16* • with an IGA score of 0 or 1 and a reduction of ≥2 points from baseline • achieving EASI 75 • achieving EASI 90 • achieving ≥4-point improvement from baseline in Pruritus NRS score who had baseline Pruritus NRS ≥4 *Percentage change from baseline to Week 16 in* • EASI • Pruritus NRS *Change from baseline to Week 16 in* • BSA • Sleep-loss score
Exploratory	
EASI, IGA • Percentage of participants with EASI 75, EASI 90 by visit • Percentage of participants with IGA score of 0 or 1 and a reduction ≥2 points from baseline by visit • Percentage change from baseline in EASI score by visit *Pruritus NRS* • Percentage change from baseline in Pruritus NRS by visit • Percentage of participants with a Pruritus NRS score of ≥4 points at baseline who achieve a ≥4-point reduction from baseline by visit *Skin Pain NRS* • Percentage change from baseline in Skin Pain NRS by visit • Percentage of participants with a Skin Pain NRS score of ≥4 points at baseline who achieve a ≥4-point reduction from baseline by visit	

Objectives	Endpoints
Sleep-loss Score • Change from baseline in Sleep-loss score by visit • Percentage of participants with a Sleep-loss score ≥2 points at baseline who achieve ≥2 points by visit *BSA* • Change from baseline in BSA by visit *POEM* • Change from baseline in POEM by visit *PROMIS*® • Change from baseline in PROMIS Anxiety measure by visit • Change from baseline in PROMIS Depression measure by visit *Rescue Medication* • Percentage of participants rescued by visit • Time to first use of rescue medication	

Abbreviations: AD = atopic dermatitis; BSA = Body Surface Area; EASI = Eczema Area and Severity Index; EASI 75 = ≥75% reduction from baseline in EASI score; EASI 90 = ≥90% reduction from baseline in EASI score; IGA = Investigator's Global Assessment; IgG = immunoglobulin G; LLOQ = lower limit of quantitation; MCV = Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine; NRS = Numeric Rating Scale; POEM = Patient-Oriented Eczema Measure; PROMIS = Patient-Reported Outcomes Measurement Information System; rSBA = rabbit complement serum bactericidal assay; Tdap = Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed.

5. Study Design

5.1. Summary of Study Design

Study J2T-MC-KGAK (KGAK) (also known as DRM06-AD18) is a randomized, double-blind, placebo-controlled, parallel-group study to assess the impact of lebrikizumab on vaccine responses in adult participants (18 to 55 years) with moderate-to-severe atopic dermatitis (AD). Approximately 240 participants will be enrolled into the study. The study has 1 treatment period (16-week). Participants completing this 16-week study will be offered continued treatment in a separate long-term extension study, J2T-DM-KGAA (DRM06-AD07). Participants who early terminate or choose not to enter the long-term extension study will undergo a follow-up visit approximately 12 weeks after the last study drug injection for safety follow-up.

5.1.1. Screening Period

Screening Period: Participants will be evaluated for study eligibility before the Baseline Visit (Day 1). Electronic diary collection will begin at screening.

5.1.2. Baseline and Double-Blinded Treatment Period (Week 0 to Week 16)

Participants found to be eligible according to all of the study entry criteria will be randomly assigned in a 1:1 ratio to receive either lebrikizumab or placebo. The treatment groups in the Blinded Treatment Period are

- Lebrikizumab 250 mg every 2 weeks (Q2W): 500 mg lebrikizumab administered at baseline and Week 2 (loading dose; 2 prefilled syringes with a pre-filled syringe needle safety device [PFS-NSD]) and 250 mg Q2W through Week 14
- Placebo: 4 mL (2 PFS-NSD) administered at baseline and Week 2 and 2 mL Q2W through Week 14

At Week 12, after the predose vaccine titers have been drawn, 1 dose of each of the 2 commercially available vaccines will be administered to all participants still on study drug:

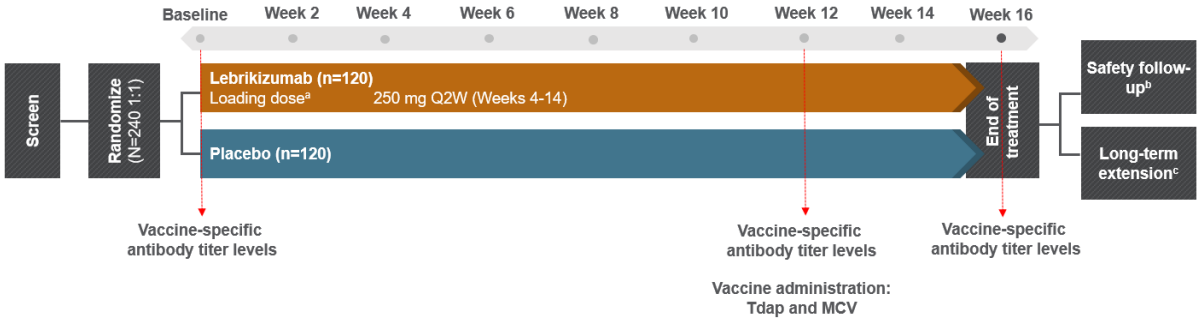
- Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (Tdap)
- Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (MCV)

Participants whose study drug has been permanently discontinued before Week 12 will not receive the vaccines.

5.1.3. Safety Follow-up Visit

Participants who terminate early from the study or do not enroll in the long-term extension study, J2T-DM-KGAA (DRM06-AD07), will undergo a follow up visit approximately 12 weeks after the last study drug injection.

Figure KGAK.5.1 illustrates the study design.



Abbreviations: MCV = Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine; N = number of planned randomized patients; n = number of planned randomized patients at each arm; Q2W = every 2 weeks; Tdap = Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed.

Figure KGAK.5.1. Illustration of study design for Protocol KGAK.

5.2. Determination of Sample Size

Approximately 240 participants will be randomly assigned to study intervention (1:1 ratio for lebrikizumab:placebo) such that approximately 218 evaluable per protocol (PP) participants complete the study.

The sample size for this study was determined based on the following information:

- The percentage of study participants with positive response to the tetanus vaccination at Week 16 is 83.7% and 83.3% for active treatment and placebo, respectively (Blauvelt et al. 2019)
- The percentage of study participants with rabbit complement serum bactericidal assay (rSBA)-Meningococcal C total seroresponse at Day 29 is 90% (Tipton et al. 2019, adjusted for adult population)

Assuming the observed booster response to tetanus toxoid for both lebrikizumab and placebo is 83% at Week 16, with 109 participants per arm, the Wald 2-sided 90% confidence interval (CI) for the difference in booster response is (−0.08, 0.08).

Similarly, assuming the positive antibody response to MCV for both lebrikizumab and placebo is 90% at Week 16, with 109 participants per arm, the Wald 2-sided 90% CI for the difference in booster response is (−0.07, 0.07).

5.3. Method of Assignment to Treatment

Assignment to treatment groups will be determined by a computer generated random sequence using an interactive web-response system (IWRS). All participants will be randomly allocated to receive the study treatment using IWRS at the baseline visit. The allocation to treatment will be prospectively stratified by disease severity (Investigator's Global Assessment [IGA] 3 versus 4). At the baseline visit (Day 1), once a participant is considered eligible to participate in the study, demographic and stratification information will be entered into the Electronic Data Capture

(EDC) system. Site personnel will confirm that they have located the correct kit by entering a confirmation number found on the kit into the IWRS.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (Lilly). The latest version of the Medical Dictionary for Regulatory Activities (MedDRA) will be used.

Analyses and summaries from the assessment of endpoints described in the protocol (for example, described in KGAK Synopsis Objectives and Endpoints) are planned to be included in a clinical study report (CSR). Analyses and summaries for key safety data are also planned to be included in the CSR. Results from additional efficacy analysis and other safety analyses may also be provided in the CSR as deemed appropriate.

Any change to the data analysis methods described in the protocol will require a protocol amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the CSR.

All statistical processing will be performed using SAS® unless otherwise stated. Some of the analyses described in this document will be incorporated into interactive display tools instead of or in addition to static displays. Except where noted, all statistical tests will be 2-sided and will be performed at the 0.05 level of significance.

The Schedule of Visits and Procedures outlined in the protocol specifies the allowable windows for assessments. Assessments performed outside these windows will not be excluded from any analysis, unless specified otherwise.

6.1.1. Analysis Populations

Analysis populations are defined in Table KGAK.6.1 along with the analysis they will be used to conduct. Table KGAK.6.2 describes the treatment groups and the comparisons for each study period and the analysis population.

Table KGAK.6.1. Analysis Populations

Population	Description
All Entered Patients	All participants who signed informed consent. Participant flow will be summarized.
Intent-to-Treat (ITT) Population	All randomized participants, even if the participant does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Participants will be analyzed according to the treatment to which they were assigned.
Modified Intent-to-Treat (mITT) Population	ITT population excluding all participants from Site 1883[a] and Site 1827[b]. Unless otherwise specified, efficacy and health outcomes analyses will be conducted on this population.
Safety Population	All randomized participants who received at least 1 dose of study treatment.
Modified Safety Population	Safety population excluding all participants from Site 1883 and Site 1827. Safety analyses will be conducted on this population.
Per-Protocol Set (PPS)	All Safety Population participants without any significant protocol deviations. Significant protocol deviations include (but not limited to) the following:

Population	Description
	• Used prohibited treatment that required permanent discontinuation of the study drug (see Protocol Section 7.1.2) that is systemic rescue medication • Missed either 1 or both Week 12 or Week 16 study visits (Visits 8 and 10) • Had not been compliant with the dosing regimen (i.e., participants must receive 80% of the expected injections of study drug and both of the vaccines during participation in the study) • Exceeded the out-of-the-visit window at the Week 16 visit (Visit 10) by more than 7 days Additional significant protocol deviations that could possibly have impact on precise evaluation of the primary objective will be recorded in a separate tracker and participants with these significant protocol deviations will also be excluded from the PPS. Primary analyses for vaccine response primary endpoints will use the PPS. Analyses for IGA0/1 and EASI 75 will be repeated using the PPS.

Abbreviations: EASI = Eczema Area and Severity Index; EASI 75 = ≥75% reduction from baseline in EASI score; IGA = Investigator's Global Assessment.

[a] The rationale for excluding participants from Site 1883 is in a directed site audit triggered by statistically implausible data in Study KGAD/AD06 at this study site, and the same site was also included in this study, KGAK/AD18. It was determined that some or all of the study participates at this site did not meet the eligibility criterion of having moderate-to-severe atopic dermatitis, and associated data was unreliable.

[b] The rationale for excluding participants from Site 1827 is a clinical site audit of lebrikizumab atopic dermatitis studies KGAK/AD18 and KGAA/AD07 at this site resulted in critical findings. It was determined by the audit that there was a lack of source documentation needed to substantiate eligibility for all participants enrolled at this site. Additionally, a quality issue was opened that participant data regarding their moderate-to-severe atopic dermatitis is either unreliable, inconsistent, and/or missing source documentation.

Table KGAK.6.2. Treatment Groups and Comparisons and Analysis Population

Study Period	Analysis Population	Treatment Groups	Abbreviation	Inferential Comparisons When Applicable
Treatment Period	mITT; Safety; Modified Safety; PPS	Placebo; Lebrikizumab 250 mg Q2W	PBO; LEB250Q2W	LEB250Q2W vs PBO

Abbreviations: LEB = lebrikizumab; mITT = modified intent-to-treat; PBO = placebo; PPS = per protocol set; Q2W = every 2 weeks; vs = versus.

6.1.2. General Considerations for Analyses

Treatment period starts after the first injection of study treatment at baseline visit (Day 1) and ends after participant completed Week 16 visit or the early termination visit (ETV) (between Day 1 and Week 16). Baseline will be defined as the last available value before the first injection for efficacy and health outcome analyses. In most cases, this will be the measure recorded at baseline visit (Day 1). If the participant does not take any injection, the last available value on or

prior to randomization date will be used. Change from baseline will be calculated as the visit value of interest minus the baseline value.

For Pruritus Numeric Rating Scale (NRS), Sleep-loss due to Pruritus, and Skin Pain NRS collected via eDiary, the baseline period is the 7-day window prior to the Baseline Visit (Day 1). A participant must have responses from at least 4 of 7 days to calculate a baseline weekly mean. If a participant has 3 or fewer responses, the baseline mean value will be considered missing. eDiary data for Pruritus NRS, Sleep-loss due to Pruritus, and Skin Pain NRS are mapped to study visit per Appendix 1.

For the safety analyses, the following baselines will be used. For safety analyses using a baseline period, the baseline period is defined as the time from Screening Visit to the date/time of the first injection in Treatment Period.

- Treatment-emergent adverse events (TEAEs): baseline will be all results recorded during the baseline period
- Treatment-emergent abnormal laboratory and vital signs results: baseline will be all results recorded during the baseline period
- Change from baseline to last postbaseline observation or to each scheduled postbaseline visit for laboratory and vital signs results: baseline will be the last scheduled nonmissing assessment recorded during the baseline period

The randomization to treatment groups is stratified by baseline disease severity (IGA 3 versus 4) as described in Section 5.3. Unless otherwise specified, the statistical analysis models for Treatment Period will adjust for baseline disease severity.

For assessments of the secondary endpoints and other binary efficacy and health outcomes endpoints, the following will be provided

- Crude proportions for each treatment group along with the 95% two-sided asymptotic (that is, not continuity corrected) CIs
- The estimated common risk difference along with 95% CIs. The common risk difference is the difference in proportions adjusted for the stratification factors as mentioned in Section 6.3. SAS PROC FREQ will be used for the estimates and CIs, where the CIs are calculated by using Mantel-Haenszel-Sato method (Sato 1989)
- Cochran-Mantel-Haenszel (CMH) test will be used to compare the treatment groups while adjusting for the stratification factors. The CMH p-value and the CMH adjusted odds ratio (OR) along with the 95% two-sided asymptotic (that is, not continuity corrected) CIs will be reported

Treatment comparisons of key continuous efficacy variables and health outcome variables at each postbaseline time point will be made using analysis of covariance (ANCOVA) with the following in the model: treatment group, baseline value, and stratification factors mentioned in Section 6.3. Type III tests for least squares (LS) means will be used for statistical comparison between treatment groups. The LS mean difference, standard error (SE), p-value, and 95% CI, unless otherwise specified, will also be reported.

Treatment comparisons of other continuous efficacy variables and health outcome variables with multiple postbaseline measurements will be made using mixed-model for repeated measures (MMRM). When MMRM is used, the model includes treatment, baseline value, visit, the interaction of the baseline value-by-visit, the interaction of treatment-by-visit, and the stratification factors mentioned in Section 6.3 as fixed factors. The covariance structure to model the within-participant errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, will be used. The restricted maximum likelihood (REML) will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III tests for the LS means will be used for the statistical comparison; the 95% CI will also be reported.

For variables that are not collected at each postbaseline visit, data may exist at visits where the variable was not scheduled to be collected. In these situations, data from the early discontinuation visit that do not correspond to the planned collection schedule will be excluded from the MMRM analysis (Andersen and Millen 2013). Also, for by-visit summaries/displays such as boxplots, the weeks when data were not scheduled to be collected may not be displayed. However, unscheduled assessments within any defined study period will still be used in the shift analyses and for imputing values for the change from baseline to last observation carried forward (LOCF) endpoint analyses.

Unless specified otherwise, Fisher's exact test will be used for adverse events (AEs) and other categorical safety measures. Odds ratios will be created with lebrikizumab treatment as the numerator and placebo as the denominator. Continuous vital sign and laboratory values will be analyzed by an ANCOVA with treatment and baseline value in the model.

There will be no adjustment for multiple comparisons.

6.2. Primary and Supportive Estimands

There will be 1 estimand of interest in analyzing the primary endpoint and 3 estimands of interest in analyzing secondary endpoints for the double-blinded treatment period. For secondary endpoints, 2 types of intercurrent events (ICEs) in terms of estimating the treatment effects for the treatment period will be considered: initiation of rescue medication as defined in Appendix 2 and permanent treatment discontinuation.

6.2.1. Primary Estimand for Primary Endpoints

The primary estimand that will be used to analyze primary endpoints will include data collected for participants who are in the per-protocol set (PPS). Missing values will not be imputed.

The primary estimand (principal stratum estimand) for primary endpoints is described by the following attributes:

- Population: PPS population as defined in Table KGAK.6.1
- Endpoint: Apply to 2 primary endpoints, seroresponses to the Tdap and MCV, as defined in Table KGAK.4.1

- How to account for ICEs: The ICEs are captured through the population definition
- Population-level summary: Difference in response proportions between treatment conditions

6.2.2. Secondary and Supportive Estimands for Secondary Endpoints

The secondary estimand for secondary endpoints is a hybrid estimand representing the secondary clinical question of interest: what is the difference between treatment conditions (that is lebrikizumab vs placebo), in the target participant population, of successful response rates or means achieved after 16 weeks, without use of rescue medication, and if all participants continued with treatment except those who discontinued due to lack of efficacy?

The **secondary estimand for secondary endpoints** is described by the following attributes:

- Population: Defined through appropriate inclusion/exclusion (I/E) criteria to reflect the targeted patient population for approval
- Endpoint: Apply to all secondary endpoints
- How to account for ICEs:
    - Subjects who used rescue medication or discontinued treatment because of lack of efficacy prior to Week 16 will be considered as treatment failures, that is, nonresponder, after the ICEs. Therefore, composite strategy is used for these types of ICEs
    - For subjects who discontinued treatment because of reasons other than lack of efficacy prior to Week 16, a hypothetical strategy will be used to estimate what the treatment effect would have been if subjects continued with treatment. Therefore, hypothetical strategy is used for these types of ICEs
- Population-level summary: Difference in response proportions or means between treatment conditions

The **supportive estimand for categorical secondary endpoints** is a composite estimand as described by the following attributes:

- Population: Defined through appropriate I/E criteria to reflect the targeted patient population for approval
- Endpoint: Apply to all category secondary endpoints
- How to account for ICEs:
    - Subjects who used rescue medication or discontinued treatment prior to Week 16 will be considered as treatment failures, that is, nonresponder, after the ICEs. Therefore, composite strategy is used for these types of ICEs
- Population-level summary: Difference in response proportions between treatment conditions

The **supportive estimand for continuous secondary endpoints** is a hypothetical estimand as described by the following attributes:

- Population: Defined through appropriate I/E criteria to reflect the targeted patient population for approval
- Endpoint: Apply to all continuous secondary endpoints
- How to account for ICEs:
    - For subjects who used rescue medication or discontinued treatment prior to Week 16, a hypothetical strategy will be used to estimate what the treatment effect would have been if rescue medications were not available and all subjects adhered to the treatment. Therefore, hypothetical strategy is used for these types of ICEs
- Population-level summary: Difference in means between treatment conditions

Table KGAK.6.3 summarized secondary and its supportive estimands.

Table KGAK.6.3. Description of Secondary and Supportive Estimands for Secondary Endpoints

Estimand	Analysis Strategy for Intercurrent Events			Missing Data Imputation Method
	Rescue Medication	Treatment Discontinuation		
		Due to Lack of Efficacy	Due to Any Other Reasons	
Primary Estimand (Hybrid)	Composite: Set to baseline	Composite: Set to baseline	Hypothetical: Set to missing	Primary analysis: MCMC-MI
Supportive Estimand for Categorical Endpoints (Composite)	Composite: Set to nonresponder	Composite: Set to nonresponder	Composite: Set to nonresponder	NRI
Supportive Estimand for Continuous Endpoints (Hypothetical)	Hypothetical: Set to missing	Hypothetical: Set to missing	Hypothetical: Set to missing	MMRM, LOCF

Abbreviations: AD = atopic dermatitis; LOCF = last observation carried forward; MCMC-MI = Markov chain Monte Carlo multiple imputation; MMRM = mixed-model repeated measures; NRI = nonresponder imputation; TCS = topical corticosteroids.

6.3. Adjustments for Covariates

Unless otherwise specified, the statistical analysis models for the Treatment Period efficacy and health outcome analysis will include the stratification factor, baseline disease severity (IGA 3 versus 4). The stratification factor will not include age group, because the study will be conducted on adults (age 18 to 55 years) in the US.

In general, when an MMRM is to be used for analyses, treatment, baseline value, visit, the interaction of the baseline value-by-visit, the interaction of treatment-by-visit, and the stratification factor, baseline disease severity (IGA 3 versus 4), will be included as covariates; when an ANCOVA is to be used for analyses, baseline value will be included as a covariate.

6.4. Handling of Dropouts or Missing Data

Depending on the estimand being addressed, different methods will be used to handle missing data. The description of estimands can be found in Section 6.2.

Table KGAK.6.4 describes the planned imputation methods for efficacy and health outcome endpoints for the treatment period.

Table KGAK.6.4. Imputation Techniques for Various Variables During Treatment Period

Type of Endpoints	Efficacy and Health Outcome Endpoints	Estimand of Secondary Endpoints (Analysis Strategy for Intercurrent Events)	Missing Data Imputation Method (Analysis Method)
Categorical	IGA, EASI, Pruritus NRS, Skin Pain NRS, and Sleep-loss related categorical endpoints at prespecified timepoints	Primary Estimand (Hybrid)	MCMC-MI (CMH)
		Supportive Estimand (Composite)	NRI (CMH)
	Remaining categorical endpoints	Supportive Estimand (Composite)	NRI (CMH)
Continuous	EASI percent change, Pruritus NRS percent change, Skin Pain NRS percent change, and Sleep-loss change from baseline	Primary Estimand (Hybrid)	MCMC-MI (ANCOVA)
		Supportive Estimand (Hypothetical)	No imputation (MMRM)
	Remaining continuous endpoints collected at multiple postbaseline timepoints including (but not limited to) BSA and POEM	Supportive Estimand (Hypothetical)	No imputation (MMRM)
	Remaining continuous endpoints collected only once postbaseline (if any)	Supportive Estimand (Hypothetical)	LOCF (ANCOVA)

Abbreviations: ANCOVA = analysis of covariance; BSA = body surface area; CMH = Cochran-Mantel-Haenszel; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; LOCF = last observation carried forward; MCMC-MI = Markov chain Monte Carlo multiple imputation; MMRM = mixed-model repeated measures; NRI = nonresponder imputation; NRS = Numeric Rating Scale; POEM = Patient-Oriented Eczema Measure.

6.4.1. Markov Chain Monte Carlo Multiple Imputation

The method of handling missing efficacy data as mentioned in Table KGAK.6.4 will be as follows for both binary and continuous endpoints.

For participants who receive rescue medication (high-potency topical corticosteroids [TCS] or systemic AD treatment, defined in Appendix 2) or discontinue from the study treatment due to lack of efficacy, values should be set to the participant's baseline value subsequent to this time through Week 16. The Markov chain Monte Carlo multiple imputation (MCMC-MI) will be used to handle the remaining missing data. Imputation will be conducted within each treatment group independently so the pattern of missing observations in 1 treatment group cannot influence

missing value imputation in another. The SAS PROC MI with the MCMC option will be used to conduct the MCMC-MI. The imputation model will include the relevant baseline and postbaseline.

For each imputation process, 25 datasets with imputations will be calculated. The initial seed values are given in Table KGAK.6.5. Each complete data set will be analyzed with the specified analysis. The results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

For binary responses related to the Eczema Area and Severity Index (EASI) and IGA, the binary response variables will be calculated based on the multiply imputed datasets that have been created. Because the MCMC algorithm is based on the multivariate normal model, imputed values for IGA will not generally be one of the discrete values used in IGA scoring (0, 1, 2, 3, or 4). Therefore, to derive the binary IGA response variable, standard rounding rules will be applied to the imputed values. For example, if a participant has an IGA score imputed as 1.4 (and assuming a baseline IGA score of 3), the imputed value would be rounded down to 1, and the minimum change from baseline of 2 would have been met. This participant would be considered a responder.

For derivation of a ≥75% reduction from baseline in EASI score (EASI 75) and ≥90% reduction from baseline in EASI score (EASI 90) response, no rounding will be performed. The imputed Week 16 EASI value will be compared directly to the observed baseline EASI value to determine whether a reduction of at least 75% or 90% was achieved.

The approach of handling missing data for Pruritus NRS, Skin Pain NRS, and Sleep-loss are the same. Using Pruritus NRS as an example, for derivation of the following Pruritus NRS responses, no rounding will be performed. The imputed Pruritus NRS value will be compared directly to the observed mean baseline Pruritus-NRS value to determine whether a response was achieved:

- Percentage of participants with a Pruritus NRS of ≥4-points at baseline who achieve a ≥4-point reduction from baseline at Week 16

Imputation of continuous data will parallel that of binary variables. The imputed values will be used for the secondary endpoints, such as

- Percentage change in Pruritus NRS from baseline
- Percentage change in EASI score from baseline
- Percentage change in Skin Pain NRS from baseline.

Table KGAK.6.5. Seed Values for MCMC-MI

Analysis	Seed values Lebrikizumab 250 mg Q2W Placebo
IGA and its related derived endpoints	970309630 1477266806
EASI and its related derived endpoints	353985587 1828572477
Pruritus NRS and its related derived endpoints	1611917356 1087836192
Skin Pain NRS and its related derived endpoints	345235233 352342343
Sleep-loss score and its related derived endpoints	574563534 645745224

Abbreviations: EASI = Eczema Area and Severity Index score; IGA = Investigator's Global Assessment; MCMC-MI = Markov chain Monte Carlo multiple imputation; NRS = Numeric Rating Scale; Q2W = every 2 weeks.

6.4.2. Mixed-Model for Repeated Measures

Mixed-model for repeated measures analyses will be performed on continuous endpoints to mitigate the impact of missing data. This approach assumes missing observations are missing at random (missingness is related to observed data) and borrows information from participants in the same treatment arm taking into account both the missingness of data through the correlation of the repeated measurements.

The values subsequent to rescue medication use (high-potency TCS or systemic AD treatment, defined in Appendix 2) or treatment discontinuation will be made missing before applying the MMRM. The MMRM is described in Section 6.1.2.

6.4.3. Last Observation Carried Forward

In this analysis, the values subsequent to rescue medication use (high-potency TCS or systemic AD treatment, defined in Appendix 2) or treatment discontinuation will be made missing. All missing values will be imputed using LOCF for the secondary endpoints. Baseline value will be used for imputation if there is no postbaseline observation.

6.4.4. Nonresponder Imputation

The nonresponder imputation (NRI) method will be used to handle missing data relative to the supportive estimand for categorical endpoints (composite). Participants who receive rescue medication (high potency TCS or systemic AD treatment, defined in Appendix 2), or discontinue treatment, will be set to nonresponse subsequent to this time through Week 16. Intermittent missing values will also be set to nonresponse.

The NRI method imputes missing values as nonresponders and can be justified based on the composite strategy (ICH E9R1) for handling ICEs. In this strategy, participants are defined as

responders only if they meet the clinical requirements for response at the predefined time AND they remain on the assigned study treatment (i.e., not using rescue medications and not having missing values due to other reasons). Failing either criteria by definition makes them nonresponders.

Randomized participants without at least 1 postbaseline observation will also be defined as nonresponders for all visits for the NRI analysis.

6.5. Multicenter Studies

This study will be conducted by multiple investigators at US sites only. Typically, a logistic regression with treatment, site, and treatment-by-site may be used to assess the consistence of treatment effect in sites. However, due to a large number of sites and relative small sample size in the study, this logistic regression model will not likely converge. Thus, no subgroup analysis by the site will be evaluated.

6.6. Patient Disposition

The following patient disposition summaries will be provided (details of the analysis populations can be found in Section 6.1.1):

- Total number and percentage of participants entering each statistical analyses population defined in Section 6.1.1
- The number and percentage of participants who entered the study, failed screening, were randomized at baseline visit (Day 1), completed Week 16, completed the safety follow-uvp isit, and entered long-term extension study. Summary will be provided by the initial randomized treatment group (Analysis population: Modified Intent-to-Treat [mITT])
- The number and percentage of participants who completed the study, and the number and percentage of participants who discontinued the study at any time, by the initial randomized treatment group and primary reason for discontinuation (Analysis population: mITT)

All participants who were randomized (that is, in the ITT population) and discontinued from study treatment during any period from the study will be listed together with the discontinuation reason, and the timing of discontinuation from the study will be reported.

Participant allocation by center/site will be summarized with number of participants who entered the study, number of mITT participants for each treatment group, number of participants discontinued from study treatment, and number of participants discontinued from the study.

6.7. Patient Characteristics

6.7.1. Demographics and Baseline Characteristics

Participant demographic variables and baseline characteristics will be summarized by treatment group for the mITT and PPS population. The continuous variables will be summarized using descriptive statistics, and the categorical variables will be summarized using frequency counts

and percentages. No formal statistical comparisons will be made between treatment groups unless otherwise specified.

The following demographic information will be included:

- Age
- Sex (male, female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple, Other, Not Reported)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown)
- Weight (kg)
- Weight category (<60 kg, ≥60 to <100 kg, ≥100 kg)
- Body mass index (BMI) (kg/m^2)
- BMI category: Underweight (<18.5 kg/m^2), Normal (≥18.5 and <25 kg/m^2), Overweight (≥25 and <30 kg/m^2), Obese (≥30 and <40 kg/m^2), Extreme obese (≥40 kg/m^2)

By-patient listings of basic demographic information for the ITT population will be provided.

The following baseline disease/clinical characteristics will be included:

- Age at onset (years): calculated as the difference between date of onset of AD and the date of birth collected on the CRF
- Duration since AD onset (years): calculated as the difference between date of Informed Consent and the date of onset of AD collected on the CRF
- Duration since AD onset category (0 to <2 years, 2 to <5 years, 5 to <10 years, 10 to <20 years, ≥20 years)
- Anatomical area affected by AD:
    - Head
    - Trunk (internal/medial axillae and groin)
    - Upper extremities (includes external axillae)
    - Lower extremities (includes buttocks and feet)
    - At least 2 areas
- AD treatment used in the past:
    - None
    - TCSs
    - Topical calcineurin inhibitors (TCIs)

  - Immunosuppressive/immunomodulating drugs: systemic corticosteroids; cyclosporine; mycophenolate-mofetil; IFN-γ; Janus kinase inhibitors; azathioprine; methotrexate
  - Phototherapy
  - Photochemotherapy (PUVA)
  - Other biologics (e.g., cell depleting biologics)
  - Other nonbiologic medication/treatment
- Antitetanus toxoid immunoglobulin G (IgG) antibody concentration
- MCV (Group C serum bactericidal antibodies) titer
- IGA for AD score: 3 versus 4
- EASI score
- Body Surface Area (BSA)
- Pruritus NRS
- Pruritus NRS: <4, ≥4
- Sleep-loss due to pruritus
- Sleep-loss due to pruritus: <2, ≥2
- Skin Pain NRS
- Skin Pain NRS: <4, ≥4
- Patient-Oriented Eczema Measure (POEM)
- Patient-Reported Outcomes Measurement Information System (PROMIS) Anxiety and Depression scores

6.7.2. Medical History

Medical histories are defined as the conditions/events recorded in the *Medical History* Electronic Case Report Form (eCRF) or the conditions/events recorded in the *Adverse Event* eCRF with a start date prior to the first study drug injection. Notice if a medical history worsens in severity on or after the date of first injection, it will be recorded as an AE on an *Adverse Event* eCRF page with the date of worsening as the start date and will be considered as an AE.

The number and percentage of participants with medical histories will be summarized by treatment group for the mITT population using the MedDRA preferred term (PT) nested within System Organ Class (SOC).

The number and percentage of participants with specific medical history events of interest prespecified on the *History Assessment* eCRF (hand dermatitis, facial dermatitis, conjunctivitis, herpes Zoster, and others) will be summarized by treatment group for the mITT population.

6.8. Treatment and Vaccination Compliance

Treatment compliance with investigational product will be summarized for participants in the Modified Safety Population in the Treatment Period. Treatment compliance for each participant will be calculated as:

$$Treatment\ compliance\ (\%) = 100\ \times \frac{Total\ number\ of\ injections\ administered}{Total\ number\ of\ injections\ expected}$$

- The number of injections expected can be derived from the IWRS study drug dispense dataset.
- The total number of injections administered will be based on the *Study Drug Administration* eCRF page and dosing diary.

Vaccination compliance for each participant will be calculated as 0%, 50%, or 100% depending on the total number of vaccines received at Weeks 12: 0, 1, or 2 respectively.

A participant will be considered compliant if he or she received 80% of the expected number of injections and 100% of vaccinations in the Treatment Period while enrolled in the study. Descriptive statistics for percent compliance will be summarized. Subintervals of interest, such as compliance between visits, may also be presented.

6.9. Prior and Concomitant Therapy

Medications will be classified into anatomical therapeutic chemical (ATC) drug classes using the latest version of the World Health Organization (WHO) drug dictionary. Medication start and stop dates will be compared to the date of first dose of treatment in the treatment period to allow medications to be classified as concomitant for the treatment period.

Prior medications are those medications that start and stop prior to the date of first dose of study treatment. *Concomitant medications* are those medications that start before, on, or after the first day of study treatment of the defined treatment period and continue into the treatment period.

Prior and Concomitant medications will be summarized for mITT population.

Specific AD treatment during the Treatment Period will be presented by the treatment groups for the mITT and PPS population separately. This will include: (1) topical AD treatment (including TCS, TCI, and crisaborole), (2) systemic AD treatment (including systemic corticosteroids, immunosuppressants, biologics, and phototherapy). Topical corticosteroids will be presented by potency. Definition of rescue medications is provided in Appendix 2.

Rescue medication resulting in permanent discontinuation of study treatment during the Treatment Period is defined as any systemic treatment.

Flare

Disease flares will be assessed based on rescue therapy usage. Flare is defined as initiation or intensification of rescue therapy. A summary of percentage of participants rescued by visit will be provided. Kaplan Meier curves for time to first rescue use may be generated.

6.10. Efficacy Analyses

Table KGAK.6.6 includes the description and derivation of the efficacy/health outcomes measures and endpoints.

Table KGAK.6.7 provides the detailed analyses including analysis type, method and imputation, population, time point, and treatment comparisons for efficacy/health outcomes analyses.

Table KGAK.6.6. Description and Derivation of Efficacy/Health Outcomes Measures and Endpoints

Measure	Description	Variable	Derivation/Comment	Imputation Approach if Missing Components
Antitetanus toxoid IgG antibody concentration	Antitetanus toxoid IgG antibody concentration is a laboratory test result.	Antitetanus IgG antibody concentration	Single item	Single item, missing if missing.
		Booster response to tetanus toxoid 4 weeks after the administration of the Tdap vaccine (Week 16)	≥4-fold increase in antitetanus toxoid IgG antibody concentration if the prevaccination level was >0.10 IU/mL and ≤2.7 IU/mL; OR ≥2-fold increase in antitetanus toxoid IgG antibody concentration if the prevaccination level was >2.7 IU/mL; OR ≥4-fold increase in antitetanus toxoid IgG antibody concentration and a postvaccination level ≥0.10 IU/mL if the prevaccination level was ≤0.10 IU/mL	Single item, missing if missing.
MCV (Group C serum bactericidal antibodies)	MCV (Group C serum bactericidal antibodies) is a laboratory test result.	MCV (Group C serum bactericidal antibodies)	Single item	Single item, missing if missing.
		Positive antibody response to MCV (Group C serum bactericidal antibodies) 4 weeks after the administration of the vaccine (Week 16)	postvaccination rSBA titer ≥4 times the LLOQ, if the pre-vaccination rSBA titer is less than the LLOQ; OR postvaccination rSBA titer ≥4 times the prevaccination titer, if the prevaccination rSBA titer is greater than or equal to the LLOQ	Single item, missing if missing.
Investigator's Global	The IGA is a static assessment and rates the severity of the participant's AD. The IGA is comprised of a	IGA score	Single item. Range: 0 to 4 0 represents "clear" 4 represents "severe"	Single item, missing if missing.

Assessment (IGA)	5-point scale ranging from 0 (clear) to 4 (severe), and a score is selected using descriptors that best describe the overall appearance of the lesions at a given time point.	IGA (0,1) with ≥2-point improvement IGA (0)	Observed score of 0 or 1 and change from baseline ≤−2 Observed score of 0	Missing if baseline or observed value is missing. Single item, missing if missing.
Eczema Area and Severity Index (EASI)	The EASI scoring system uses a defined process (Steps 1 through 5 below) to grade the severity of the signs of eczema and the extent affected. The extent of disease (percentage of skin affected: 0 = 0%; 1 = 1% to 9%; 2 = 10% to 29%; 3 = 30% to 49%; 4 = 50% to 69%; 5 = 70% to 89%; 6 = 90% to 100%) and the severity of 4 clinical signs (erythema, edema/papulation, excoriation, and lichenification), each on a scale of 0 to 3 (0 = none, absent; 1 = mild; 2 = moderate; 3 = severe) at 4 body sites (head and neck, trunk, upper limbs, and lower limbs). Half scores are allowed between Severities 1, 2 and 3. Each body site will have a score that ranges from 0 to 72, and the final EASI score will be obtained by weight-averaging these 4 scores. Hence, the final EASI score will range from 0 to 72 for each time point.	EASI score	Derive EASI region score for each of head and neck, trunk, upper limbs, and lower limbs as follows: $EASI_{region}$ = (Erythema + edema/papulation + Excoriation + Lichenification) × (value from percentage involvement), where erythema, edema/papulation, excoriation, and lichenification are evaluated on a scale of 0 to 3 and value from percentage involvement is on a scale of 0 to 6. Then total EASI score is as follows: $EASI = 0.1 \times EASI_{head\ and\ neck} + 0.3 \times EASI_{trunk} + 0.2 \times EASI_{upper\ limbs} + 0.4 \times EASI_{lower\ limbs}$	N/A – partial assessments cannot be saved.
		Change from baseline in EASI score Percent change from baseline EASI score	Change from baseline: observed EASI score—baseline EASI score Percentage change from baseline: $100 \times \frac{Observed\ score - Baseline}{Baseline}$	Missing if baseline or observed value is missing.

		EASI 50	Percentage improvement in EASI score from baseline ≥50%: Percentage change from baseline ≤−50	Missing if baseline or observed value is missing.
		EASI 75	Percentage improvement in EASI score from baseline ≥75%: Percentage change from baseline ≤−75	Missing if baseline or observed value is missing.
		EASI 90	Percentage improvement in EASI score from baseline ≥90%: Percentage change from baseline ≤−90	Missing if baseline or observed value is missing.
Body Surface Area (BSA)	The BSA assessment estimates the extent of disease or skin involvement with respect to AD and is expressed as a percentage of total body surface. BSA will be determined by the Investigator or designee using the participant palm = 1% rule.	BSA score	BSA Total = $BSA_{head\ and\ neck}$ + BSA_{trunk} + $BSA_{upper\ extremities}$ + $BSA_{lower\ extremities}$	N/A – partial assessments cannot be saved.
		Change from baseline in BSA score	Change from baseline: observed BSA score—baseline BSA score	Missing if baseline or observed value is missing.
Pruritus Numeric Rating Scale (NRS)	The Pruritus NRS is a an 11-point scale used by participants to rate their worst itch severity over the past 24 hours with 0 indicating "No itch" and 10 indicating "Worst itch imaginable." Assessments will be recorded daily by the participant using an electronic diary.	Pruritus NRS prorated weekly mean score	The prorated weekly mean is based on previous 7 days. If the participant has at least 1 daily score, the weekly mean is the prorated average of daily scores within the given week. Single item; range 0 to 10. eDiary data are mapped to study visit per Appendix 1.	Weekly mean score missing if the participant has no Pruritus-NRS responses within the week.
		Change from baseline in Pruritus NRS prorated weekly mean score Percent change from baseline in Pruritus NRS prorated weekly mean score	Change from baseline: observed Pruritus NRS prorated weekly mean score – baseline Pruritus weekly mean score Percentage change from baseline: $100 \times \frac{Observed\ score - Baseline}{Baseline}$	Missing if baseline or observed value is missing.

		4-point improvement in Pruritus NRS prorated weekly mean score	Change from baseline ≤−4 in Pruritus NRS prorated weekly mean score	Missing if baseline is missing or observed value is missing.
Sleep-loss due to pruritus	Sleep-loss due to pruritus will be assessed by the participant. Participants rate their sleep based on a 5-point Likert scale (0 [not at all] to 4 [unable to sleep at all]). Assessments will be recorded daily by the participant using an electronic diary.	Sleep-loss prorated weekly mean score	The prorated weekly mean is based on previous 7 days. If the participant has at least 1 daily score, the weekly mean is the prorated average of daily scores within the given week. Single item; range 0 to 10. eDiary data are mapped to study visit per Appendix 1.	Weekly mean score missing if the participant has no Sleep-loss due to pruritus responses within the week.
		Change from baseline in Sleep-loss prorated weekly mean score Percent change from baseline in Sleep-loss prorated weekly mean score	Change from baseline: observed sleep loss prorated weekly mean score—baseline sleep loss score Percentage change from baseline: $100 \times \frac{Observed\ score - Baseline}{Baseline}$	Missing if baseline or observed value is missing.
		2-point improvement in Sleep-loss prorated weekly mean score	Change from baseline in Sleep-loss prorated weekly mean score ≤−2	Missing if baseline is missing or observed value is missing.
Skin Pain NRS	Skin Pain NRS is a participant-administered, validated, 11-point horizontal scale anchored at 0 and 10, with 0 representing “no pain” and 10 representing “worst pain imaginable.” Overall severity of a participant’s skin pain is indicated by selecting the number that best describes the worst level of skin pain in the past 24 hours. Assessments will be recorded daily by the participant using an electronic diary.	Skin Pain NRS prorated weekly mean score	The prorated weekly mean is based on previous 7 days. If the participant has at least 1 daily score, the weekly mean is the prorated average of daily scores within the given week. Single item; range 0 to 10. eDiary data are mapped to study visit per Appendix 1	Weekly mean score missing if the participant has no Skin pain NRS responses within the week.
		Change from baseline in Skin Pain NRS prorated weekly mean score Percent change from baseline in Skin Pain	Change from baseline: observed Skin Pain prorated weekly mean score – baseline Skin Pain weekly mean score Percentage change from baseline: $100 \times \frac{Observed\ score - Baseline}{Baseline}$	Missing if baseline or observed value is missing.

		NRS prorated weekly mean score		
		4-point improvement in Skin Pain NRS prorated weekly mean score	Change from baseline in Skin Pain NRS prorated weekly mean score ≤-4	Missing if baseline is missing or observed value is missing.
Patient-Oriented Eczema Measure (POEM)	The POEM is a 7-item, validated, questionnaire used by the participant to assess disease symptoms over the last week. The participant is asked to respond to 7 questions on skin dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping. All 7 answers carry equal weight with a total possible score from 0 to 28 (answers scored as: No days = 0; 1 to 2 days = 1; 3 to 4 days = 2; 5 to 6 days = 3; everyday = 4). A high score is indicative of a poor quality of life. POEM responses will be captured using an electronic diary and transferred into the clinical database.	POEM score	POEM total score: sum of Questions 1 to 7, Range 0 to 28	If a single question is left unanswered, then that question is scored as 0. If more than 1 question is unanswered, then the tool is not scored. If more than 1 response is selected, then the response with the highest score is used.
		Change from baseline in POEM score	Change from baseline: observed POEM score—baseline POEM score	Missing if baseline or observed value is missing.
		4-point improvement	Change from baseline ≤−4	Missing if baseline is missing or observed value is missing.
Patient-Reported Outcomes Measurement Information System (PROMIS)	PROMIS is a set of person-centered measures that evaluates and monitors physical, mental, and social health in adults and children. Pediatric and tools for anxiety and depression.	PROMIS anxiety total score	A PROMIS anxiety has 8 questions on Emotion Distress-Anxiety (or Pediatric Anxiety)—Short Form 8a. Each ranges 1 to 5. Total raw scores are converted to T-Scores with higher scores representing greater anxiety.	Total score can be derived even with partial response as instrument use item response theory method.
		PROMIS depression total score	A PROMIS depression has 8 questions on Emotion Distress-Depression (or Pediatric Depressive Symptom)—Short Form 8a. Each ranges 1 to 5. Total raw scores are converted to T-score with higher scores representing greater depression.	

			Calculation is made by HealthMeasures Scoring Service, powered by Assessment Center℠	
		Change from baseline in PROMIS anxiety total score	Change from baseline: observed score—baseline PROMIS anxiety total score	Missing if baseline or observed value is missing.
		Change from baseline in PROMIS depression total score	Change from baseline: observed score—baseline PROMIS depression total score	

Abbreviations: AD = atopic dermatitis; EASI 50 = ≥50% reduction from baseline in EASI score; EASI 75 = ≥75% reduction from baseline in EASI score; EASI 90 = ≥90% reduction from baseline in EASI score; IgG = immunoglobulin G; LLOQ = lower limit of quantitation; MCV = Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine; N/A = not applicable; rSBA = rabbit complement serum bactericidal assay; Tdap = Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed.

Table KGAK.6.7. Description of Primary, Secondary, and Sensitivity Efficacy/Health Outcome Analyses

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.1.1)	Comparison/Time Point	Analysis Type
Booster response to tetanus toxoid 4 weeks after the administration of the Tdap vaccine (Week 16)	Percentage of participants achieving booster response to tetanus toxoid 4 weeks after the administration of the Tdap vaccine (Week 16)	90% CI for the difference between treatment arms using the stratified (by baseline IGA severity) Newcombe approach	PPS	LEB 250 mg Q2W vs PBO; Week 16	Primary analysis
			mITT		Supplementary analysis (As Observed)
Positive antibody response to MCV (Group C serum bactericidal antibodies) 4 weeks after the administration of the vaccine (Week 16)	Percentage of participants achieving positive antibody response to MCV (Group C serum bactericidal antibodies) 4 weeks after the administration of the vaccine (Week 16)	90% CI for the difference between treatment arms using the stratified (by baseline IGA severity) Newcombe approach	PPS	LEB 250 mg Q2W vs PBO; Week 16	Primary analysis
			mITT		Supplementary analysis (As Observed)
IGA	Proportion of participants achieving IGA [0,1] with a ≥2-point improvement	CMH analysis with MCMC-MI	mITT	LEB 250 mg Q2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Secondary analysis
			PPS	LEB 250 mg Q2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Supplementary analysis
		CMH analysis with NRI	mITT	LEB 250 mg Q2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Supplementary analysis

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.1.1)	Comparison/Time Point	Analysis Type
	Proportion of participants achieving IGA (0)	CMH analysis with MCMC-MI	mITT	LEB 250 mg Q2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Secondary analysis
Eczema Area and Severity Index (EASI)	Change from baseline in EASI score Percent change from baseline in EASI score	ANCOVA with MCMC-MI	mITT	LEB 250 mg Q2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Secondary analysis
			PPS	LEB 250 mgQ2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Supplementary analysis
		MMRM	mITT	LEB 250 mg Q2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Supplementary analysis
	Proportion of participants achieving EASI 75 Proportion of participants achieving EASI 90	CMH analysis with MCMC-MI	mITT	LEB 250 mgQ2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Secondary analysis
			PPS	LEB 250 mg Q2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Supplementary analysis
		CMH analysis with NRI	mITT	LEB 250 mg Q2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Supplementary analysis
	Proportion of participants achieving EASI 50	CMH analysis with MCMC-MI	mITT	LEB 250 mg Q2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Secondary analysis

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.1.1)	Comparison/Time Point	Analysis Type
Body Surface Area (BSA) Affected by AD	Change from baseline in BSA score	MMRM	mITT	LEB 250 mg Q2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Secondary analysis
Pruritus Numeric Rating Scale (NRS)	Change from baseline in Pruritus NRS Percent Change from baseline in Pruritus NRS	ANCOVA with MCMC-MI	mITT	LEB 250 mg Q2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Secondary analysis
		MMRM	mITT	LEB 250 mg Q2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Supplementary analysis
	Proportion of participants achieving at least 4-point improvement in pruritus NRS in participants who had baseline pruritus NRS ≥4	CMH analysis with MCMC-MI	mITT participants with baseline pruritus NRS ≥4	LEB 250 mg Q2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Secondary analysis
		CMH analysis with NRI	mITT participants with baseline pruritus NRS ≥4	LEB 250 mg Q2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Supplementary analysis
Sleep-loss Score	Percent Change from baseline in Sleep-loss Score Change from baseline in Sleep-loss Score	ANCOVA with MCMC-MI	mITT	LEB 250 mg Q2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Secondary analysis
		MMRM	mITT	LEB 250 mg Q2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Supplementary analysis
		CMH analysis with MCMC-MI	mITT participants with baseline Sleep-loss ≥2	LEB 250 mg Q2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Secondary analysis

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.1.1)	Comparison/Time Point	Analysis Type
	Proportion of participants achieving at least 2-point improvement in sleep-loss in participants who had baseline Sleep-loss ≥2	CMH analysis with NRI	mITT participants with baseline Sleep-loss ≥2	LEB 250 mg Q2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Supplementary analysis
Skin Pain NRS	Percent Change from baseline in Skin Pain Score	ANCOVA with MCMC-MI	mITT	LEB 250 mg Q2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Secondary analysis
	Change from baseline in Skin Pain Score	MMRM	mITT	LEB 250 mg Q2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Supplementary analysis
	Proportion of participants achieving at least 4-point improvement in Skin Pain NRS in participants who had baseline Skin Pain NRS ≥4	CMH analysis with MCMC-MI	mITT participants with baseline Skin Pain NRS ≥4	LEB 250 mgQ2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Secondary analysis
		CMH analysis with NRI	mITT participants with baseline Skin Pain NRS ≥4	LEB 250 mg Q2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Supplementary analysis
Patient-Oriented Eczema Measure (POEM)	Change from baseline in POEM score	MMRM	mITT	LEB 250 mg Q2W vs PBO; Week 16 and all scheduled visits in the Treatment Period	Secondary analysis
Patient-Reported Outcomes Measurement Information System (PROMIS)	Change from baseline in PROMIS Anxiety score	ANCOVA with LOCF	mITT	LEB 250 mg Q2W vs PBO; Week 16	Secondary analysis

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.1.1)	Comparison/Time Point	Analysis Type
	Change from baseline in PROMIS Depression score				

Abbreviations: AD = atopic dermatitis; ANCOVA = analysis of covariance; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EASI 50 = ≥50% reduction from baseline in EASI score; EASI 75 = ≥75% reduction from baseline in EASI score; EASI 90 = ≥90% reduction from baseline in EASI score; IGA = Investigator's Global Assessment; LEB = lebrikizumab; LOCF = last observation carried forward; MCMC-MI = Markov chain Monte Carlo multiple imputation; MCV = Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; NRI = nonresponder imputation; PBO = placebo; PPS = per protocol set; Q2W = every 2 weeks; Tdap = Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed.

6.10.1. Primary Outcome and Methodology

The primary analysis of the study is to confirm that lebrikizumab 250 mg Q2W is the same as placebo when evaluating the booster response to the Tdap vaccine and the response to positive antibody response to MCV (Group C serum bactericidal antibodies) (proportion of participants) at Week 16 in the PPS population.

The primary estimand addresses the treatment response as directed. A 90% CI for the difference of proportion between treatment groups will be constructed using the stratified Newcombe approach (Yan and Su 2010; Kim and Won 2013) for each of the coprimary endpoints separately. Missing values will not be imputed. Descriptive statistics of antitetanus toxoid IgG antibody concentration (including the number of participants, mean, standard deviation, median, minimum, maximum, geometric mean, and coefficient of variation) and Meningococcal Group C serum rSBA titers (including the number and percentage of participants in each titer level) at Week 0, Week 12, and Week 16 will also be provided.

Primary outcomes booster response to the Tdap vaccine and the response to positive antibody response to MCV (Group C serum bactericidal antibodies), and the analysis are described in Table KGAK.6.6.

6.10.2. Sensitivity Analyses

Sensitivity analyses are included to demonstrate robustness of analyses methods using different missing data imputations, populations, and analyses assumptions. Supplementary analysis for the primary endpoints and sensitivity analyses for secondary endpoints are described in Table KGAK.6.6 and Table KGAK.6.7.

6.10.3. Secondary Efficacy Analyses

Secondary outcomes and the analyses are described in Table KGAK.6.6 and Table KGAK.6.7.

6.11. Health Outcomes/Quality-of-Life Analyses

Analyses of Pruritus NRS, Sleep-loss NRS, Skin pain NRS, POEM, and PROMIS are described in Table KGAK.6.6 and Table KGAK.6.7.

6.12. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Details of pharmacokinetic (PK)/pharmacodynamic (PD) analyses can be found in a separate PK/PD analysis plan.

6.13. Safety Analyses

The planned analyses of safety data will be performed with an intent to maintain consistency with compound level standard safety analyses. These standards are based on internal standards that were informed by Clinical Data Interchange Standards Consortium (CDISC) standards, regulatory guidance (for example, FDA Clinical Review Template), and cross-industry standardization efforts (for example, Pharmaceutical Users Software Exchange [PhUSE] white

papers from the Standard Analyses and Code Sharing Working Group provided in the PhUSE Computational Science Deliverables Catalog).

Safety evaluations will be based upon the Modified Safety Population (Treatment Period) and Safety Population (Treatment Period).

Analysis populations are fully defined in Table KGAK.6.1 while Table KGAK.6.2 describes the treatment groups, associated study periods, and the comparisons for each analysis population.

For document writing purposes for safety, tests with 2-sided p-values less than .05 will be referred to as having strong statistical evidence for a treatment difference, unless otherwise noted. However, p-values should not be over-interpreted for these safety analyses. Except for prespecified hypotheses, they correspond to data-driven hypotheses and hence are only useful as a flagging mechanism.

Not all displays described in this section will necessarily be included in the CSRs. Any display described and not provided in the CSR will be available upon request. Not all displays will necessarily be created as a "static" display. Some may be incorporated into interactive display tools instead of or in addition to a static display. Any display created interactively will be included in the CSR if deemed relevant to the discussion.

6.13.1. Extent of Exposure

Exposure will be reported for participants in the Modified Safety Population and will be summarized by treatment group. Drug interruption time period due to the use of systemic rescue therapies will not be removed from study drug exposure calculations as described in compound level safety standards.

The duration of exposure will be calculated as

$$\begin{aligned} &Duration\ of\ exposure\ (days) \\ &\quad = Date\ of\ last\ visit\ (scheduled\ or\ unscheduled)\ in\ the\ Treatment\ Period \\ &\quad - Date\ of\ first\ dose + 1 \end{aligned}$$

The number and percentage of participants in each of the following categories will be included in the summaries:

- >0, ≥7 days, ≥14 days, ≥30 days, ≥60 days, ≥90 days, ≥112 days, ≥120 days. Note that participants may be included in more than 1 category
- >0 to <7 days, ≥7 to <14 days, ≥14 to <30 days, ≥30 to <60 days, ≥60 to <90 days, ≥90 to <120 days, ≥120 days

Additional exposure ranges may be considered if necessary. No p-values will be reported.

The summaries will also include the following information:

- Total exposure in patient years, calculated as

$$Total\ exposure\ in\ patient\ years = \frac{Sum\ of\ duration\ of\ exposures\ for\ all\ patients\ in\ treatment\ group}{365.25}$$

- Mean and median total dose. Total dose (in mg) is calculated by the number of active injections taken during the treatment period multiplied by dose. The total dose (in mg) taken during the Treatment Period will be calculated as follows: *Total lebrikizumab dose = Total number of active injections (including loading doses, if any) received in Treatment Period × 250 mg*.
- Total number of injections received will be derived based on the *Study Drug Administration* eCRF pages and dosing diary.

6.13.2. Adverse Events

A TEAE is defined as an event that first occurred or worsened in severity after baseline (date of first injection). The MedDRA Lowest Level Term (LLT) will be used in the treatment-emergent computation. The maximum severity for each LLT during the baseline period will be used as baseline. The treatment period will be included as postbaseline for the analysis. For events with a missing severity during the baseline period, it will be treated as "mild" in severity for determining treatment-emergence. Events with a missing severity during the postbaseline period will be treated as "severe" and treatment-emergence will be determined by comparing to baseline severity. For events occurring on the day of first taking study medication, it will be assumed to be posttreatment.

The planned summaries for AEs are provided in Table KGAK.6.8 and are described more fully in compound level safety standards and in the AE-related PhUSE white paper (Analysis and Displays Associated with Adverse Events: Focus on Adverse Events in Phase 2-4 Clinical Trials and Integrated Summary Document [PhUSE 2017]).

Summary tables as described in Table KGAK.6.8 will be presented for the following periods/analysis populations as indicated. Summary tables will include the number and percentage of participants reporting an event. For events that are gender-specific (as defined by MedDRA), the number of participants at risk will include only participants from the given gender.

Table KGAK.6.8. Summary Tables/Listing Related to Adverse Events

Analysis	Population (Section 6.1.1)
Overview of AEs	mS, S
Summary of TEAE by PTs	mS
Summary of TEAE by PTs occurring in ≥1% of participants	mS
Summary of TEAE by PTs within SOC	mS
Summary of TEAE PTs by maximum severity	mS, S
Summary of SAE by PT within SOC	mS, S
Summary of AEs leading to treatment discontinuation by PT with SOC	mS
Summary of TEAE possibly related to study drug by PTs within SOC	mS

Analysis	Population (Section 6.1.1)
Listing of SAEs (including Death)	ITT
Listing of primary AEs leading to study treatment discontinuation	ITT
Listing of TEAE (for Japan submission only)	S
Listing of AE for Participants from Site 1883 and Site 1827	-

Abbreviations: AE = adverse event; ITT = Intent-to-Treat; mS = Modified Safety Population; PT = preferred term; SAE = serious adverse event; S = Safety Population; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

Statistical comparisons will be performed using Fisher's exact test. Odds ratio will be provided. For AE related listings, AEs occurring on or after the date of Informed Consent and before the date of first injection in KGAK study will also be reported if proper.

6.13.2.1. Common Adverse Events

The percentages of participants with TEAEs will be summarized by treatment using the MedDRA PT for the common TEAEs (occurred in ≥1% before rounding in any column in the table).

6.13.2.2. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events

The number and percentage of participants reported with an SAE during the treatment period will be summarized by treatment using the MedDRA PT. A listing of SAEs will be provided.

The number and percentage of participants who permanently discontinued from study treatment due to an AE (including AEs that led to death) during the treatment period will be summarized by treatment using MedDRA PT. Events will be ordered by decreasing frequency in all treatment groups for both AE and SAE.

6.13.3. Clinical Laboratory Evaluation

As described more fully in compound level safety standards and in the laboratory-related PhUSE white papers (PhUSE 2013, 2015), the clinical laboratory evaluations will be summarized as described in Table KGAK.6.9.

Table KGAK.6.9. Analysis for Clinical Laboratory Evaluations

Analysis	Population
Box plots of observed values by visit Box plots for change values by visit	mS
Change from baseline to last observations. ANCOVA model with treatment and baseline value in the model	mS
Scatter plots of baseline-by-maximum values and baseline-by-minimum values	mS
Treatment-emergent abnormal high lab values (i.e., participants shifting from a normal/low maximum baseline value to a high maximum postbaseline value) or abnormal low lab values (i.e., participants shifting from normal/high minimum baseline value to a low minimum postbaseline value)	mS

Analysis	Population
Shift tables showing the number of participants who shift from each category of maximum (minimum) baseline observation to each category of maximum (minimum) postbaseline observation. Here categories may be low, normal, or high with cut-offs defined in the compound level safety standards.	mS
Listing of abnormal findings for laboratory analyte measurements, including qualitative measures	All Enrolled

Abbreviations: ANCOVA = analysis of covariance; mS = Modified Safety Population.

6.13.4. Vital Signs and Other Physical Findings

As described more fully in compound level safety standards and in the laboratory-related PhUSE white papers (PhUSE 2013, 2015), vital signs will be summarized similarly to the clinical laboratory evaluation (Table KGAK.6.10). For vital signs, treatment-emergent low and high are based on a combination of a specified value and a change or percentage change as defined in the compound level safety standards.

Table KGAK.6.10. Analysis Related to Vital Signs

Analysis	Population
Box plots for observed values by visit	mS
Box plots for change from baseline values by visit	mS
Scatterplots of baseline-by-maximum values and baseline-by-minimum values	mS
Tables with the number and percentage of subjects who shift from normal/high to low (i.e., treatment-emergent low) and the number and percentage of subjects who shift from normal/low to high (i.e., treatment-emergent high); the limits are defined in the compound level safety standards	mS

Abbreviation: mS = Modified Safety Population.

6.13.5. Immunogenicity

An individual sample is potentially examined multiple times in a hierarchical procedure to produce a sample antidrug antibody (ADA) assay result and may yield a sample neutralizing ADA (NAb) assay result. Treatment-emergent ADAs (TE-ADAs) are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). A participant is considered TE-ADA positive when at least 1 postbaseline ADA sample meets the definition of TE-ADA. A participant is evaluable for TE-ADA if there is at least 1 nonmissing test result for ADA for both the baseline and the postbaseline visits.

Compound level safety standards will be followed in the analyses of immunogenicity. Listings of immunogenicity assessments will be provided for the Safety Population. The summary of TE-ADA and NAb status will be produced for the Modified Safety Population, where the postbaseline period for reporting is the same as described for AEs in Section 6.13.2. Additional assessments of the relationship between immunogenicity and efficacy will be performed as part of the integrated analysis including other Phase 3 lebrikizumab AD trials.

6.13.6. Special Safety Topics including Adverse Events of Special Interest

This section includes areas of interest whether due to observed safety findings, potential findings based on drug class, or safety topics anticipated to be requested by a regulatory agency for any reason. In general, potential adverse events of special interest (AESIs) relevant to these special safety topics will be identified by 1 or more Standardized MedDRA Query(ies) (SMQ[s]), by a Lilly-defined MedDRA PT listing based upon the review of the most current version of MedDRA, or by treatment-emergent relevant laboratory changes, as described below. Additional special safety topics may be added as warranted.

Unless otherwise specified, the special safety topic will be summarized for the Modified Safety Population during the Treatment Period as described in Section 6.13.

Full details of the search terms and rules for deriving special safety topic in each of the sections below are described in the compound level safety standards along with information about the types of summaries and listings to be provided. In the event that the listing of terms or analysis changes for a special safety topic, it will be documented in the compound level safety standards that will supersede this document; it will not warrant an amendment to the individual study SAP.

6.13.6.1. Hepatic Safety

Hepatic labs include alanine aminotransferase (ALT), aspartate transaminase (AST), total bilirubin (TBL), and serum alkaline phosphatase (ALP).

Table KGAK.6.11. Summary Tables Related to Hepatic Safety

Analysis	Population
ALT and AST: The number and percentage of subjects with a measurement greater than or equal to 3 times (3×), 5 times (5×), and 10 times (10×) the performing lab upper limit of normal (ULN) during the treatment period for all subjects with a postbaseline value and for subsets based on various levels of baseline value TBL and ALP: The number and percentage of subjects with a measurement greater than or equal to 2 times (2×) the performing lab ULN during the treatment period will be summarized for all subjects with a postbaseline value and for subsets based on various levels of baseline value	mS
Plot of maximum post-baseline ALT vs maximum postbaseline total bilirubin	Modified Safety Population for All Periods: ever on lebri and never on lebri

Abbreviations: ALP = serum alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate transaminase; lebri = lebrikizumab; mS = Modified Safety Population; TBL = total bilirubin.

6.13.6.2. Eosinophilia and Eosinophil-Related AE

In addition to the standard laboratory analysis (Section 6.13.3), eosinophilia and eosinophil-related AE will be summarized. Details regarding eosinophil-related PTs are in Compound Level Safety Standard.

Table KGAK.6.12. Summary Tables Related to Eosinophilia and Eosinophil-Related AE

Analysis	Population
Shift table summarizing the number and percentage of participants within each maximum baseline category versus each maximum postbaseline category by treatment	mS
Summary of eosinophil-related TEAE by PT	mS

Abbreviations: AE = adverse event; PT = preferred term; mS = Modified Safety Population; TEAE = treatment-emergent adverse event.

6.13.6.3. Infections, Including Herpes Infections and Relevant Parasitic Infections

Infections will be defined using the PTs from the MedDRA Infections and Infestations SOC. The MedDRA terms used to identify infections considered to be opportunistic infections (OI) in participants with immune mediated inflammatory conditions treated with immunomodulatory drugs are based on Winthrop et al. (2015) and are listed in the compound level safety standards. The list contains narrow (more specific) and broad (less specific) PTs with respect to these prospectively defined OIs. Definitions of herpes infections, parasitic infections, and skin infections are listed in the compound level safety standards.

Table KGAK.6.13. Summary Tables/Listing Related to Infection Related AE

Analysis	Population
Summary of treatment-emergent infections by PT	mS
Summary of serious infections by PT	mS
Summary of infection AEs resulting in permanent study drug discontinuation	mS
Treatment-emergent AEs, herpes and parasitic infections	mS
Treatment-emergent AEs, skin infection	mS
Summary and/or listing of Infection follow-up form	mS (summary only), S (listing only)
Treatment-emergent potential OI by PT nested with categories for narrow terms and broad terms separately	mS
A listing of participants with potential OI, Serious Infection, Herpes, and Parasitic Infections	S

Abbreviations: AE = adverse event; OI = opportunistic infections; mS = Modified Safety Population; S = Safety Population; PT = Preferred Term.

6.13.6.4. Conjunctivitis

Conjunctivitis are events of special interest and will be identified using PTs nested within the categories of conjunctivitis and Keratitis as described in the Compound Level Safety Standards.

Table KGAK.6.14. Summary Tables/Listing Related to Conjunctivitis

Analysis	Population
Summary of TEAE of conjunctivitis within categories	mS
Summary and/or listing of conjunctivitis and eye inflammation follow-up form	mS (summary only), S (listing only)
A listing of participants with conjunctivitis	S

Abbreviations: mS = Modified Safety Population; S = Safety Population; TEAE = treatment-emergent adverse event.

6.13.6.5. Hypersensitivity

Potential hypersensitivity reactions will be determined using the following SMQs: anaphylactic reaction, hypersensitivity, and angioedema. Potential hypersensitivity will be categorized as immediate (i.e., occurring the same day as drug administration) and nonimmediate (that is, occurring after the day of study drug administration but prior to subsequent drug administration). The planned summaries are provided in Table KGAK.6.15.

Table KGAK.6.15. Summary Tables/Listing Related to Hypersensitivity

Analysis	Population
For immediate hypersensitivity: (1) combined narrow/algorithmic search (that is, any narrow term from any one of the SMQs, or anaphylaxis algorithm); (2) narrow search (that is, any narrow term) by SMQ; (3) broad search (that is, any narrow or broad term) by SMQ; and (4) TEAEs (occurring on the day of study drug administration) by PT not in any of the 3 SMQs	mS
For nonimmediate hypersensitivity: (1) combined narrow search (that is, any narrow term from any one of the SMQs); (2) narrow search (that is, any narrow term) by SMQ; and (3) broad search (that is, any narrow or broad term) by SMQ	mS

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; mS = Modified Safety Population; SMQ = Standardized MedDRA Query; TEAE = treatment-emergent adverse event.

6.13.6.6. Injection Site Reactions

Injection site reactions (ISRs) are AEs localized to the immediate site of the administration of a drug. The evaluation of study drug related ISRs will be through the unsolicited reporting of ISR TEAEs. Injection site reactions will be defined using the MedDRA High Level Term (HLT) of Injection Site Reaction, excluding certain PTs related to joints as described in the Compound Level Safety Standards.

Table KGAK.6.16. Summary Tables Related to Injection Site Reactions

Analysis	Population
Summary of TEAE of ISR overall and by PT	mS

Abbreviations: ISR = injection site reaction; mS = Modified Safety Population; PT = preferred term; TEAE = treatment-emergent adverse event.

6.13.6.7. Malignancies

Malignancies will be defined using PTs from the Malignant tumors SMQ and summarized separately for the 2 categories: Nonmelanoma skin cancer (NMSC) and Malignancies excluding NMSC as below.

Table KGAK.6.17. Summary Tables Related to Malignancies

Analysis	Population
Summary of TEAE of malignancies within categories of NMSC and malignancy excluding NMSC	mS

Abbreviations: mS = Modified Safety Population; NMSC = nonmelanoma skin cancer; TEAE = treatment-emergent adverse event

6.13.6.8. Atopic Dermatitis Exacerbation

Atopic dermatitis exacerbation will be defined using PTs specified in the Compound Level Safety Standards and summarized below.

Table KGAK.6.18. Summary Tables Related to Atopic Dermatitis Exacerbation

Analysis	Population
Summary of TEAE of atopic dermatitis exacerbation	mS

Abbreviations: mS = Modified Safety Population; TEAE = treatment-emergent adverse event.

6.13.6.9. Suicide/Self-injury SMQ

Suicide/self-injury will be defined as described in the Compound Level Safety Standards and summarized below.

Table KGAK.6.19. Summary Tables Related to Suicide/Self-injury

Analysis	Population
Summary of TEAE of Suicide/self-injury	mS

Abbreviations: mS = Modified Safety Population; TEAE = treatment-emergent adverse event.

6.14. Subgroup Analyses

6.14.1. Efficacy Subgroup Analyses

Subgroup analyses will be conducted for the secondary endpoints IGA (0,1), EASI 75 at Week 16 in the mITT Population using the MCMC-MI approach (Section 6.4.1). A logistic regression analysis with treatment, subgroup, and treatment-by-subgroup interaction as factors will be used. The treatment-by-subgroup interaction will be tested using the Firth correction (Firth 1993) at the 10% significance level. Treatment group differences will be evaluated within each subgroup using the Chi-Square test, regardless of whether the interaction is statistically significant. If any group within the subgroup (for example, yes, no) is <10% of the total population, only descriptive statistics will be provided for that subgroup (that is, no inferential testing).

Forest plots may be created to illustrate the treatment differences with 95% CIs between each of the lebrikizumab treatment groups and placebo group, by each subgroup category.

The following subgroups will be analyzed:

- Sex (male, female)
- Race (Asian, Black or African American, White, Other)
- Weight category (<60 kg, ≥60 to <100 kg, ≥100 kg)
- BMI category (Underweight [<18.5 kg/m^2], Normal [≥18.5 and <25 kg/m^2], Overweight [≥25 and <30 kg/m^2], Obese [≥30 and <40 kg/m^2], Extreme obese [≥40 kg/m^2])

- Duration since AD onset category (0 to <2 years, 2 to <5 years, 5 to <10 years, 10 to <20 years, ≥20 years)
- Baseline IGA 3 versus 4
- Baseline pruritus <4 versus ≥4

Some additional subgroup analyses may be added to meet regulatory requirement. The analysis of additional subgroups will not require an amendment to the SAP.

6.14.2. Safety Subgroup Analyses

Subgroup analysis for safety related endpoints will be performed within the context of the integrated safety analysis. No safety subgroup analysis will be performed specifically for this study unless there is a potentially relevant finding during the periodic study safety reviews.

6.15. Protocol Deviations

Protocol deviations will be identified throughout the study. Important protocol deviations (IPDs) are defined as those deviations from the protocol likely to have a significant impact on the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being. Out of all IPDs identified, a subset occurring during the Treatment Period with the potential to affect primary efficacy analysis will result in exclusion from the PP population.

Potential examples of IPDs include participants who violated the inclusion/exclusion criteria, used an interfering concomitant medication, and significant noncompliance with study medication (<80% of expected injections). Refer to a separate document called "KGAK Trial Issues Management Plan" for the IPDs with categorizations and whether or not these deviations will result in the exclusion of participants from PP set.

The number and percentage of participants having IPD(s) will be summarized within category and subcategory of deviation by treatment group for the Treatment Period using the ITT population.

A by-patient listing of IPDs will be provided.

6.15.1. Impact of COVID-19

Impact of pandemic (for example, COVID-19) on analyses will be systemically addressed prior to study unblinding at Week 16 DBL, once the impact on study conducts are fully understood. In general, any missing assessments/visit window will be documented as protocol deviations. There are no skin efficacy assessments that will be processed or collected in remote visits. Detailed demonstration of "Provisions for Changes in Study Conduct During Exceptional" is in the KGAK protocol. A summary or listing may be provided to summarize missing visits due to COVID-19.

6.16. Interim Analyses and Data Monitoring

Data Monitoring Committee/Data Safety Monitoring Board (DMC/DSMB): The lebrikizumab Phase 3 AD programs' DSMB is an independent expert advisory group commissioned and charged with the responsibility of evaluating cumulative safety at regular intervals, as well as on an ad hoc basis, as needed. The DSMB will consist of members external to Lilly and follow the rules defined in the DSMB charter, focusing on potential and identified risks for this molecule. Data Monitoring Committee membership will include, at a minimum, a physician with expertise in dermatology and a statistician. No member of the DSMB may have contact with study sites. This committee will make recommendations as to a) continue the clinical studies without modification; or b) continue the clinical studies with modifications; or c) terminate one or more of the clinical studies. Details outlining the roles and responsibilities of the DMC are documented in the "Dermira DRM06 DSMB Program Charter" and the planned analyses are outlined in the DMC analysis plan prior to the first unblinded assessment.

Access to the unblinded safety data will be limited to the DSMB. The study team will not have access to the unblinded data. Only the DSMB is authorized to evaluate unblinded data. The purpose of the DSMB is to advise Lilly regarding participant safety; however, the DSMB may request key efficacy data to put safety observations into context and to confirm a reasonable benefit/risk profile for ongoing participants in the study. Hence, there will be no alpha adjustment for these interim assessments.

Week 16 DBL: An unblinded interim analysis will be performed at the time (that is, a cut-off date) the last participant completes Week 16 or the ETV from the study. At the time of Week 16 DBL, the primary endpoint analysis related to booster response to tetanus toxoid has been performed. At the time of Week 16 DBL, the MCV hSBA data is considered as invalid because the assay procedure was not successfully validated at Eurofins Scientific®. Only a small group of statisticians working on the data analysis at the time of the Week 16 DBL had access to the patient-level data. A small internal group of Lilly personnel have been unblinded with a high-level summary result including Global Patient Safety and Medical study team representatives. The patient-level data was quarantined once MCV issues were identified. Personnel who have access to the patient-level data have no access to the biospecimen for the MCV hSBA. The primary endpoint analysis related to MCV response will be on hold until final DBL.

The study will not be terminated early on the basis of efficacy following these interim analyses.

Final DBL: A final DBL will occur after all participants have completed the safety follow-up period of the study, discontinued current study, or enrolled into the long-term extension study DRM06-AD07.

Lilly identified Nexelis as an alternate vendor for analyzing the MCV response using a fully validated rabbit complement serum bactericidal assay (rSBA) in order to deliver results for the final DBL and for analysis. The final DBL will include all data collected by the date of final DBL except Eurofins hSBA data. Final DBL will not occur until new fully validated rSBA is completed by Nexelis and all MCV response data is transferred. The primary endpoint analysis related to booster response to tetanus toxoid will be performed with the Eurofins Tdap data that

is a retransfer of the Week 16 DBL Eurofins Tdap data. The primary endpoint analysis related to MCV response will be performed with the Nexelis retested rSBA data based on the biospecimen collected through Week 16 DBL. For other efficacy and safety analysis, all data collected by the date of final DBL will be included.

6.17. Annual Report Analyses

Based on regulatory requirements for the Development Safety Update Report (DSUR), reports will be produced (if not already available from the study CSR) for the reporting period covered by the DSUR.

6.18. Clinical Trial Registry Analyses

Additional analyses will be performed (if not already available from the study CSR) for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of AEs, provided as a dataset, will be converted to an XML file. Both serious adverse events (SAEs) and 'Other' AEs will be summarized by treatment group and by MedDRA PT.

- An AE is considered 'Serious' whether or not it is a TEAE.
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term, and
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

7. Unblinding Plan

Unblinding details are specified in a separate unblinding plan.

8. References

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9. Appendices

Appendix 1. Study Visit Mapping for Pruritus NRS, Skin Pain NRS, Sleep-loss Diary and POEM

Pruritus NRS, Skin Pain NRS, and Sleep-loss score are collected as a daily diary; entries will be mapped to study week by the following:

Week	Start Day	End Day
Baseline	Date of First Injection[a] – 7	Date of First Injection – 1
Week 1	Max (Date of First Injection, Week 2 Visit Date – 14)	Week 2 Visit Date – 8
Week 2	Week 2 Visit Date – 7	Week 2 Visit Date – 1
Week 4	Week 4 Visit Date – 7	Week 4 Visit Date – 1
Week 6	Week 6 Visit Date – 7	Week 6 Visit Date – 1
Week 8	Week 8 Visit Date – 7	Week 8 Visit Date – 1
Week 10	Week 10 Visit Date – 7	Week 10 Visit Date – 1
Week 12	Week 12 Visit Date – 7	Week 12 Visit Date – 1
Week 14	Week 14 Visit Date – 7	Week 14 Visit Date – 1
Week 16	Week 16 Visit Date – 7	Week 16 Visit Date – 1

[a] If date of first injection is missing, the randomization date will be used.

If multiple assessments on a single day are present, use the first assessment. If an assessment could be mapped to different weeks, it will be mapped to the earlier week. Derivation of the weekly mean scores for Pruritis NRS, Skin Pain NRS, Sleep-loss could be found in Table KGAK.6.6. If at least 1 of the 7 days contains nonmissing daily assessments, postbaseline weekly score will be calculated using prorated weekly average. If the range of 7 days are all missing daily assessments, then the weekly score is missing.

Patient-Oriented Eczema Measure is collected every week via eDiary, the visit week mapping will follow the following rule: the last collected POEM data before the visit date would be used, the evaluation window is injection date −7 to injection date −1 for baseline and visit date –7 to visit date –1 for postbaseline. For example, if a participant gets an injection on the 14th, the scale completed in between the 13th and the seventh would be used.

Appendix 2. Definition of Rescue Medications

The AD rescue therapy in this study is defined as: high-potency TCS and systemic AD therapy. The topical treatments and systemic treatments are defined as following:

1. **Topical AD Treatment (including TCSs, TCI, and crisaborole)**

Route of topical treatments includes: Topical and Transdermal.

TCS: ATC code is D07

High Potency TCS: ATC codes are D07AC or D07AD

Low or moderate potency TCS: ATC code is D07, excluding D07AC or D07AD

TCI: PT includes: TACROLIMUS, PIMECROLIMUS

Crisaborole: PT includes: CRISABOROLE

2. **Systemic AD Treatment (including systemic corticosteroids, immunosuppressant, biologics, and phototherapy/PUVA)**

Route of systemic treatments administration includes: Oral, Intra-Arterial, Intramuscular, Intraperitoneal, Intravenous, Subcutaneous, and Transdermal. (This condition applies to the following categories except for phototherapies.)

Systemic Corticosteroids: ATC code is H02

Immunosuppressant: Defined as: ATC2 is L04 or PTs of Abrocitinib or Ruxolitinib excluding PTs mentioned in Biologics

Biologics: Defined as following PTs:

Infliximab, Infliximabum, Etanercept, Etanerceptum, Adalimumab, Adalimumabum, Certolizumab, Certolizumabum, Certolizumab pegol, Golimumab, Golimumabum, Ozoralizumab, Afelimomab, Afelimomabum, Tumor Necrosis Factor Alpha (TNF-) Inhibitors, Tabalumab, Tregalizumab, Anakinra, Basiliximab, Basiliximabum, Daclizumab, Daclizumabum, Tocilizumab, Tocilizumabum, Mepolizumab, Mepolizumabum, Rilonacept, Rilonaceptum, Ustekinumab, Canakinumab, Briakinumab, Fezakinumab, Sirukumab, Sarilumab, Lebrikizumab, Secukinumab, Olokizumab, Gevokizumab, Brodalumab, Ladarixin, Ixekizumab, Dupilumab, Tildrakizumab, Tildrakizumabum, Reslizumab, Reslizumabum, Guselkumab, Guselkumabum, Olamkicept, Fletikumab, Bimekizumab, Mirikizumab, Risankizumab, Abatacept, Ligelizumab, Vedolizumab, Belimumab, Nemolizumab, Tralokinumab, Omalizumab

Phototherapy or PUVA:

Programming search of medication name (actual term or PT) contains ‘photo’ then medicals to manually review to confirm whether the medication in question is indeed ‘Phototherapy’ or ‘Photochemotherapy’.

Appendix 3. Details of Combining Estimates and Test Statistics for Categorial Endpoints with Multiple Imputation

Following the implementation of MCMC-MI imputation as specified in Section 6.4.1, the 25 data sets with imputations should be set together and sorted by imputation number. The following sections describe the processes for combining inferences for the individual imputed data sets into 1 inference for reporting. All calculations are performed in SAS Software Version 9.4.

Summarize Unadjusted Response Rate

The response rates, overall and by treatment arm, and their associated SEs are computed for each imputed data set using PROC FREQ with the *riskdiff* option specified for the appropriate column in the TABLES statement. The response rates and SEs from the resulting output are combined across the 25 imputed data sets using PROC MIANALYZE, separately for each arm and the overall group.

Note that the estimate and 95% CI bounds output by PROC MIANALYZE are percentages (that is, they are in terms of the response rate). To obtain the number of responders, the estimated percentage is multiplied by the number of individuals in the analysis population and rounded to the nearest integer.

Compute Stratified Measures of Association

The common risk difference, common OR, and CMH test statistic are computed for each imputed data set using PROC FREQ with the *riskdiff* option for the appropriate column (for risk difference) and the *cmh* option (for OR and CMH test statistic) specified in the TABLES statement. Each of these analyses are stratified by geographic region, age group, and baseline disease severity via inclusion of these variables in the TABLES statement with the treatment and outcome variables.

Note that the PROC FREQ output corresponding to the Mantel-Haenszel method is used for the risk difference, and the output corresponding to the General Association statistic is used for the CMH statistic. PROC MIANALYZE is then called separately for each of these measures, with further details in the sections below.

Common Risk Difference

No transformation is necessary before using PROC MIANALYZE to combine the risk difference estimates and their associated SEs across the 25 imputed data sets. This procedure outputs an estimate of the common risk difference and the associated 95% CI bounds.

Common OR

The OR from each imputed data set is first transformed using the natural logarithm. The SE for each log OR (SE_{lOR}) is derived from the OR 95% CI bounds (LB_{OR}, UB_{OR}) according to the following equation: $SE_{lOR} = (\ln(UB_{OR}) - \ln(LB_{OR}))/(2 * 1.96)$. The log OR and derived SE are then combined using PROC MIANALYZE, which outputs a combined estimate of the log OR and the associated 95% CI. Finally, these measures can be exponentiated to transform them back to the OR scale.

CMH Test

The CMH test statistic (CMH) from each imputed data set is transformed using the Wilson-Hilferty transformation and standardized so that it has approximately a standard normal distribution (Ratitch et al. 2013). In particular, the transformed CMH statistic is computed as follows: $CMH_{WH} = \left(\frac{CMH}{df}\right)^{\frac{1}{3}} - \frac{1-\frac{2}{9*df}}{\sqrt{\frac{2}{9*df}}}$,

where df is the degrees of freedom of the CMH statistic. Then the SE for each CMH_{WH} is 1, and PROC MIANALYZE is used to output a combined estimate of the transformed CMH statistic. Note that the 2-sided p-value output by PROC MIANALYZE is not used directly, but instead the 1-sided p-value is computed manually using both the t statistic and 2-sided p-value output by PROC MIANALYZE; if t statistic is >0, then the 1-sided p-value is computed as one half of the 2-sided p-value; otherwise, the 1-sided p-value is computed as one half of the 2-sided p-value. The resulting 1-sided p-value is reported as the pooled p-value for the CMH test.

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