Statistical Analysis Plan

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Dose-Ranging, Phase 2b Study to Evaluate Efficacy and Safety of Tezepelumab for the Treatment of Chronic Spontaneous Urticaria
Short Protocol Title:	INCEPTION- **IN**vestigational Multi**CE**nter Teze**P**elumab **T**reatment in chron**I**c sp**ON**taneous Urticaria study
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	22Feb2022	
Amendment 1 (v2.0)	07Jun2022	1. Section 2.1: removed 'Time to loss' and 'Time to first event of subjects receiving H1-antihistamine rescue medication' endpoints. 2. Section 2.1: updated endpoints definitions with 'Reduction from baseline' to 'Change from baseline'. 3. Section 2.2: removed key secondary endpoint related hypotheses and third hypotheses. Added primary endpoint comparison content from protocol. 4. Section 3: updated anti-IgE experienced sample size. 5. Section 3.2: updated total sample size. 6. Section 3.2: updated power statistics from protocol. 7. Section 3.3: updated interim analysis 2 trigger criteria. 8. Section 4.1: removed covariates for key secondary endpoint and 2nd and 3rd estimand. 9. Section 4.2: removed second subgroup analysis for key secondary endpoint and third hypotheses. 10. Section 5.1: updated actual treatment definition when subject receives different treatment other than the randomized treatment. 11. Section 5.2: updated prohibited medication definition. 12. Section 5.3: added derivation method for prohibited medication analysis week. 13. Section 5.3: removed derivation method for time-to-loss of status after discontinuation of IP.

		14. Section 5.4: added any eDiary data post EOS will be excluded from analyses. 15. Section 5.4: updated UAS definition from protocol. 16. Section 5.4: added derivation method when subject changes background medication during the study. 17. Section 7.1: updated interim analysis 2 trigger criteria. 18. Section 8.3.2: added missing data for continuous efficacy endpoints will be handled using a repeated measure model. 19. Section 9.1: added summary statistics will be presented with observed data. 20. Section 9.1: added descriptive statistics and analysis results will be summarized by combined tezepelumab group. 21. Section 9.1: added alpha split between two populations of interest description and figure from protocol. 22. Section 9.1: updated adjusting factor terms for primary endpoint from protocol. 23. Section 9.5: removed convergence issues related content for all continuous endpoints. 24. Section 9.5: updated convergence issues related content from using (>median vs <= median) to (≥28 vs < 28 for UAS7 and ≥median vs < median for others) for binary endpoints. 25. Section 9.5: moved key secondary endpoint related content to secondary endpoint section. 26. Section 9.5: updated summary and analysis method for cumulative related secondary endpoints. 27. Section 9.5: removed 'Time to loss' and 'Time to first event of

		subjects receiving H1-antihistamine rescue medication' endpoints. 28. Section 9.5.1: added descriptive statistics and analysis results will be summarized by combined tezepelumab group. 29. Section 9.5.2: moved key secondary endpoint related content to secondary endpoint section. 30. Section 9.6.1: updated Meddra version from 23.1 to 25.0 31. Appendix A: removed 'Time to loss' and 'Time to first event of subjects receiving H1-antihistamine rescue medication' endpoints.

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List of Abbreviations

Abbreviation or Term	Definition/Explanation
AAS	Angioedema Activity Score
AAS7	Angioedema Activity Score over 7 days
AECT	Angioedema Control Test
AE-QoL	Angioedema Quality of Life Questionnaire
AE	Adverse Event
BOCF	Baseline Observation Carried Forward
CBD	Clinical Biomarkers and Diagnostics
CFB	Change From Baseline
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CPMS	Clinical Pharmacology Modeling and Simulation
CR	Complete Response
CRH	Complete Resolution of Hives
CRI	Complete Resolution of Itch
[redacted]	
CSU	Chronic Spontaneous Urticaria
CU-Q2oL	Chronic Urticaria Quality of Life Questionnaire
DLQI	Dermatology Life Quality Index
DXDT	Date of Diagnosis
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
EOIP	End of Investigational Product
EOS	End of Study
EOT	End of Treatment
ET	Early Termination
FAS	Full Analysis Set
fgAH	First Generation Antihistamines
GEE	Generalized Estimating Equations
GSO-DM	Global Study Operations – Data Management
HSS	Hives Severity Score
HSS7	Hives Severity Score over 7 days
IA	Interim Analysis
Ig	Immunoglobulin

IP	Investigational Product
IPD	Important Protocol Deviation
ISS	Itch Severity Score
ISS7	Itch Severity Score over 7 days
ITT	Intent-to-treat
KM	Kaplan-Meier
LSLV	Last Subject Last Visit
LSM	Least Square Mean
LTRA	Leukotriene Receptor Antagonists
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MID	Minimal Important Difference
MNAR	Missing not at Random
MRD	Minimal Residual Disease
NCT	National Clinical Trials
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PH	Proportional Hazards
PK	Pharmacokinetics
PRO	Patient-reported Outcome
Q2W	Every 2 Weeks
Q4W	Every 4 Weeks
QoL	Quality of Life
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SC	Subcutaneous
SCS	Systemic Corticosteriods
SE	Standard Error
sgAH	Second Generation Antihistamines
SIS	Sleep Inference Score
SIS7	Weekly Sleep Inference Score
SOC	System Organ Class
SQS	Sleep Quality Score
SQS7	Weekly Sleep Quality Score
SSAP	Supplemental Statistical Analysis Plan
UAS	Urticaria Activity Score

UAS7	Urticaria Activity Score over 7 days
UCT	Urticaria Control Test
WHODRUG	World Health Organization Drug Dictionary
WPAI-CU	Work Productivity and Activity Impairment Questionnaire: Chronic Urticaria

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol amendment **2** for study 20190194, AMG 157 Tezepelumab dated **26 April 2022**. The scope of this plan includes the interim analysis, the primary analysis, and the final analysis that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified. **The statistical analysis plan presented in this document will supersede the statistical analysis methods described in protocol. Any deviations/changes from the planned analyses described in this SAP will be identified, with justification, in the appropriate section of the clinical study report**.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints/Estimands

Objectives	Endpoints
Primary	
• To evaluate the effect of tezepelumab on improvement in the Urticaria Activity Score over 7 days (UAS7)	• Change from baseline in UAS7 at week 16
The first estimand of the primary objective consists of: • Target population – Adults with chronic spontaneous urticaria (CSU) who are symptomatic (inadequately controlled) despite treatment with second generation H1-antihistamines (sgAH) • Endpoint – Change from baseline in UAS7 score at week 16 • Intercurrent events – Use of protocol-excluded medications due to CSU (regardless of discontinuation of investigational product (IP)): treatment failure will be considered and the composite strategy will be applied where subject' s post-baseline effect will be similar as the baseline starting from the protocol-excluded medication use until the end of study; Use of protocol-excluded medications not due to CSU (regardless of discontinuation of IP): [redacted]; Discontinuation of investigational product due to reasons other than protocol-excluded medication use: treatment policy will be applied, where data will be used as collected from these subjects regardless of whether subjects completed 16 weeks of study treatment. • Summary measure – **Difference of mean change from baseline in UAS7 score at week 16** between tezepelumab 420 mg subcutaneous (SC) every two weeks Q2W or 210 mg subcutaneous (SC) every four weeks Q4W and	

<table>
<tr><td colspan="2">placebo (tezepelumab 420 mg subcutaneous (SC) Q2W or 210 mg subcutaneous (SC) Q4W minus placebo)

In summary, the first estimand of the primary endpoint is the difference of mean change from baseline in UAS7 score at week 16 between two tezepelumab dose groups and placebo (420 mg SC Q2W - placebo, 210 mg SC Q4W - placebo) respectively, in adults with CSU who are symptomatic (inadequately controlled) despite treatment with sgAH, regardless of whether subjects complete 16 weeks of study treatment.

The second estimand of the primary endpoint consists of the same definitions of endpoint, intercurrent event, and summary measures in the target population of adults with CSU who are symptomatic (inadequately controlled) despite treatment with sgAH and are also anti-immunoglobulin (Ig) E naïve.

The third estimand of the primary endpoint consists of the same definitions of endpoint, intercurrent event, and summary measures in the target population of adults with CSU who are symptomatic (inadequately controlled) despite treatment with sgAH and are anti-IgE experienced (intolerant, inadequate responder, or have discontinued for other reason).</td></tr>
<tr><td colspan="2">Secondary</td></tr>
<tr><td>• To evaluate the effect of tezepelumab on improvement in itch using the Itch Severity Score over 7 days (ISS7)</td><td>• Change from baseline in ISS7 at week 16</td></tr>
<tr><td>• To evaluate the effect of tezepelumab on improvement in hives using the Hives Severity Score over 7 days (HSS7)</td><td>• Change from baseline in HSS7 score at week 16</td></tr>
<tr><td>• To evaluate the effect of tezepelumab on subjects achieving minimal residual disease using the UAS7</td><td>• UAS7 ≤ 6 at week 16</td></tr>
<tr><td>• To evaluate the effect of tezepelumab on subjects achieving the minimal important difference (MID) on change from baseline in the UAS7</td><td>• Change from baseline in UAS7 ≤ -10 at week 16</td></tr>
<tr><td>• To evaluate the effect of tezepelumab compared with placebo in chronic spontaneous urticaria (CSU) subjects using the Urticaria Activity Score over 7 days (UAS7)</td><td>• Complete response in UAS7 defined as UAS7 = 0 at week 16</td></tr>
<tr><td>• To evaluate the effect of tezepelumab on complete resolution of itch using the ISS7</td><td>• ISS7 = 0 at week 16</td></tr>
</table>

• To evaluate the effect of tezepelumab on subjects achieving the MID on change from baseline in the ISS7	• **Change** from baseline in ISS7 ≤ -5 at week 16
• To evaluate the effect of tezepelumab on the complete resolution of hives using the HSS7	• HSS7 = 0 at week 16
• To evaluate the effect of tezepelumab on subjects achieving the MID on change from baseline in the HSS7	• **Change** from baseline in HSS7 ≤ -5.5 at week 16
• To evaluate the effect of tezepelumab on sleep interference and quality (falling asleep, nighttime awakenings, restfulness upon awakening)	• Change from baseline in sleep interference score at week 16 • Change from baseline in the sleep interference and quality diary items at week 16
• To evaluate the effect of tezepelumab on improvement in urticaria disease control using the Urticaria Control Test (UCT)	• Change from baseline UCT score at week 16
• To evaluate the effect of tezepelumab on angioedema using the Angioedema Activity Score over 7 days (AAS7)	• Change from baseline in AAS7 at week 16
• To evaluate the effect of tezepelumab on the cumulative time period that treated subjects are angioedema occurrence-free using the AAS7	• Cumulative weeks that subjects achieve AAS7 = 0 responses between baseline and week 16
• To evaluate the effect of tezepelumab on subject urticaria-specific quality of life (QoL) using the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL)	• Change from baseline in the CU-Q2oL at week 16
• To evaluate the effect of tezepelumab on subject QoL using the Dermatology Life Quality Index (DLQI)	• Change from baseline in DLQI at week 16
• To evaluate the effect of tezepelumab on subject angioedema-specific QoL using the Angioedema Quality of Life Questionnaire (AE-QoL)	• Change from baseline in the AE-QoL at week 16

• To evaluate the effect of tezepelumab on improvement in angioedema disease control using the Angioedema Control Test (AECT)	• Change from baseline in the AECT score at week 16
• To evaluate the effect of tezepelumab on subjects achieving complete control of angioedema disease using the AECT	• Complete control in AECT (AECT = 16) at week 16
• To evaluate the effect of tezepelumab on the improvement in productivity and activity impairment using the Work Productivity and Activity Impairment Questionnaire: Chronic Urticaria (WPAI-CU)	• Change from baseline in WPAI-CU score at week 16
• To evaluate the effect of tezepelumab on H1-antihistamine rescue medication utilization	• Cumulative frequency of H1-antihistamine rescue medication utilization from baseline to week 16
• To characterize the pharmacokinetics (PK) of tezepelumab	• Serum concentrations of tezepelumab at scheduled visits
• To evaluate the safety and tolerability of tezepelumab	• Subject incidence of adverse events (including serious adverse events)

Exploratory	
• To evaluate the effect of tezepelumab on improvement in CSU	• Achieving minimal disease activity, MID score, time to MID, complete response and the change from baseline of defined CSU disease activity on all primary and secondary endpoints (UAS7, ISS7, HSS7, AAS7) at all measured timepoints other than week 16
• To evaluate the effect of tezepelumab on the cumulative time period that treated subjects are urticaria symptom-free	• Cumulative weeks that subjects achieve UAS7 = 0, ISS7 = 0, or HSS7 = 0 responses between baseline and week 16

• To evaluate the effect of tezepelumab on the cumulative time period that treated subjects have minimal disease using the UAS7	• Cumulative weeks that subjects achieve UAS7 ≤ 6 between baseline and week 16
• To evaluate the effect of tezepelumab on QoL as measured by all patient-reported outcomes (PROs)	• Achieving minimal disease activity and the change from baseline of defined CSU QoL measures (DLQI, CUQ2oL AECT, AE-QoL, WPAICU) at all other measured timepoints other than week 16
• To evaluate the effect of tezepelumab on sleep	• Change from baseline in sleep interference and sleep quality items at all measured timepoints other than week 16
• To evaluate the effect of tezepelumab on subjects achieving the MID on the DLQI	• Achieving MID defined as **change** from baseline in DLQI ≤ **-**2.24 at week 16 and all other measured timepoints • Time to achieve the MID
• To evaluate the effect of tezepelumab on subjects achieving the MID on the CUQ2oL	• Achieving MID defined as **change** from baseline in CU-Q2oL ≤ **-**15 at week 16 and all other measured timepoints • Time to achieve the MID
• To evaluate the effect of tezepelumab on subjects achieving the MID on the AE-QoL	• **Change** from baseline in AEQoL ≤ **-**6 at week 16 and all other measured timepoints • Time to achieve the MID
• To evaluate the effect of tezepelumab on the improvement in urticaria disease control using the UCT	• Change from baseline UCT score at all measured timepoints other than week 16 • UCT ≥ 12 at week 16 and all other measured timepoints • UCT =16 at week 16 and all other measured timepoints
• To evaluate the effect of tezepelumab on subjects achieving the MID on the UCT	• Improvement from baseline in UCT ≥ 3 at week 16 and all other measured timepoints • Time to achieve the MID on the UCT
• To evaluate the effect of tezepelumab on subjects	• AECT ≥ 10 at week 16 and all other measured timepoints

achieving well controlled disease using the AECT	
• To evaluate the effect of tezepelumab on the improvement in Patient Global Impression of Severity (PGI-S)	• Response of PGI-S at week 16 and all other measured timepoints
• To evaluate the effect of tezepelumab on the Patient Global Impression of Change (PGI-C)	• PGI-C at week 16 and all other measured timepoints
• To evaluate the effect on tezepelumab on time to achieve disease control using the UAS7, ISS7, and HSS7	• Time to achieve UAS7 = 0, ISS7 = 0, and HSS7 = 0 • Time to achieve minimal disease defined as UAS7 ≤ 6
• To evaluate the duration of tezepelumab effect after discontinuation of investigational product	• Complete response on UAS7 after discontinuation of investigational product at weeks 24 and 32 • Minimum residual disease, defined as all subjects with UAS7 ≤ 6, after discontinuation of investigational product at weeks 24 and 32 • Complete response on ISS7 or HSS7 after discontinuation of investigational product at weeks 24 and 32
• To evaluate the effect of tezepelumab on H1-antihistamine rescue medication utilization	• Receiving H1-antihistamine rescue medication
[redacted]	
• To evaluate the immunogenicity of tezepelumab	• Incidence of anti-tezepelumab antibodies at all measured timepoints

2.2 Hypotheses and/or Estimations

The **primary hypothesis is**:

Tezepelumab effectively decreases UAS7 scores at week 16 from baseline compared to placebo in the overall population consisting of the anti-IgE naïve stratum and the anti-IgE experienced stratum.

The **secondary hypothesis is**:

Tezepelumab effectively decreases UAS7 scores at week 16 from baseline compared to placebo within the anti-IgE naïve stratum.

For primary endpoint, the primary hypothesis and the secondary hypothesis will be tested using the Bonferroni procedure to control the type 1 error rate. For each hypothesis, tezepelumab 420 mg SC Q2W and 210 mg SC Q4W compared to placebo will be tested **sequentially adjusting** for **covariates specified in Section 4.1**.

The remaining comparisons for the effects of tezepelumab over placebo on secondary/exploratory endpoints will be tested without adjusting for multiple tests. Nominal p-values will be provided.

3. Study Overview

3.1 Study Design

A randomized, double-blind, placebo-controlled, multicenter, dose-ranging, phase 2b study to evaluate the efficacy and safety of tezepelumab in adults with CSU for ≥ 6 months at the time of screening, who remain symptomatic despite treatment with second generation H1-antihistamines (sgAH) and are anti-IgE naïve or who were previously treated with anti-IgE therapies (either intolerant, inadequate responder, or discontinued for other reason). Subjects who are symptomatic despite treatment with sgAH and are anti-IgE naïve will be randomized to placebo, omalizumab, or 1 of 2 tezepelumab treatment groups (30 subjects per group for a total of 120 subjects). Subjects who are symptomatic despite treatment with sgAH and were previously treated with anti-IgE therapies (intolerant, inadequate responder, or discontinued for other reason) will be randomized to placebo or 1 of 2 tezepelumab treatment groups (**approximately 13** subjects per group for a total of **approximately 39** subjects).

3.2 Sample Size

A sample size of **approximately 159 subjects** will be **enrolled to anti-IgE naïve stratum and anti-IgE experienced stratum** to 1 of 2 doses of tezepelumab, omalizumab (**ie,** anti-IgE naïve

stratum only), and placebo. For the anti-IgE naïve stratum, 120 subjects will be randomized in a ratio of 1:1:1:1 (30 each for tezepelumab 420 mg SC Q2W, tezepelumab 210 mg SC Q4W, omalizumab 300 mg SC, and placebo), where the omalizumab group serves as the active control. For the anti-IgE experienced stratum, **approximately 39** subjects will be randomized in a ratio of 1:1:1 (**approximately 13** each for tezepelumab 420 mg SC Q2W, tezepelumab 210 mg SC Q4W, and placebo).

The treatment effect comparison on the primary endpoint for the primary hypothesis will be made between **placebo and one of** the 2 tezepelumab treatment groups **respectively** in the overall **CSU** population. [redacted]

The secondary hypothes**is** of treatment effect comparison on the primary endpoint will be made between each of **the 2** tezepelumab **treatment groups** versus **the** placebo **group** within **anti-IgE naïve** stratum. In the anti-IgE naïve stratum, [redacted]

3.3 Adaptive Design

Up to 2 interim analyses for futility will be performed approximately: 1) **the first interim analysis for futility will be performed** after the first 60 enrolled **subjects in the** anti-IgE naïve **stratum** have had the opportunity to complete the week 16 assessments or early terminate from the study, and 2) **the second interim analysis for administrative decision making will be performed** after **120 subjects in the** anti-IgE **naïve stratum** have had the opportunity to

complete the week 16 assessments or early terminate from the study. Further information given in the Section 7.1 and supplemental statistical analysis plan (SSAP).

4. Covariates and Subgroups

4.1 Planned Covariates

The **analysis** of the primary endpoint will be adjusted for the following **as appropriate**:

- Anti-IgE naïve versus anti-IgE experienced
- Baseline score of endpoint

The analyses of other endpoints will be adjusted for the following covariates as appropriate:

- Baseline score of **corresponding** endpoint
- Stratification factors:
  - Anti-IgE naïve versus anti-IgE experienced
  - Disease severity (UAS7 at baseline ≥ 28 versus < 28)

Additional covariates may be considered if specified elsewhere.

4.2 Subgroups

Two types of subgroup analyses will be conducted **for overall and anti-IgE naïve subjects**:

1) The first subgroup analyses are to explore the internal consistency of the detected overall treatment effect on the **primary efficacy** variable (change from baseline in UAS7 at week 16).

To explore the consistency of treatment effect, below subgroup analyses may be performed as appropriate.

- Age (18-40 years, 41-64 years, vs. >= 65 years)
- Sex (Male vs. Female)
- Race (White vs. Non-white)
- Region (US/CAN vs. EU vs APAC(Japan, S Korea))
- Baseline disease characteristics:
  - UAS7 at baseline ≥ 28 vs. <28,
  - Previous number of CSU medications, single sgAH vs. sgAH + additional prescription (second sgAH, **l**eukotriene receptor antagonists (LTRA), H2-antihistamine, **f**irst generation anti-histamine (fgAH), **s**ystemic corticosteriods (SCS))

- sgAH dose: 1x, 2x, 3x and 4x approved dose, may collapse several groups in subgroup analysis in case of not enough subjects
- Presence of Angioedema: Yes vs. No

- Comorbidities of interest: Yes/No (e.g. asthma, depression, rhinoconjunctivitis, Osteoporosis, atopic dermatitis, diabetes mellitus)

The study is not powered to draw conclusions from the first type of subgroup analysis and nominal p-values will be provided.

The first subgroup analysis will be analyzed using same approach for primary endpoint.

2) The second subgroup analyses are to explore a treatment effect in the prespecified subpopulations (anti-IgE naïve stratum and anti-IgE experienced stratum) on the primary endpoint. **The treatment effect on the primary endpoint will be tested only in the anti-IgE naïve stratum.**

The second subgroup analysis will be conducted as secondary **hypothesis** on the primary endpoint. This subgroup analysis is further detailed in Section 9.5.1.**2.**

5. Definitions

5.1 Basic Definitions

Age at enrollment

Subject age at screening visit 1 will be collected in years in the clinical database.

Actual treatment received

Safety analyses will be performed on the Safety Analysis Set, which utilizes actual treatment received. Actual treatment received will be defined as the treatment to which the subject is randomized, with the following exceptions:

- When a subject receives a different treatment other than the randomized treatment, actual treatment received will be set to the investigational product the subject received **with most times**.
- When a subject randomized to Placebo receives any active drug (i.e. tezepelumab or omalizumab),
    - the actual treatment received is defined as the active dose arm with more doses received;

Electronic Diary (eDiary):

The eDiary, which collects certain PRO measures, will be completed by the subject at home each morning using an electronic device according to the Schedule of Activities and should be completed prior to other study assessments to avoid the possibility of introducing bias to subject responses. Use of daily standard sgAH and any need for rescue medication dosing, including the number of additional tablets, should also be recorded daily in the subject's eDiary.

Treatment-Emergent Adverse Events

Events categorized as Adverse Events (AEs) starting on or after first dose of investigational product as determined by "Did event start before first dose of investigational product" equal to "No" or missing on the Events Electronic Case Report Form (eCRF) and up to the subject's End of Study date.

5.2 Study Time points

Randomization Date:

Randomization Date is defined as the date subject was assigned to a treatment group.

Study Day 1:

Study day 1 is defined as the first day of IP administration after randomization. If a subject is never dosed but randomized, then set study day 1 as randomization date.

Baseline:

Baseline is defined as the last non-missing measurement for the endpoint of interest taken before the first dose of investigational product unless specified (e.g., eDiary related endpoints, sgAH/rescue medication use and prohibitted medication use).

Study Day:

The number of days from Study Day 1, inclusive, given by the following formula:

Study Day = (Date of interest – Date of Study Day 1) + 1, if date of interest is on/after Study Day 1.

Study Day = (Date of interest – Date of Study Day 1), if date of interest is before study day 1.

Visit:

For the purposes of this SAP, "Visit" refers to the scheduled assessment for a given endpoint according to the Schedule of Activities in Protocol Section 1.3. For eDiary endpoints collected daily, "Visit" refers to "Week" defined by the analysis windows for eDiary detailed in Appendix-B.

Treatment Duration (weeks) for Each Study Drug:

Treatment duration (weeks) = [Min(date of last non-missing IP dose + <dosing frequency> days – 1, EOS date) – Study Day 1 + 1] / 7, dosing frequency will be 14 days.

Prohibited Medication:

Prohibited medication is defined as any excluded treatment, medical devices, and/or procedures per Protocol Section 6.1.7 , collected as concomitant medications **that ongoing at any timepoint** between screening visit 1 and end of study.

End of Investigational Product (EOIP):

A subject's EOIP date is the date indicated on the "End of Investigational Product Administration" eCRF form.

End of Study (EOS) Date:

The EOS date for a subject is defined as the date the subject completes the study including the safety follow-up, or the date of the Early Termination (ET) visit. The date the subject has ended the study is recorded on the End of Study Electronic Case Report Form (eCRF).

The EOS date for the entire study is the EOS date of the last subject of the sutdy

5.3 Derived Variables

Prohibited Medication Event Rate:

Prohibited medication event rate is calculated as:

(The total number of occurrences of prohibited medications used during the targeted time period / Total subject-weeks during the targeted time period) * 100

Individual subject week at a targeted time period equals to total number of days in the targeted time period divide by 7.

Prohibited Medication Analysis Week:

Prohibited medication will be counted in following circumstance based on analysis window in Appendix- B:

- **If prohibited medication started on or before 1st IP dose date and end date is missing, it will be queried with site first. If confirmed ongoing, it will be counted in all available visits.**
- **If prohibited medication started and ended between first screen visit and 1st IP dose date (inclusive), it will only be counted in baseline.**
- **If prohibited medication started on or before 1st IP dose date and ended in week X (based on analysis window), it will be counted from baseline to week X.**

Change From Baseline (CFB):

Change from baseline is defined as (Post-baseline Value – Baseline Value).

Duration of Chronic Spontaneous Urticaria:

The number of years between the date of diagnosis (DXDT) and Study Day 1, rounded to one decimal place, is given by formula below to calculate the duration:

> Duration of CSU diagnosis (year) = (Study Day 1 – DXDT + 1)/365.25(See Appendix C for missing or partial start dates on DXDT)

Time-to-1st Event:

Time-to-Achievement-of-Event (Days) = Earliest Date of Achievement of Endpoint of Interest During the Study Period – Study Day 1 + 1.

> For example, for subjects who achieve a MID:
>
> Time to Minimally Important Difference (MID) = Earliest Date of Achievement of MID – Study Day 1 + 1.

The subjects who do not experience the event of interest will be censored at earlier of any use of protocol-excluded medication regardless of indication or the last non-missing assessment

date for the endpoint of interest. Only time to subject's *first* instance of each event of interest will be evaluated.

Cumulative Weeks of Achieving A Response of Interest

Cumulative Weeks of Achieving a Response of Interest = ∑ (Weeks of Response of Interest)

5.4 Study Endpoints

In all analyses, total PRO scores requiring calculation with component-level scoring will be calculated by Amgen. **Any eDiary data post EOS will be excluded from analyses.** Missing eDiary data for all PRO scores will be handled based on Table 5-1 if not specified.

Urticaria Activity Score (UAS):

The UAS is a CSU-specific PRO measure used to assess CSU activity/severity. It contains 2 components: **the H**ives **Severity Score** (HSS) **for number of wheals (ie, hives)** and **Itch Severity Score** (ISS) **for itch intensity,** which are scored from 0 (no wheals, no itch) to 3 (many wheals, severe itch). Subjects are asked to document **both scores daily with a recall period over past 24-hours**, and the summed result **of daily HSS and ISS** gives a daily UAS score (range: 0 to 6 points/day).

ISS	
Itch Severity	Score
None	0
Mild (present but not annoying or troublesome)	1
Moderate (troublesome but does not interfere with normal daily activity or sleep)	2
Severe	3
HSS	
Number of wheals per day	Score
0 (no wheals)	0
<20	1
20-50	2
>50	3

Post-baseline weekly scores: The weekly ISS (ISS7) and weekly HSS (HSS7) scores are the summation of daily itch and hive scores over 7 days with a range of 0 to 21 respectively. The weekly urticaria score (UAS7) is the summation of daily ISS and daily HSS with a possible range of 0 to 42 points (Mathias et al, 2012a). The UAS7 values were assigned to five severity levels, reflecting urticaria-free to severe disease activity as shown below:

UAS7	Description

0	Itch and hive free- indicative of no symptoms of CSU and considered a complete treatment response
1–6	Well-controlled urticaria—indicates a good response to treatment
7–15	Mild urticaria—indicates also a lower response level
16–27	Moderate activity urticaria—entry criteria for clinical trials in CSU
28–42	Severe activity urticaria

Baseline Score: The baseline UAS7 score is the summation of daily HSS and ISS over 7 days **on and prior** to first IP dose. Similarly, the baseline ISS7 is the sum of daily ISS and baseline HSS7 is the sum of daily HSS scores over 7 days on and prior to 1st IP dose (Day 1 is expected to be included as baseline since the first dose of IP is intended to be given after the eDiary is filled out).

Derived endpoints: The derived endpoints from UAS7, ISS7 and HSS7 are summarized below:

Derived Endpoint (UAS)	Definition
UAS7	
Complete response (CR)	1: UAS7=0 indicates a CR; 0: UAS7>0 indicates a non-CR
Minimal residual disease (MRD)	1: UAS7≤6 indicates MRD; 0: UAS7>6 indicates non-MRD
Minimal important difference (MID)*	1: CFB in UAS7≤-10 indicates achieving a MID 0: CFB in UAS7>-10 fails to achieve a MID
ISS7	
Complete resolution of itch (CRI)	1: ISS7=0 indicates a CRI; 0: ISS7>0 indicate a non-CRI
Minimal important difference (MID)	1: CFB in ISS7≤-5 indicates achieving a MID; 0: CFB in ISS7>-5 fails to achieve a MID
HSS7	
Complete resolution of hives (CRH)	1: HSS7=0 indicates a CRH; 0: HSS7>0 indicate a non-CRH
Minimal important difference (MID)	1: CFB in HSS7≤-5.5 indicates achieving a MID; 0: CFB in HSS7>-5.5 fails to achieve a MID

* The minimal important difference (MID) on change from baseline is between 9.5 and 10.5 points (equivalent to 10 points) for UAS7.

Missing eDiary handling: When a subject has 4 days or more missing daily ISS and/or HSS scores within a given week, then ISS7 and/or HSS7 will be set to missing. When ISS7 and/or HSS7 is missing, the UAS7 will also be set to missing. If a subject has less than 4 days missing in a given week for ISS, HSS, and/or UAS, then the weekly score (ISS7, HSS7 and UAS7) will be prorated as below:

	Missing handling for weekly scores	
	≥4 days missing	**>0 but <4 days missing**
UAS7	ISS7=. or HSS7=. → UAS7=.	$UAS7 = HSS7 + ISS7$
ISS7	Set to missing	$ISS7 = \frac{Sum\ of\ daily\ ISS\ scores\ during\ a\ week}{Number\ of\ days\ with\ ISS\ daily\ score} x7$
HSS7	Set to missing	$HSS7 = \frac{Sum\ of\ daily\ HSS\ scores\ during\ a\ week}{Number\ of\ days\ with\ HSS\ daily\ score} x7$

Intercurrent events handling: Primary and secondary efficacy endpoints related to UAS, ISS and HSS will be handled at **daily** level data with a combination of composite strategy, hypothetical strategy, and treatment policy as detailed below:

1) Composite Strategy: When subjects take protocol-excluded medication after first IP dose due to CSU disease flare (regardless of discontinuation of IP), the concomitant medication will be associated with disease flare and the Composite Strategy will be implemented:

- subjects will be considered as treatment failure at the time of the prohibited drug therapy **(start date of prohibited drug use + 1)** until the end of study (up to and including Week 32). That is, subject's post-baseline effect will be similar as the baseline.

  The identification of protocol-excluded medication due to CSU disease flare is when the protocol-excluded medication:

  i) is indicated on the Concomitant medication (**Urticaria** Related including SgAH) eCRF pages with indication signifying chronic spontaneous urticaria,

  ii) or leads to IP discontinuation (as determined by the End of Investigational Product eCRF page, primary reason for ending IP = "Requirement for alternate therapy" AND Requirement for alternate therapy associated with CSU disease flare = "YES")

2) Hypothetical Strategy: When subjects take protocol-excluded medication after first IP dose *not* due to CSU disease flare, the concomitant medication will *not* be associated with disease flare and the Hypothetical Strategy will be implemented:

- the efficacy endpoints will be set to missing at the time of the prohibited drug therapy [redacted].

  The identification of protocol-excluded medication not due to disease flare is as follows:

  i) protocol-excluded medication recorded on Concomitant Medication (**General**) eCRF page with indication not equal to "Chronic Spontaneous Urticaria".

3) Treatment Policy: When subjects discontinue investigational product due to reasons other than protocol-excluded medication use, treatment policy will be applied, where

data collected from these subjects will be used regardless of whether subjects complete 16 weeks of study treatment.

[redacted].

Angioedema Activity Score (AAS):

The AAS is a 5-item PRO measure used to determine angioedema activity (Weller et al, 2013). Subjects prospectively document, as part of the daily diary, each morning, the presence or absence of angioedema during the past 24 hours.

a. If angioedema was present (response of "Yes"), subjects score 5 key factors (duration, physical discomfort, impact on daily activities, impact on appearance, and overall severity) each with 0 to 3 points. For the duration question, each checked duration (midnight to 8am, 8am to 4pm and 4pm to midnight) receives a score of 1 with a total of 0 to 3 points daily.

b. If angioedema was not present (response of "No"), all 5 key factors receive a daily score of 0.

Therefore, the possible score range for each of 5 key factors is from 0 to 3 points. The AAS daily score range is from 0 to 15 points. The daily AAS scores are summed for 7 days to form the AAS7 with a range of 0 to 105. The MID on change from baseline for AAS7 is 8 points (Weller et al, 2013). The AAS will be measured once daily according to the Schedule of Activities per protocol.

Baseline score: The baseline AAS7 score is the summation of daily AAS over 7 days on and prior to first IP dose.

The missing eDiary and intercurrent event will be handled in an analogous way to UAS.

Sleep Related Outcomes:

The sleep related outcomes consist of 4 daily items: 1 sleep interference score (SIS) and 3 items on sleep quality score (SQS). The sleep interference score is part of the Urticaria Patient Daily Diary, which has been validated in adults and adolescents with chronic idiopathic urticaria and CSU (Mathias et al, 2012b; Mathias et al, 2010). Sleep interference will be

assessed by the subject, once daily in the morning and recorded in the eDiary. Subjects will score sleep interference on a scale of 0 to 3 (Mathias et al, 2010), where:

0 = no interference
1 = mild, little interference with sleep
2 = moderate, woke up occasionally, some interference with sleep
3 = substantial, woke up often, severe interference with sleep.

The weekly sleep interference score (SIS7) will be generated by summing the daily scores over 7 days.

The sleep quality items consist of 3 questions: falling asleep, wakefulness, and feeling rested in the morning. These are adapted from the CU-Q2oL sleep items (Baiardini et al, 2011; Baiardini et al, 2005).

Details on the questions are as follows:

Q1. How much difficulty did you have falling asleep last night because of your urticaria?

Q2. How often did you wake up during the night because of your urticaria?

Q3. To what degree did you wake up this morning feeling rested?

Item	Response			
	0	1	2	3
Q1	No difficulty	A little difficulty	Moderate difficulty	A lot of difficulty
Q2	Not at all	Rarely	Occasionally	Quite often
Q3	Not at all	Slightly	Moderately	Very much

Q3 will need to be reversed to be consistent with other items in the direction of a higher score indicating poorer sleep quality/greater sleep interference. Each item will be summed to generate a weekly score (SQS7) with a range of 0 to 21 (SQS7 – Q1, SQS7 – Q2, SQS7 – Q3, respectively). A weekly total score will also be generated by (1) averaging three daily sleep quality items and then summing up over 7 days with a score range of 0 to 21 (SQS7 – sum of average daily Q1-Q3); (2) summing up three daily sleep quality items over 7 days with a score range of 0 to 63 (SQS7 – sum of SQS7 – Q1, SQS7 – Q2, SQS7 – Q3).

Baseline score: The baseline score is the summation of daily sleep interference and quality items over 7 days on and prior to first IP dose respectively.

The missing eDiary will be handled in an analogous way to UAS.

Patient Global impression of severity (PGI-S):

The PGI-S is a single item designed to capture the subject's perception of overall symptom severity at the time of completion on a 5-point categorical response scale (no symptoms: 1 = none to very severe symptoms: 5 = very severe).

Patient Global impression of change (PGI-C):

The PGI-C is a single item designed to capture the subject's perception of overall response to treatment at the time of completion. The assessment uses a 7-point rating scale: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse.

Post-baseline responses will be categorized as follows:

- Improved: subjects in this category will include those with responses of 'very much improved', 'much improved 'and 'minimally improved'.
- Much Improved: subjects in this category will include those with responses of 'very much improved' and 'much improved'.
- Very Much Improved: subjects in this category will include those with responses of 'very much improved'.

Urticaria Control Test (UCT):

The UCT is a retrospective, simple validated scoring system that evaluates the physical symptoms of chronic urticaria (itch, hives and/or angioedema) and the effectiveness of treatment over 4 weeks (Weller et al, 2012). The UCT is designed to assess disease control in patients with CSU. The questions cover severity of physical symptoms, how much symptoms have affected QoL, how often treatment has been inadequate to control symptoms, and how well symptoms have been under control. It consists of 4 questions with 5 answer options each that are scored from 0 to 4. The UCT score is the sum of all 4 questions with a lowest and highest possible value of 0 (no control) and 16 (complete control), respectively. A score of $\geq$ 12 indicates well-controlled urticaria, while a score of $\leq$ 11 points toward poor disease control (Weller et al, 2012). The minimal clinical change, which can be regarded as meaningful to patients, is determined to be 3 points (Weller et al, 2017) on the change from baseline. The UCT will be completed by the subject at the study center according to the Schedule of Activities.

Angioedema Control Test (AECT):

This PRO measure is only applicable for subjects with angioedema. The AECT is a simple retrospective, questionnaire evaluating disease control that consists of questions in the domains of signs and symptoms, QoL, anxiety/fear, and effectiveness of therapy (Weller et al, 2019). Subjects answer the 4 questions with 5 answer options based on their symptoms over the last 3 months. Each item scores from 0 (indicating a poor disease control) to 4 (indicating a well disease control). The total AECT score is the sum of all 4 items with a range of 0 to 16, and a higher score indicating better controlled disease. The results of the validation of the AECT have been validated (Weller et al, 2020). A cutoff value of ≥ 10 points is used to identify well-controlled disease and < 10 points is used to identify poorly controlled disease (Weller et al, 2020). The MID has not been established (Weller et al, 2019). The AECT will be completed by the subject at the study center according to the Schedule of Activities in the protocol.

Chronic Urticaria quality of life questionnaire (CU-Q2oL):

The CU-Q2oL is a 23-item, self-reported urticaria-specific measure which evaluates 6 dimensions of QoL: pruritus (2 items), impact on life activities (6 items), sleep problems (5 items), limitations (3 items), looks (5 items), and swelling (2 items). Subjects are asked how bothered they have been by each symptom in the previous 2 weeks. Each item is assessed on a 5-point Likert scale (1 = never to 5 = very much). The raw total score is the sum of all 23 items with a range of 23 to 115. The raw total score is transformed to a linear scale of 0 to 100 with a higher CU-Q2oL score indicating a higher QoL impairment (Baiardini et al, 2011; Baiardini et al, 2005). The transformed score is calculated as:

$$CU - Q2oL\ score = \frac{\sum item\ scores}{max \sum item\ scores}\ x\ 100$$

Where, $\sum item\ scores$ is the sum of responded scores from non-missing items;

$max \sum item\ scores$ is the sum of maximum of non-missing item-specific score

A study by Kulthanan et al suggests that the minimal clinically important difference on change from baseline in CU-Q2oL corresponds to a reduction of 15 points (Kulthanan et al, 2016). The CU-Q2OL will be completed by the subject at the study center according to the Schedule of Activities.

Angioedema Quality of Life Questionnaire (AE-QoL):

This PRO measure is only applicable for subjects with angioedema. The AE-QoL is the first validated angioedema QoL questionnaire (Weller et al, 2012) and is only completed if the subject has angioedema. It consists of 17 questions in 4 domains (functioning, fatigue/mood,

fear/shame, and food) and has a recall period of 4 weeks. Each question has 5 answer options scored 0 to 4, with higher numbers indicating a more adverse impact. The total score is calculated and then transformed to a linear scale of 0 to 100, with a higher score indicating worse impairment in QoL. The transformed score is calculated as:

$$AE - QoL\ score = \frac{\sum item\ scores}{max \sum item\ scores}\ x\ 100$$

Where, $\sum item\ scores$ is the sum of responded scores from non-missing items;

$max \sum item\ scores$ is the sum of maximum of non-missing item-specific score

For example, a subject completed 16 items out of 17, the sum of respond score is 40, and the sum of maximum of non-missing item-specific score is 16 x 4 = 64. The total AE-QoL score is (40/64) x 100 = 62.5.

The minimal clinically important difference on change from baseline is 6 points (Weller et al, 2016). This questionnaire is to be completed by those subjects with recurrent angioedema as determined by baseline AAS7 score and AE-QoL will be measured at the study center according to the Schedule of Activities in the protocol.

Missing item handling:

(1) Total score calculation will only include non-missing items;

(2) An AE-QoL dimension score should not be calculated if more than one item is missing in that dimension;

(3) The AE-QoL total score should not be calculated if more than 25% of items (>4 items) are missing.

Dermatology Life Quality Index (DLQI):

The DLQI is a 10-item, subject-completed, health-related QoL assessment with content specific to those with dermatology conditions. The recall period is 1 week (Finlay and Kahn, 1994). The DLQI content captures respondent perceptions of six sub-scales including (1) dermatology-related symptoms and feelings (embracement) (Q1 - Q2), (2) impacts on daily activities (Q3 - Q4), (3) leisure (Q5 – Q6), (4) work or school (Q7), (5) personal relationships (Q8 – Q9), and (6) the side effects of treatment (Q10). Each item is scored on a 4-point Likert scale: 0 = not at all/not relevant; 1 = a little; 2 = a lot; and 3 = very much/yes for question 7 (Basra et al, 2008).

The DLQI total score is to sum the scores of 10 questions resulting a score range of 0 to 30. The higher score indicates a more impaired quality of life. The DLQI is validated in CSU and the established MID is 2.24 (Shikjar et al, 2005). The DLQI will be completed by the subject at the study center according to the Schedule of Activities in the protocol.

Missing item handling:

a. If one question is left unanswered, this is allocated a score of 0 and the DLQI score summed in the usual way, out of a maximum of 30.
b. If two or more questions are left unanswered, the questionnaire is not scored.

Work productivity and activity impairment-Chronic Urticaria (WPAI-CU):

The WPAI-CU is a questionnaire that assesses the impact of an intervention on work productivity. It evaluates presenteeism, work productivity loss, and activity impairment over the past 7 days (Reilly et al, 1993). The WPAI-CU will be completed by the subject at the study center according to the Schedule of Activities in the protocol.

The WPAI yields four types of scores:

(1) Absenteeism (work time missed);

(2) Presenteeism (impairment at work / reduced on-the-job effectiveness)

(3) Work productivity loss (overall work impairment / absenteeism plus presenteeism)

(4) Activity impairment

WPAI outcomes are expressed as impairment percentages, with higher number indicating greater impairment and less productivity, i.e. worse outcomes, as follows:

Questions:

1 = currently employed;

2 = hours missed due to health problems;

3 = hours missed other reasons;

4 = hours actually worked;

5 = degree health affected productivity while working;

6 = degree health affected regular activities

Scores:

a. Multiply scores by 100 to express in percentages;

b. **Absenteeism**: Percent work time missed due to problem:

$$\frac{Q2}{Q2+Q4}\ x100$$

c. **Presenteeism**: Percent impairment while working due to problem:

$$\frac{Q5}{10}\ x100$$

d. **Work productivity loss**: Percent overall work impairment due to problem:

$$\left\{\frac{Q2}{Q2+Q4}+\left(1-\frac{Q2}{Q2+Q4}\right)x\ \frac{Q5}{10}\right\}x100$$

e**. Activity impairment**: Percent activity impairment due to problem:

$$\frac{Q6}{10}\ x100$$

Skipped pattern handling:
The questionnaire on the device automatically skips irrelevant questions (jumps to Question 6 if "NO" is answered on Question 1, jumps to question 6 if "0" is entered on Question 4). Thus:
if the response to Question 1 is "YES" and response to Question 4 is "0", WPAI-CU scores for presenteeism and work productivity loss will be set to missing

- if the response to Question 1 is "NO", WPAI-CU scores for absenteeism, presenteeism, and work productivity loss will be set to missing.

<u>sgAH Background and Rescue Medication:</u>

The study background medication of one type of sgAH is required from screening visit 2 (start of the 14 day sgAH stabilization period), throughout the study until the EOS visit. The type of sgAH and dose for each individual subject should be directed by subject's physician.
Subjects should maintain a stable dose of a sgAH (either 1x, 2x, 3x or 4x approved dose) as they entered at screening visit 2. The type of sgAH and dose must not be changed while they are on the study.
The same sgAH that the subject taken at screening visit 2 will be allowed **to take higher dose** as a rescue medication at up to 4x the approved dose. A switch of medication type for rescue for an individual subject is not permitted. Subjects should be directed to use rescue medication dosing only if there is worsening of urticaria symptoms (e.g., a daily UAS score of 6 or angioedema). The use of rescue medication will be recorded on both the concomitant

medication CRF page and daily eDiary (the number of tablets taken over the past 24 hours). The dose per day of rescue medication (collected in eDiary) will be calculated as the additional daily number of tablets. The dose per week of sgAH will be calculated as the sum of the daily dose (daily dose of background medication plus rescue medication), over 7 days.

When subject changes background medication during the study with non-overlapping end date of original background medication and start date of changed background medication, the protocol deviation will be identified and rescue medication should be derived using the background medication taken in corresponding time period.

If rescue medication use was not recorded on one or more days over the week, then the missing eDiary will be handled in an analogous way to UAS. .

The approved dose of sgAH usually is 1 tablet per **day in US**. Due to formulation or other reasons, **the** approved dose **strength may be different** than **the one in US. In this case**, the dose will be converted **to number of US standardized tablet(s)** prior to any calculation for endpoints. For example, when the approved **dose strength is 10mg/tablet and US standard dose strength is 20mg/tablet**, **the number of US standardized tablets** will be **10mg/tablet times number of tablets taken per day** divided by **20mg/tablet**. This is applicable for both the background medication and rescue medication.

Table 5-1 summarizes all PROs included in this study regarding the number of items, score range, MID values, score direction for interpretation and missing eDiary handling. Appendix- A summarizes the derived secondary and exploratory endpoints and corresponding evaluating study timepoint(s).

Table 5-1. Summary of PROs (Number of Items, Score Range, MID, Interpretation and Missing eDiary Handling)

No	PROs	Data Collection	No items	Score Range	MID point	Interpretation	Missing daily eDiary & item handling	
							<4 days	≥4 days
1	**Urticaria activity score, weekly (UAS7)**	Daily	2	0 - 42	10	Higher score→severe disease activity	prorate	ISS7=. or HSS7=. → UAS7=.
	Itch severity, weekly (ISS7)	Daily	1	0 - 21	5.0	Higher score→severe disease activity	prorate	Set to missing
	Wheals or hives, weekly (HSS7)	Daily	1	0 - 21	5.5		prorate	Set to missing
2	**Angioedema Activity Score, weekly (AAS7)**	Daily	5	0 - 105	8	Higher score → worse activity	prorate	Set to missing
3	**Sleep related outcomes**						prorate	Set to missing
	Sleep Interference Score, weekly (SIS7)	Daily	1	0 - 21		Higher score→worse sleep interference		
	Sleep quality							
	Q1. Falling asleep	Daily	1	0 - 21		Higher score→worse sleep quality		
	Q2. Wakefulness	Daily	1	0 - 21		Higher score→worse sleep quality		
	Q3. Feeling rested in morning **(Reverse)**	Daily	1	0 - 21		Higher score→worse sleep quality		
	Average of Q1 to Q3	Daily	3	0 - 21		Higher score→worse sleep quality		
4	**Patient global impression of severity (PGI-S)**	2 wks	1	1-5		Higher score→worse symptoms	N/A	
5	**Patient global impression of change (PGI-C)**	2 wks	1	1 - 7		Higher score→worse treatment response	N/A	
6	**Urticaria Control Test (UCT)**	4 wks	4	0 - 16	3	Higher score→**better** control of urticaria	If 1 item is missing, set overall score to missing	
7	**Angioedema Control Test (AECT)**	4 wks	4	0 - 16		Higher score→**better** control disease	Sum of non-missing items only	
8	**Chronic Urticaria Quality of Life (CU-Q2oL)**						Sum of non-missing items only	
	CU-Q2oL (raw)	2 wks	23	23-115				
	CU-Q2oL (transformed)			0 - 100	15	higher score → higher QoL impairment		
9	**Angioedema Quality of Life (AE-QoL)**						If >25% item missing, set total to missing	
	AE-QoL (raw)	4 wks	17	0 - 68				
	AE-QoL (transformed)			0 - 100	6	higher score → worse impairment of QoL		
10	**Dermatology Life Quality Index (DLQI)**	2 wks	10	0 - 30	2.24	Higher score → more impaired QoL	If 2+ items missing, set total to missing	
11	**WPAI-Chronic Urticaria (WPAI-CU):**	2 wks	6	0-100		higher score → greater impairment/less productivity	If any items missing unexpectedly (See Section 5), set score to missing.	

6. Analysis Sets

6.1 All Subjects Randomized

All subjects randomized will be used in analysis of disposition **information** according to their randomized treatment group.

6.2 Full Analysis Set

The full analysis set (FAS) will consist of all randomized subjects who received at least 1 dose of investigational product. The FAS will be used in demographic **information**, baseline disease characteristics and efficacy analyses unless otherwise specified, and analyzed by randomized treatment group as intent-to-treat (ITT) concept.

6.3 Safety Analysis Set

The safety analysis set (SAS) will consist of all randomized subjects who received at least 1 dose of investigational product. Subjects will be analyzed according to their actual treatment received, as defined in Section 5.1. Analyses for safety endpoints and summary of IP administration will be based on the SAS.

6.4 Pharmacokinetic/Pharmacodynamic Analyses Set(s)

Subjects who received tezepelumab and have at least 1 sample with a measurable serum concentration for computing PK parameters will be included in the PK analysis set.

6.5 Interim Analyses Set(s)

The Interim Analyses Sets will be defined in the corresponding supplemental statistical analysis plan (SSAP) for the interim analysis.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

Up to 2 interim analyses will be performed approximately: 1) the first interim analysis for futility will be performed after the first 60 enrolled subjects in the anti-IgE naïve stratum have had the opportunity to complete the week 16 assessments or early terminate from the study; and 2) the second interim analysis for administrative decision will be performed after 120 subjects in the anti-IgE naïve stratum have had the opportunity to complete the week 16 assessments or early terminate from the study.

The interim analysis will be performed by the internal interim analysis review steering committee (IARSC) including Global Biostatistics Sciences and Biostatistical programming, who are

independent of the study team. The detailed process, decision criteria and analysis methods will be described in the IARSC charter and a SSAP for interim analysis.

7.2 Primary Analysis

The primary analysis will occur when all subjects have had the opportunity to complete the week 16 assessments or have early terminated from the study.

7.3 Final Analysis

The final analysis will occur after the last subject either completes the week 32 follow-up and ends the study or early terminates from the study.

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database for clinical data. PRO data (eDiary) will be transferred from Clinical Ink database.

8.3 Handling of Missing and Incomplete Data

Subjects may be missing specific data points for a variety of reasons. In general, data may be missing due to a subject's early withdrawal from study, a missed visit, or inability to evaluate an endpoint at a particular point in time. The general procedures outlined below describe what will be done when a data point is missing.

8.3.1 Missing Baseline Value

Missing baseline evaluations will not be imputed.

8.3.2 Missing Post-Baseline Evaluation

Handling of missing diary responses are detailed in Table 5-1 .

Missing data for continuous efficacy endpoints will be handled using a repeated measure model. Missing data in binary efficacy endpoints may be addressed through multiple imputation of the continuous versions of the endpoints or may be imputed using non-responder imputation in efficacy analysis.

Further details on the handling of missing data are provided in Section 9.5.1 analyses for the primary endpoint.

Missing post-baseline safety data will not be imputed.

8.3.3 Missing and Incomplete Dates:

For any listings, missing or incomplete dates will be listed as is.

For AE and concomitant medication, if any missing or incomplete date is reported, the imputation rule will be imputed as outlined in Appendix C.

8.3.4 Duplicate Data handling of questionnaires:

All questionnaires are completed either daily or at site visits. In the case of more than one completed questionnaire in a single day, the questionnaire with the latest completion date and time will be used in the analysis.

8.4 Detection of Bias

This study has been designed to minimize potential bias using randomization of subjects into treatment groups and the use of blinding. Other factors that may bias the results of the study include:

- Major protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints
- Subject level unblinding before final database lock and formal unblinding
- IP dosing non-compliance
- Reasons for early withdrawal from treatment or from study

Important protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints, and would significantly affect subject's right, safety or wellbeing will be tabulated by treatment group in the Clinical Study Report (CSR). Any unblinding of individual subjects prior to formal unblinding of the study will be documented in the CSR.

8.5 Outliers

Various methods, including univariate summaries, histogram, scatter plots, box plots and line groups may be used (as appropriate) to identify the potential outliers for primary and secondary efficacy endpoints. For all other endpoints and safety data, descriptive summaries will be examined to identify unexpected values.

Outliers due to data entry errors will be corrected by the study team before data lock. Outliers that are not due to data entry will be included in the analysis. If it is deemed necessary after the team reviews the output from the planned analyses after data lock, a post-hoc sensitivity analysis excluding subjects with outliers may be performed

8.6 Distributional Characteristics

For categorical endpoints, descriptive summary will be provided. For continuous endpoints, normality will be assumed due to having at least 30 subjects per treatment arm. However, normality of change from baseline in ISS7, HSS7, UAS7, AAS7 may be assessed graphically. Should the normality assumption be violated, the non-parametric analysis may be performed.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

Subject disposition**, demographics, and baseline disease** characteristics will be summarized descriptively by randomized treatment group **based on the FAS, or** all randomized **subjects**. All safety analyses will be performed using the safety analysis set.

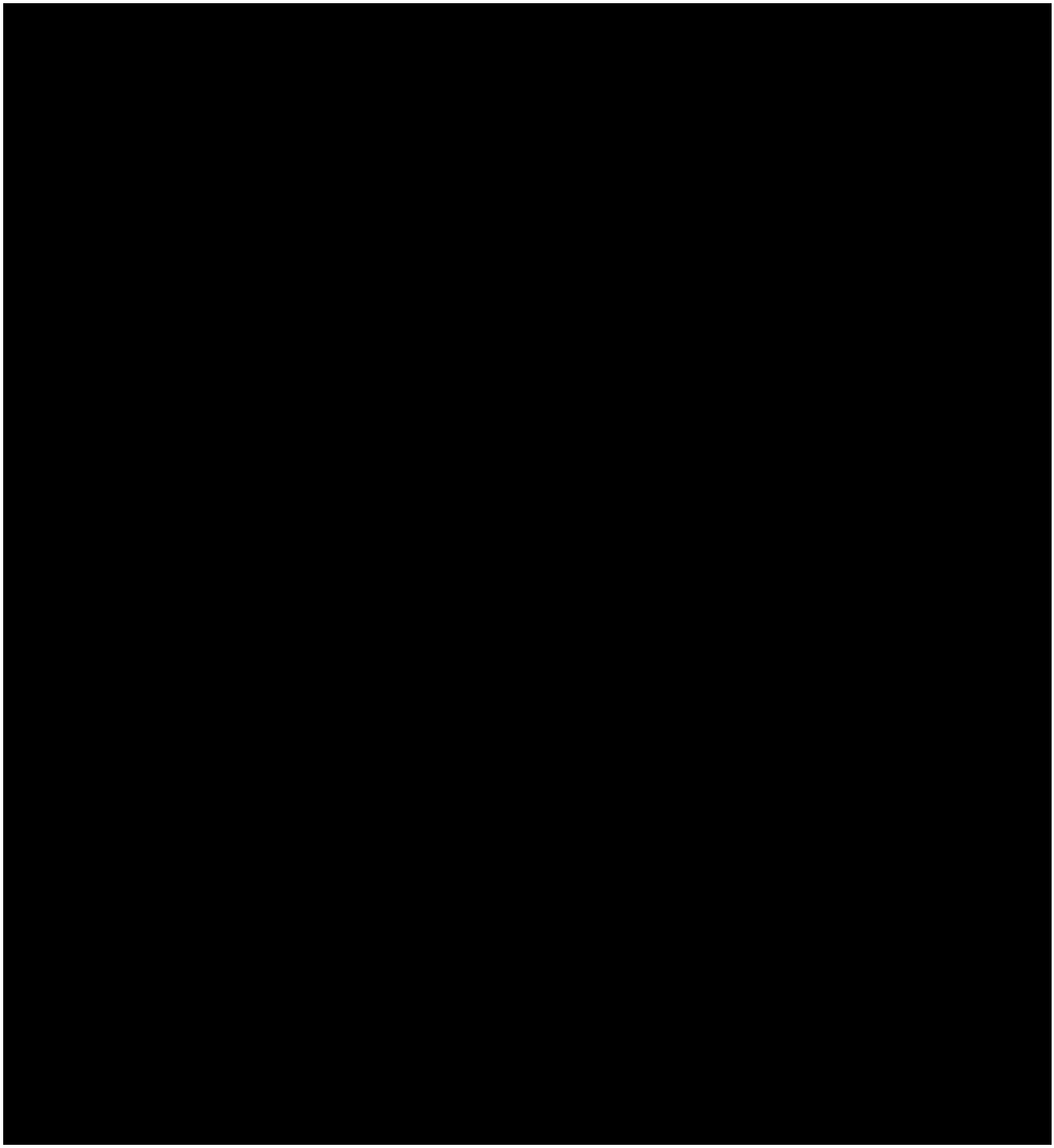
Endpoints recorded on a daily basis (e.g. eDiary) will be summarized by week. Other endpoints will be summarized by scheduled visit.

For categorical endpoints, descriptive statistics will contain frequency and percentage. For continuous endpoints, descriptive statistics will include the number of **observations**, mean, standard deviation, median, first quartile, third quartile, minimum, and maximum. All summary statistics related to UAS, ISS, HSS, and AAS will **be presented with intercurrent event handling data and observed data**.

Descriptive statistics and analysis results (e.g. **as appropriate** from repeated measure model or generalized estimating equation (GEE) model) will be summarized by treatment arm**s as well as combined tezepelumab group**.

All available data will be included in analysis. Unscheduled measurements will be used depending on analytical window.

For endpoints analysis related with UAS7, ISS7, HSS7, and AAS7, intercurrent event handling rule applied data will be used.



9.2 Subject Accountability

Key study dates for the first subject enrolled, last subject enrolled, last subject's end of study, and last subject's end of IP will be presented.

Subject disposition will be summarized descriptively for all randomized subjects by randomized treatment group among anti-IgE naïve stratum, anti-IgE experienced stratum, and overall subjects respectively.

The disposition for the treatment period will include the number of subjects who

- are randomized
- are dosed with at least one investigational product (IP)
- utilize rescue therapy
- complete IP and their reasons for ending IP
- complete the study (EOS)
- discontinued the study prematurely and their primary reasons for withdrawal.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol.

9.4 Demographic and Baseline Characteristics

Demographic and baseline disease characteristics will be assessed using the a) FAS by treatment arm, b) anti-IgE naïve subgroup by treatment arm, and c) anti-IgE experienced subgroup by treatment arm.

Demographic and baseline characteristics will tabulate subgroups defined in Section 4.2, and will also include:

- Age (18-40 years, 41-65 years, vs. >65 years);
- Sex (Male vs. Female);
- Race (White, Black or African-American, vs. all other races) (or white vs. non-white);
- Ethnicity (Hispanic or Latino vs. not Hispanic or Latino);
- Region (US/CAN vs. EU vs APAC(Japan, S Korea));
- Baseline weight (kg) (continuous, <80 vs. ≥80kg);
- Baseline height (cm);
- Baseline BMI (kg/m2) (Continuous, <30, ≥ 30 kg/m2);

Baseline disease characteristics will include:

- Duration of chronic spontaneous urticaria from diagnosis until Study Day 1;
- Anti-IgE status (naïve vs. experienced);
- Disease severity (continuous UAS7, UAS7≥28 vs. UAS7<28);
- [redacted]
- Angioedema presence (yes vs. no);
- Recurrent angioedema since the diagnosis of CSU (yes vs. no);
- [redacted]
- [redacted]
- Absolute Eosinophils (continuous);
- Absolute Basophils (continuous)

9.5 Efficacy Analyses

Table 9- 1 Summary of Primary Efficacy Endpoint

Primary Endpoint	Summary and Analysis Method	Model Details	Sensitivity Analysis
CFB in UAS7 at week 16	Repeated measure model will be performed for change from baseline of UAS7 to produce the estimates of Least Square Mean (LSM), Standard Error (SE), Difference of LSMs (SE) and 95% CI of difference of LSMs (tezepelumab – placebo), and p-values	**Full Analysis Set:** adjust for treatment, **study week**, treatment**-by-week interaction**, baseline UAS7 **score**, **stratification factor (prior anti-IgE status)**; **Anti-IgE naive subgroup:** adjust for treatment, **study week**, **treatment-by-week interaction**, baseline UAS7 **score** **Anti-IgE experienced subgroup:** adjust for treatment, **study week**, **treatment-by-week interaction**, baseline UAS7 **score**	Intercurrent event handling method will be applied on data before sensitivity analysis except 'As Observed' analysis. *Placebo- based Multiple Imputation (Missing not at random (MNAR))*: Placebo-controlled multiple imputation followed by repeated measure model using change from baseline in UAS7; *Baseline Observation Carried Forward (BOCF) for missing data*: Baseline observation carried forward for missing data, followed by repeated measure model; *As Observed:* repeated measure model in change from baseline in UAS7 using UAS7 data as collected regardless of occurrence of intercurrent events;

Table 9- 2 Summary of Secondary Efficacy Endpoints

Secondary Endpoints	Summary and Analysis Method	Model Details	Missing Data Handling
CFB in following endpoints at week 16: (1) ISS7; (2) HSS7; (3) Sleep interference score (SIS7); (4) Sleep quality (SQS7 – Q1); (5) Sleep quality (SQS7 – Q2); (6) Sleep quality (SQS7 – Q3); (7) Sleep quality (SQS7 – sum of average daily Q1-Q3); (8) Sleep quality (SQS7 – sum of SQS7 – Q1, SQS7 – Q2, SQS7 – Q3) (9) UCT; (10) AAS7; (11) CU-Q2OI; (12) DLQI; (13) AE-QoL; (14) AECT; (15) WPAI-CU (Absenteeism); (16) WPAI-CU (Presenteeism); (17) WPAI-CU (Work productivity loss); (18) WPAI-CU (Activity impairment);	*Repeated measure model will be used*	Adjust for treatment, **study week**, **treatment-by-week interaction**, baseline continuous value of the endpoint **and stratification factors (prior anti-IgE therapy status).**	Through repeated measure model
Achieving at week 16 **(1) Complete response of CSU UAS7 = 0;** (2) Minimal residual disease UAS7 ≤ 6; (3) MID on CFB in UAS7 ≤ -10; (4) Complete resolution of itch ISS7 = 0;	GEE model will be used	Adjust for treatment, **study week**, **treatment-by-week interaction**, baseline **score and stratification factor (prior anti-IgE status).**	

Secondary Endpoints	Summary and Analysis Method	Model Details	Missing Data Handling
(5) MID on CFB in ISS7 ≤ -5; (6) Complete resolution of hives HSS7 = 0; (7) MID on CFB in HSS7 ≤ -5.5; (8) AECT = 16		In the case of computational or convergence issues, replace baseline score with dichotomized covariate **(>=28 vs < 28 for UAS7 and > median vs <= median for others)** in that model only. **When GEE does not converge and CMH does not provide an odds ratio and a p value, p value from fisher exact test will be presented.**	
Cumulative weeks AAS7=0 between baseline and week 16	**GLM model will be used**	**Adjust for treatment, prior anti-IgE therapy status, and baseline disease severity**	No imputation
Cumulative frequency (days) of sgAH rescue medication use from baseline to week 16	**GLM model will be used**	**Adjust for treatment, prior anti-IgE therapy status, and baseline disease severity**	No imputation

Table 9- 3 Summary of Exploratory Efficacy Endpoints

Exploratory Endpoints	Summary and Analysis Method	Model Details	Missing Data Handling
CFB in endpoints below at all time points other than week 16: • UAS7; • ISS7; • HSS7; • AAS7	Summary statistics for raw score and change from baseline by visit. Analysis methods for primary effeciacy endpoint will be used.	Adjust for treatment, visit, treatment*visit, baseline continuous value of the endpoint, baseline anti-IgE status (naive vs experienced);	Through repeated measure model

Exploratory Endpoints	Summary and Analysis Method	Model Details	Missing Data Handling
Achieving endpoints below at all time points other than week 16: • Complete response UAS7=0; • Complete resolution of itch ISS7=0; • Complete resolution of hives HSS7=0; • Angioedema occurrence-free AAS7=0; • Minimal disease activity (UAS7≤6) • MID in CFB of UAS7 (≤ -10) • MID in CFB of ISS7 (≤ -5) • MID in CFB of HSS7 (≤ -5.5) • MID in CFB of AAS7 (≤ -8)	Count (percentage) of subjects achieving endpoint; Plot depicting percentage of subjects achieving endpoint over time Analysis method for **binary** secondary efficacy endpoint**s** will be used and the same summary statistics will be reported.	GEE: adjust for treatment, visit, treatment*visit, baseline continuous value of the endpoint, baseline anti-IgE status (naive vs experienced) In the case of computational or convergence issues, replace baseline score with dichotomized covariate (**>=28 vs < 28 for UAS7 and** > median vs <= median **for others**) in that model only. **When GEE does not converge and CMH does not provide an odds ratio and a p value, p value from fisher exact test will be presented.**	
Time to MID in endpoints to week 16: • UAS7; • ISS7; • HSS7; • AAS7	Kaplan-Meier (KM) curve and estimates with log-rank test comparing tezepelumab 210 vs placebo and tezepelumab 420 vs placebo. Cox proportional hazards (PH) model	Cox PH model will adjust for: treatment, baseline value of the continuous endpoint, anti-IgE status (naïve vs. experienced)	Censored at earlier of: 1) any use of protocol-excluded medication regardless of indication 2) last non-missing assessment date for endpoint of interest

Exploratory Endpoints	Summary and Analysis Method	Model Details	Missing Data Handling
Cumulative weeks of achieving the following from baseline (exclusive) to week 16: • UAS7=0; • ISS7=0; • HSS7=0; • UAS7≤6	Descriptive summary statistics	Summaries only	No imputation
CFB in the following at all visits other than week 16: • DLQI; • CU-Q2oL; • AECT; • AE-QoL; • WPAI-CU (Absenteeism); • WPAI-CU (Presenteeism); • WPAI-CU (Work productivity loss); • WPAI-CU (Activity impairment); • Sleep interference score SIS7; • Sleep quality (SQS7 – Q1); • Sleep quality (SQS7 – Q2); • Sleep quality (SQS7 – Q3); • Sleep quality (SQS7 – sum of average daily Q1-Q3); • Sleep quality (SQS7 – sum of SQS7 – Q1, SQS7 – Q2, SQS7 – Q3); • UCT	Summary statistics for raw score and change from baseline by visit; repeated measure model (using data as collected)	Adjust for treatment, visit, treatment*visit, baseline continuous value of the endpoint, baseline anti-IgE status (naive vs experienced)	Through repeated measure model

Exploratory Endpoints	Summary and Analysis Method	Model Details	Missing Data Handling
Achieving the following at week 16 and all measured timepoints: • DLQI: MID of CFB ≤ -2.24; • CU-Q2oL: MID of CFB ≤ -15; • AE-QoL: MID of CFB ≤ -6; • UCT: MID of CFB ≥ 3; • UCT ≥ 12; • UCT = 16; • AECT ≥ 10;	GEE using similar approach as for GEE of binary secondary endpoints	Similar approach as for binary secondary endpoints	
Time to MID in endpoints below to week 16 • DLQI MID of CFB ≤ -2.24; • CU-Q2oL MID of CFB ≤ -15; • AE-QoL MID of CFB ≤ -6; • UCT MID of CFB ≥ 3	Kaplan-Meier (KM) curve and estimates with log-rank test comparing tezepelumab 210 vs placebo and tezepelumab 420 vs placebo. Cox proportional hazards (PH) model	Cox PH model: adjust for treatment, baseline continuous value of the endpoint, baseline Anti-IgE status (naïve vs experienced)	Censored at earlier of: 1) any use of protocol-excluded medication regardless of indication 2) last non-missing assessment date for endpoint of interest
PGI-S and PGI-C at week 16 and all other time points	Summary of percentages of categories by visit	Summaries only.	No imputation
Time to achieve the following up to week 16: • Complete response (UAS7 = 0);	KM curve, Cox PH model	Cox PH model: adjust for treatment, baseline continuous value of the endpoint, baseline	Censored at earlier of:

Exploratory Endpoints	Summary and Analysis Method	Model Details	Missing Data Handling
• Complete resolution of itch (ISS7 = 0); • Complete resolution of hives (HSS7 = 0); • Minimal disease UAS7 ≤ 6	The Cox PH model will be performed only if number of events is greater than or equal to 10.	anti-IgE status (naïve vs experienced)	last non-missing assessment date for endpoint of interest
Endpoints below after discontinuation of IP (EOIP reason = completed) at weeks 24 and 32 • Complete response in UAS7 = 0; • Minimal residual disease UAS7 ≤ 6; • Complete resolution of itch ISS7 = 0; • Complete resolution of hives HSS7 = 0	Frequency (percentage) of subjects achieving endpoints at weeks 24 and 32	Summaries only.	No imputation
• Use of sgAH medication; • Use of sgAH rescue medication	Frequency (percentage) of subjects by week	Summaries only.	No imputation
• Weekly dose of sgAH medication use; • Weekly dose of sgAH rescue medication use;	Summary statistics for endpoints	Summaries only.	No imputation
• Change from baseline in weekly dose of sgAH rescue medication use	summary statistics	Summary only	No imputation

9.5.1 Analyses of Primary Efficacy Endpoint(s)/Estimand(s)

The primary endpoint of change from baseline in UAS7 at week 16 will be analyzed by first handling the data as: [redacted]. Once the completed data sets are formed, repeated measure model will be applied. The repeated measure model will include fixed **effect** for treatment, study week, treatment-by-week interaction, prior anti-IgE therapy status, and baseline UAS7 as **covariates**. The analysis will be performed in FAS with randomized treatment groups. Participants will be included in the model using the REPEATED statement (no RANDOM statement will be specified). The model parameters will be estimated using restricted maximum likelihood method with an unstructured (UN) variance-covariance matrix. To address potential convergence problems in the repeated measure model, the following covariance structure sequence will be utilized until convergence is met: (1) Unstructured, (2) heterogeneous Toeplitz; (3) heterogeneous AR(1); (4) Toeplitz; (5) AR(1); (6) Compound symmetry. The Kenward-Roger approximation to estimating the degrees of freedom will be used for tests of fixed effects derived from the model.

The descriptive statistics for baseline UAS7, the adjusted least square mean (LSM), standard error (SE) of the LSM, and difference of the LSMs between tezepelumab dose groups and placebo (tezepelumab 420 mg minus placebo**,** tezepelumab 210 mg minus placebo **and combined tezepelumab group minus placebo**) and corresponding SE, 95% CI of the difference, and p-value at week16 from repeated measure model will be reported.

9.5.1.1 Sensitivity Analyses for Primary Endpoint

Sensitivity analyses will be carried out after intercurrent event handling method applied on data (except ‘As Observed’ analysis) using the following approaches for the primary endpoint:

1. Placebo-based Multiple imputation (MI) (MNAR): A sensitivity analysis implementing placebo-based multiple imputation will be used to fill in missing values. This approach may be considered as “worst-case” sensitivity analysis as it assumes that after discontinuation, subject from the active treatment arms would adopt the outcome model estimated from the placebo arm. The imputed datasets will be analyzed using repeated measure model.

2. Baseline observation carried forward (BOCF): BOCF will be used to impute missing UAS7 scores at each week. UAS7 change from baseline will then be calculated at each subsequent post-baseline week, followed by repeated measure model. repeated measure model will adjust for treatment arm and baseline UAS7 score as covariates.

3. As Observed: the collected UAS7 score will be used regardless of occurrence of intercurrent events, followed by repeated measure model.

Should the distribution of change from baseline in UAS7 show to deviate from normality, a further sensitivity analysis using the Wilcoxon rank sum test of the median change from baseline will be performed.

Analysis of the primary efficacy endpoint is summarized in Table 9- 1.

9.5.1.2 Subgroup Analyses of Primary Endpoint

The treatment effect by the subgroups defined in Section 4.2 will be explored. The repeated measure model will be the same as defined in section 9.5.1, with additional factors for the subgroup variable. In other words, subgroup analyses repeated measure model will include: treatment arm, study week, treatment * week, prior anti-IgE therapy status, baseline UAS7, subgroup variable, treatment * subgroup, and treatment * subgroup * week. This model will be used to estimate the treatment effect and 95% CIs within each of the subgroup categories at Week 16. The treatment effect estimates within the overall FAS, anti-IgE naïve subgroup, and**/or** anti-IgE experienced subgroup will also be included in the plot**s**. No multiplicity adjustments will be made; nominal p-values will be provided.

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

The analysis of all secondary endpoints will be tested without multiplicity adjustments; nominal p-values will be provided.

The continuous secondary endpoints of change from baseline in ISS7, HSS7, AAS7, UCT, CU-Q2oL, DLQI, AE-QoL, AECT, and WPAI-CU will be analyzed using the same approach for the primary endpoint except intercurrent event handling. The intercurrent events will be applied only to change from baseline of UAS7, ISS7, HSS7 and AAS7 and handling of intercurrent event is consistent with primary endpoint (overall subjects only). The descriptive statistics for the observed baseline value, the estimated LS means, SE, difference and SE of the LS means (teze arm - placebo), 95% CI of the difference, and p-value for each time point will be presented in the summary table.

Binary secondary endpoints **of response rate** (**eg,** UAS**7, HSS7, ISS7,** AAS**7**) will be analyzed **with generalized estimating equations (GEE) model using the data after intercurrent event applied as done for the primary efficacy endpoint**. **GEE model will be applied for the Full Analysis Set, anti-IgE naïve subgroup, and the anti-IgE experienced subgroup. The difference in proportion of subjects with complete response in each tezepelumab dose group versus placebo as well as combined tezepelumab group vs placebo will be reported. Odds ratio (reference = placebo), corresponding 95% confidence intervals (CIs), and p-value will be estimated using GEE with unstructured covariance structure (no constraints imposed on covariance matrix). The model will include treatment, week, interaction between treatment and study week, prior anti-IgE therapy status (for analysis of Full Analysis Set only), and baseline UAS7. To address potential convergence issues in the GEE model, the following covariance structure sequence will be utilized until convergence is met: (1) unstructured, (2) AR(1), (3) exchangeable/compound symmetry. If convergence is still not met, the endpoint will be analyzed using CMH, adjusting for treatment, baseline anti-IgE status, and baseline dichotomized covariate (>28 vs <= 28 for UAS7 and > median vs <= median for others). When GEE does not converge and CMH does not provide an odds ratio and a p value, p value from fisher exact test will be presented.** Other binary endpoints (e.g., AECT=0 vs. AECT>0) will be analyzed directly using the GEE model.

Details of analyses of secondary endpoints are detailed in **Table 9- 2**.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

The analysis of exploratory endpoints will be tested without adjusting for multiple tests. Nominal p-values will be provided. Binary exploratory endpoints will be analyzed using an analogous approach to binary secondary endpoints, adjusting for baseline value of the respective endpoint.

Continuous exploratory endpoints will be analyzed using an approach analogous to continuous secondary endpoints.

Cumulative frequency of rescue medication use and weekly doses of sgAH will be summarized descriptively. Cumulative number of weeks for different responder statuses will be summarized using count and percentage of subjects.

PGI-S and PGI-C will be summarized descriptively only. Specifically, in the summary of PGI-S, proportions in each category will be tabulated as observed, by visit. Calculation of percentages

will be based on the number of subjects in the FAS. There will be no imputation for missing values.

In the summary of PGI-C, subjects will be categorized as Improved, Much Improved, and Very Much Improved as defined in Section 5.4. Subjects can be counted in more than one category at a given time point. Calculation of percentages will be based on the number of subjects in the FAS with a completed assessment. There will be no imputation for missing values.

For time to event endpoints as defined in Section 5.3, Kaplan-Meier (KM) curves and estimates, median and interquartile range of time to event occurrence will be provided. The Cox proportional hazard model will be used to estimate tezepelumab vs placebo hazard ratios, 95% confidence intervals, and p-values.

Details of exploratory efficacy endpoint analyses are shown in Table 9- **3**.

9.6 Safety Analyses

9.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version **25.0** or later will be used to code all events categorized as adverse events, to a system organ class and a preferred term.

The subject incidence of adverse events will be summarized for all treatment-emergent adverse events, severity, relationship to investigational IP, serious adverse events, adverse events leading to discontinuation of investigational product, fatal adverse events, and adverse events of interest.

Subject incidence of all treatment-emergent adverse events, serious adverse events, adverse events leading to discontinuation of investigational product, and fatal adverse events will be tabulated by system organ class and preferred term in alphabetical order.

Subject incidence of events of interest (standardized MedDRA queries and/or Amgen Medical Queries) will also be summarized according to their categories and preferred term. The adverse events of interest include:

- Hypersensitivity (including anaphylactic reactions and immune complex disease [Type III hypersensitivity reactions])
- Malignancy
- Severe infections
- Helminth infections
- Injection site reactions
- Guillain-Barre syndrome

In addition, summaries of treatment-emergent and serious adverse events occurring in at least 5% of the subjects by preferred term in any treatment arm will be provided in descending order of frequency.

Summaries of treatment-emergent and serious adverse events will be tabulated by system organ class, preferred term, and grade.

Subgroup analyses by prior anti-IgE therapy (naïve vs experienced) will be presented for adverse event summarized by system organ class (SOC) and preferred term in descending order of frequency.

9.6.2 Laboratory Test Results

Laboratory tests for coagulation and immunology will only be taken on screen visit 1, all other laboratory tests will be taken and analyzed based on analytical window in Appendix – B.

The absolute value and change from baseline for continuous laboratory parameters defined in protocol will be summarized descriptively by treatment group at each visit.

Mild, moderate, or severe, as defined by the Amgen Standard Grading Scale will be presented for each laboratory parameter, when available.

Central laboratory normal reference ranges will be used for identifying individual clinically important abnormalities. A shift table will be produced for toxicity grade shifts, low, normal, and high values. Shift tables will be created for hematology and IgE.

Shift plots showing individual subjects' laboratory values at baseline and at maximum/minimum/ last post-baseline value may be created for continuous laboratory variables. A diagonal line referencing no change will be included on the shift plots.

9.6.3 Vital Signs

Absolute value and change from baseline in vital signs will be summarized descriptively by treatment group and visit. Should there be unexpected safety findings, vital sign categories may be summarized descriptively along with baseline disease summaries, and shift tables may be generated.

9.6.4 Physical Measurements

Height and weight will be summarized descriptively as baseline summaries.

9.6.5 Electrocardiogram

The electrocardiogram (ECG) measurements from this clinical study were performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QT interval corrected (QTc) effect. Because these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; neither summaries nor statistical analyses will be provided, and these data would not be expected to be useful for meta-analysis with data from other trials.

9.6.6 Exposure to Investigational Product

Exposure to investigational product will be summarized by treatment group. The summary of investigational product exposure will include descriptive statistics for the number of investigational product doses administered, total amount of investigational product exposure, number of investigational product doses missed and duration of investigational product.

9.6.7 Exposure to Non-investigational Product

Descriptive statistics will be produced to describe the exposure to omalizumab arm.

9.6.8 Exposure to Other Protocol-required Therapy

Descriptive statistics will be produced to describe the exposure to approved sgAH throughout the entire duration of study.

9.6.9 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest will be summarized for each treatment group as coded by the World Health Organization Drug Dictionary (WHODRUG). The use of study medication not allowed in the study (excluded medication) will be summarized and analyzed.

Safety and efficacy analyses excluding subjects who have received a COVID-19 vaccine within 7 days of the IP administration may be performed if team evaluation observes a potential impact of the vaccine on the primary or secondary endpoints. An additional set of safety analyses may be repeated excluding events attributed to the COVID-19 vaccine as described in the Symptoms line of the eCRF by the investigator.

9.7 Other Analyses

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

Not applicable for this SAP. Amgen Clinical Pharmacology Modeling and Simulation (CPMS) will conduct PK/PD and exposure-response analyses as needed.

9.7.2 Analyses of Clinical Outcome Assessments

Please refer Section 9.5 for detail.

[redacted]

10. Changes From Protocol-specified Analyses

[redacted]

[redacted]

11. Literature Citations / References

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12. Prioritization of Analyses

Not Applicable for this SAP.

13. Data Not Covered by This Plan

Not applicable for this SAP.

14. Appendices

Appendix- A. Derived Secondary and Exploratory endpoints and Evaluating study endpoints

Derived Endpoints (Data Collection Frequency)	Timepoint	
	Secondary	**Exploratory**
UAS7		
Change from baseline (CFB)		Wks 2-14, 24, 32
Complete response (CR)		Baseline, wks 2-14, 24, 32
Minimal residual disease (MRD)	Wk 16	Baseline, wks 2-14, 24, 32
MID	Wk 16	Wks 2-14, 24, 32
Time to MID		Up to wks 16, 24, 32
Time to achieve UAS7=0		Up to wks 16, 24, 32
Weeks of achieving UAS7=0		Baseline to wks 16, 24, 32
Weeks of achieving UAS7≤6		Baseline to wks 16, 24, 32
CR after discontinuation of IP		Wks 24, 32
MRD		Wks 2-14, 24, 32
ISS7		
Complete resolution of itch (CRI)	Wk 16	Baseline, wks 2-14, 24, 32
CFB	Wk 16	Wks 2-14, 24, 32
MID	Wk 16	Wks 2-14, 24, 32
Time to MID		Up to wks 16, 24, 32
Time to achieve ISS7=0		Up to wks 16, 24, 32
Weeks of achieving ISS7=0		Baseline to wks 16, 24, 32
CRI at week 24 and 32 after discontinuation of IP		Wks 24, 32
HSS7		
Complete resolution of hives (CRH)	Wk 16	Baseline, wks 2-14, wks 24, 32
CFB	Wk 16	Wks 2-14, 24, 32
MID	Wk 16	Wks 2-14, 24, 32
Time to MID		Up to wks 16, 24, 32
Time to achieve HSS7=0		Up to wks 16, 24, 32
Weeks of achieving HSS7=0		Baseline to wks 16, 24, 32
CRH at week 24 and 32 after discontinuation of IP		Wks 24, 32
ISS7 and HSS7		
CRI or CRH at week 24 and 32 after discontinuation of IP		Wks 24, 32
Sleep interference score (SIS7)		
Change from baseline (CFB)	WK 16	Wks 2-14, 24, 32
Sleep quality score (SQS7)		
Change from baseline (CFB)	WK 16	Wks 2-14, 24, 32
Q1. Falling asleep	WK 16	Wks 2-14, 24, 32
Q2. Wakefulness	WK 16	Wks 2-14, 24, 32
Q3. Feeling rested	WK 16	Wks 2-14, 24, 32
Average of Q1-Q3 (not in protocol)		All time points
Sum of Q1-Q3 (not in protocol)		All time points
UCT (4 wks)		
CFB	WK 16	Wks 4-12, 24, 32

Derived Endpoints (Data Collection Frequency)	Timepoint	
	Secondary	**Exploratory**
Well vs. poor controlled		All time points
Completed vs. incomplete controlled		All time points
MID		Wks 4-16, 24, 32
Time to MID		Up to 16, 24, 32
AAS7		
CFB	WK 16	Wks 2-14, 24, 32
Weeks of achieving AAS7=0	Baseline to wk 16 (incl.)	Wk 16 (excl.) – 24 (incl.) Wk 24 (excl.) – 32 (incl.) Wk 16 (excl.) – 32 (incl.)
MID		Wks 2-16, 24, 32
Time to MID		Up to 16, 24, 32
CU-Q2oL (2 wks)		
CFB (standardized score)	Wk 16	Wks 2-14, 24, 32
MID (standardized score)		Wks 2-16, 24, 32
Time to MID		Up to 16, 24, 32
DLQI (2 wks)		
CFB	Wk 16	Wks 2-14, 24, 32
MID		Wks 2-16, 24, 32
Time to MID		Up to 16, 24, 32
AE-QoL (4 wks)		
CFB (standardized score)	Wk 16	Wks 4-12, 24, 32
MID (standardized score)		Wks 4-16, 24, 32
Time to MID		Up to 16, 24, 32
AECT (4 wks)		
CFB	Wk 16	Wks 4-12, 24, 32
Well vs. poor controlled		All time points
WPAI-CU (2 wks)		
CFB in absenteeism, presenteeism, work productivity loss, and activity impairment	Wk 16	Wks 2-12, 24, 32
PGI-S (2 wks)		All time points
PGI-C (2 wks)		All time points
sgAH Rescue Medication Utilization (Daily)		
Cumulative frequency (days) on sgAH rescue medication	Baseline–wk16	
Weekly dose of sgAH medication (# tablets)		Baseline-wks16, 24, 32
Weekly dose of sgAH rescue medication (# tablets)		Baseline-wks16, 24, 32
Subjects with ≥ 1 use of rescue medication		Baseline-wks16, 16-24, 24-32, all combined

Appendix- B. Analytical Window

Per protocol, visits are to be performed within 3 days of the protocol-specified study day. To allow for variations in scheduling, the following visit windows will be applied to selected efficacy and safety evaluations (i.e., vital signs, laboratory evaluations) to assign a most appropriate nominal visit for analysis. If more than one assigned visit falls within the same defined window, the closest visit to the target day (i.e., scheduled visit week x 7 + 1) will be considered for analysis. If two assessment dates are the same distance from the target day, then the latest visit will be considered for analysis. If more than one evaluation falls on the same date and time for laboratory results, then the value with the smallest accession number will be used.

For the purposes of this SAP, “Visit” refers to the scheduled assessment for a given endpoint according to the Schedule of Activities in Protocol Section 1.3. For eDiary endpoints collected on a daily basis, “Visit” refers to “Study week” defined by the analysis windows defined below:

Analysis Window for Daily eDiary (UAS, AAS, Sleep Related Outcomes, and sgAH dose)

Study Week	Target Day	Window Definition
Pre-baseline	-7	Study day -13 to -7
Baseline	1	Study day -6 to Day 1 (inclusive)
Week 1	8	Study day 2 to 8
Week 2	15	Study day 9 to 15
Week 3	22	Study day 16 to 22
Week 4	29	Study day 23 to 29
Week 5	36	Study day 30 to 36
Week 6	43	Study day 37 to 43
Week 7	50	Study day 44 to 50
Week 8	57	Study day 51 to 57
Week 9	64	Study day 58 to 64
Week 10	71	Study day 65 to 71
Week 11	78	Study day 72 to 78
Week 12	85	Study day 79 to 85
Week 13	92	Study day 86 to 92
Week 14	99	Study day 93 to 99
Week 15	106	Study day 100 to 106
Week 16	113	Study day 107 to 113
Week 17	120	Study day 114 to 120
Week 18	127	Study day 121 to 127

Week 19	134	Study day 128 to 134
Week 20	141	Study day 135 to 141
Week 21	148	Study day 142 to 148
Week 22	155	Study day 149 to 155
Week 23	162	Study day 156 to 162
Week 24	169	Study day 163 to 169
Week 25	176	Study day 170 to 176
Week 26	183	Study day 177 to 183
Week 27	190	Study day 184 to 190
Week 28	197	Study day 191 to 197
Week 29	204	Study day 198 to 204
Week 30	211	Study day 205 to 211
Week 31	218	Study day 212 to 218
Week 32	225	Study day 219 to 225

Analysis Window for Bi-weekly Questionnaires [PGI-S, PGI-C (exclude Day 1)]

Study Week	Target Day	Window Definition
Baseline	1	Last evaluation prior to or on Study Day 1 unless specified elsewhere
Week 2	15	Study day 2 to 21
Week 4	29	Study day 22 to 35
Week 6	43	Study day 36 to 49
Week 8	57	Study day 50 to 63
Week 10	71	Study day 64 to 77
Week 12	85	Study day 78 to 91
Week 14	99	Study day 92 to 105
Week 16	113	Study day 106 to 119
Week 24	169	Study day 120 to 175
Week 32	225	Study day 176 to 231

Analysis Window for Four Weekly Questionnaires (UCT, AECT, AE-QoL, CU-Q2oL, DLQI and WPAI-CU)

Visit Week	Target Day	Window Definition
Baseline	1	Last evaluation prior to or on Study Day 1 unless specified elsewhere
Week 4	29	Study day 2 to 42
Week 8	57	Study day 43 to 70
Week 12	85	Study day 71 to 98
Week 16	113	Study day 99 to 126
Week 24	169	Study day 127 to 196
Week 32	225	Study day 197 to 294

Analysis Window for Vitals and Concomitant Medication

Visit week	Target Day	Window definition
Baseline	1	Last evaluation prior to or on Study Day 1 unless specified elsewhere
Week 2	15	Study day 2 to 21
Week 4	29	Study day 22 to 35
Week 6	43	Study day 36 to 49
Week 8	57	Study day 50 to 63
Week 10	71	Study day 64 to 77
Week 12	85	Study day 78 to 91
Week 14	99	Study day 92 to 105
Week 16	113	Study day 106 to 119
Week 24	169	Study day 120 to 175
Week 32	225	Study day 176 to 231

Analysis Window for Serum and/or Urine Pregnancy Test

Study Week	Target Day	Window Definition
Baseline	1	Last evaluation prior to or on Study Day 1 unless specified elsewhere
Week 4	29	Study day 2 to 42
Week 8	57	Study day 43 to 70
Week 12	85	Study day 71 to 98
Week 16	113	Study day 99 to 140
Week 24	169	Study day 141 to 196
Week 32	225	Study day 197 to 231

Analysis Window for Hematology Lab Test

Study Week	Target Day	Window Definition
Baseline	1	Last evaluation prior to or on Study Day 1 unless specified elsewhere
Week 2	15	Study day 2 to 21
Week 4	29	Study day 22 to 42
Week 8	57	Study day 43 to 70
Week 12	85	Study day 71 to 98
Week 16	113	Study day 99 to 140
Week 24	169	Study day 141 to 196
Week 32	225	Study day 197 to 231

Analysis Window for Chemistry and Urinalysis Lab Test

Study Week	Target Day	Window Definition
Baseline	1	Last evaluation prior to or on Study Day 1 unless specified elsewhere
Week 8	57	Study day 2 to 84
Week 16	113	Study day 85 to 168
Week 32	225	Study day 169 to 231

Analysis Window for Anti-tezepelumab Antibody Lab Test

Study Week	Target Day	Window Definition
Baseline	1	Last evaluation prior to or on Study Day 1 unless specified elsewhere
Week 4	29	Study day 2 to 70
Week 16	113	Study day 71 to 168
Week 32	225	Study day 169 to 231

In situations where randomization date and Study Day 1 are not the same, if a subject repeats a questionnaire on both dates, the data from Study Day 1 will be utilized in definition of baseline.

Appendix- C. Handling of Dates, Incomplete Dates and Missing Dates

Imputation Rules for Partial or Missing Start Dates

The reference date for the following rules is the date of first dose.

Start Date		Stop Date						
		Complete: *yyyymmdd*		**Partial: *yyyymm***		**Partial: *yyyy***		**Missing**
		< 1st dose	**≥ 1st dose**	**< 1st dose *yyyymm***	**≥ 1st dose *yyyymm***	**< 1st dose *yyyy***	**≥ 1st dose *yyyy***	
Partial: *yyyymm*	**= 1st dose *yyyymm***	2	1	n/a	1	n/a	1	1
	≠ 1st dose *yyyymm*		2	2	2	2	2	2
Partial: *yyyy*	**= 1st dose *yyyy***	3	1	3	1	n/a	1	1
	≠ 1st dose *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1=Impute the date of first dose; 2=Impute the first of the month; 3=Impute January 1 of the year; 4=Impute January 1 of the stop year
Note: For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month or first day of year if month is also missing.

Imputation Rules for Partial or Missing Stop Dates

Initial imputation

- If the month and year are present, impute the last day of that month.
- If only the year is present, impute December 31 of that year.
- If the stop date is entirely missing, assume the event or medication is ongoing.

If the imputed stop date is before the start date, set stop date to missing.