Title Page

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
Protocol Number:		20190194
Investigational Product:		Tezepelumab
Trade Name:		**TEZSPIRE™**
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This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

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Investigator's Agreement:

I have read the attached protocol entitled 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, dated **26 April 2022**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by: me (including, if applicable, my spouse or legal partner and dependent children) and my sub investigators (including, if applicable, their spouses or legal partners and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____

Signature

_____ _____

Name of Investigator Date (DD Month YYYY)

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1. Protocol Summary

1.1 Synopsis

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

Study Phase: Phase 2b

Indication: Chronic Spontaneous Urticaria

Rationale

Tezepelumab has been approved by the U.S. Food and Drug Administration (FDA) for the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma. Tezepelumab is **also** being developed for the treatment of chronic spontaneous urticaria (CSU). Thymic stromal lymphopoietin (TSLP), an epithelial cytokine shown to be elevated in numerous inflammatory diseases, impacts multiple biological pathways involved in CSU. Thymic stromal lymphopoietin has been shown to be increased in the skin of patients with CSU. Mast cell numbers are also known to be increased up to 3-fold in the skin of CSU patients. Recently, TSLP has been identified as a potent survival promoter of human skin mast cells and is hypothesized to be responsible for the increased number of mast cells in the skin of patients. Blocking TSLP may reduce both problematic immunoglobulin (Ig) E species and mast cells, which jointly act as the central driver of CSU skin inflammation.

Two dose levels of tezepelumab, 210 mg subcutaneous (SC) injections every 4 weeks (Q4W), and 420 mg SC injections every 2 weeks (Q2W) were selected based on available data from evaluation of tezepelumab in an asthma and asthma allergen challenge study. The tezepelumab dose of 210 mg SC injection Q4W was efficacious in the treatment of severe asthma and impacted biomarkers including interleukin (IL)-5, eosinophils, and IgE. Although the impact of tezepelumab on CSU endpoints has not been previously evaluated, since in CSU like in asthma, eosinophils, mast cells, and IgE play an important role in the pathophysiology, this dose of tezepelumab has the potential to show efficacy. A higher dose, tezepelumab 420 mg Q2W will also be included to allow for the evaluation of tezepelumab efficacy and impact on skin mast cells at higher nonoverlapping exposures than with the 210 mg Q4W dose. Inclusion of the 420 mg Q2W dose will also allow for exposure-response analysis to better inform dose selection for future CSU studies. The safety of the selected doses is supported by clinical and preclinical data. The selected doses were previously tested in clinical trials and were deemed safe.

Objective(s)/Endpoint(s)

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 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 complete 16 weeks of study treatment. • Summary measure – **D**ifference **of mean change from baseline in UAS7 score at week 16** between tezepelumab 420 mg subcutaneous (SC) every 2 weeks (Q2W) or 210 mg SC every 4 weeks (Q4W) and placebo (tezepelumab 420 mg SC Q2W or 210 mg 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 tezepelumab 420 mg SC Q2W or 210 mg SC Q4W and placebo, 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 the 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).

Secondary	
• To evaluate the effect of tezepelumab on improvement in itch using the Itch Severity Score over 7 days (ISS7)	• Change from baseline in ISS7 at week 16
• To evaluate the effect of tezepelumab on improvement in hives using the Hives Severity Score over 7 days (HSS7)	• Change from baseline in HSS7 score at week 16
• To evaluate the effect of tezepelumab on subjects	• UAS7 $\leq$ 6 at week 16

achieving minimal residual disease using the UAS7	
• To evaluate the effect of tezepelumab on subjects achieving the minimal important difference (MID) on change from baseline in the UAS7	• **Change** from baseline in UAS7 ≤ **-**10 at week 16
• **To evaluate the effect of tezepelumab compared with placebo in CSU subjects using the UAS7**	• **Complete response in UAS7 defined as UAS7 = 0 at week 16**
• To evaluate the effect of tezepelumab on complete resolution of itch using the ISS7	• ISS7 = 0 at week 16
• 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	• Change from baseline in the CU-Q2oL at week 16

urticaria-specific quality of life (QoL) using the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL)	
• 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)

Overall 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).

Number of Subjects

Approximately **159** subjects will be **enrolled to the** anti-IgE naïve **stratum and the** anti-IgE experienced **stratum** with an approximately **3:1 ratio**: 120 CSU subjects who are symptomatic despite treatment with sgAH and are anti-IgE naïve**,** and **approximately 39** subjects who were symptomatic despite treatment with sgAH and are anti-IgE experienced (intolerant, inadequate responder, or discontinued for other reason).

Summary of Key Subject Eligibility Criteria

Eligible subjects will include adults with a clinical diagnosis of CSU for ≥ 6 months at the time of screening who are symptomatic despite treatment with sgAH (up to 4x the approved dose) and are anti-IgE naïve or who are symptomatic despite treatment with sgAH (up to 4x the approved dose) and anti-IgE experienced (intolerant, inadequate responder, or discontinued for other reason).

For a full list of eligibility criteria, please refer to Section 5.1 to Section 5.2.

Treatments

Study treatment includes tezepelumab, omalizumab, or placebo as outlined in the table below.

Study Treatment Name	Amgen Investigational Product:[a] Tezepelumab	Placebo	Non-Amgen Investigational Product:[b] Omalizumab (Xolair®)
Dosage Formulation	[redacted] mg/mL in [redacted] mM acetate, [redacted]% weight/volume L-proline, [redacted]% weight/volume polysorbate 80, pH [redacted]	[redacted]% weight/volume sodium carboxy methyl cellulose in [redacted] mM acetate, [redacted] mM L-proline, [redacted]% weight/volume polysorbate 80, pH [redacted]	150 mg/mL in a pre-filled syringe (Xolair)
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	Each subject will receive 2 injections per visit. For subjects randomized to 210 mg Q4W and 420 mg Q2W, volumes for injections from vials will be detailed in the IPIM. Subjects randomized to Q4W dosing will receive placebo at intervening visits, such that all subjects receive an injection Q2W.	Each subject will receive 2 injections per visit. For subjects randomized to placebo, volumes for injections from vials provided will be detailed in the IPIM. Subjects will receive placebo dosing Q2W.	Each subject will receive 2 injections per visit. Subjects randomized to 300 mg Q4W dosing will receive placebo at intervening visits, such that all subjects receive an injection Q2W.
Route of Administration	SC injection	SC injection	SC injection

IPIM = Investigational Product Instruction Manual; SC = subcutaneous; Q2W = every 2 weeks; Q4W = every 4 weeks

[a] Tezepelumab will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

[b] Omalizumab will be manufactured and packaged by Novartis Pharmaceuticals Corporation and/or Genentech, Inc. and distributed using Amgen (or designee) clinical study drug distribution procedures.

Procedures

Key study procedures will include a daily assessment of Urticaria Activity Score over 7 days (UAS7), Angioedema Activity Score over 7 days (AAS7), other measures of CSU disease activity, and documentation of daily sgAH dose. Blood samples will be collected for pharmacokinetic (PK) analysis [redacted]

An end of study (EOS) visit will be conducted 18 weeks after the final dose of study drug (16 weeks after the end of treatment [EOT] visit). Any adverse events observed by the investigator or reported by the subject that occur after screening visit 2 through the EOS/safety follow-up or 18 weeks after the last administration of investigational product are to be collected/reported. Serious adverse events observed by the investigator or reported by the subject after the signing of informed consent through the EOS/safety follow-up visit or for 18 weeks after the last administration of investigational product are reported using the Event Case Report Form (CRF).

For a full list of study procedures, including the timing of each procedure, please refer to Section 8.2 and the Schedule of Activities (SoA) in Table 1-1 and Table 1-2.

Statistical Considerations

Approximately **159** subjects will be **enrolled in**: the anti-IgE naïve stratum (CSU subjects who are symptomatic despite treatment with a sgAH and anti-IgE naïve) or the anti-IgE experienced stratum (CSU subjects who are symptomatic despite treatment with a sgAH and previously treated with anti-IgE therapy [intolerant, inadequate responder, or discontinued for other reason]). 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 an 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]

Subject disposition, demographics, and baseline disease characteristics will be summarized descriptively by randomized treatment group based on the full analysis set (FAS), **or** all randomized subjects. For categorical endpoints, the descriptive statistics will contain frequency and percentage. For continuous endpoints, the descriptive statistics will include the number of observations, mean, standard error, standard deviation, median, first quartile, third quartile, minimum, and maximum.

For primary endpoint, tezepelumab 420 mg SC Q2W and 210 mg SC Q4W compared to placebo **in the overall and** the anti-IgE naïve **population** will be tested **sequentially** using the Bonferroni procedure to control for the type I error rate adjusting for covariates specified in Section 9.3.2.

Up to 2 interim analyses will be performed: 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 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 week 16 assessments or early terminate from the study.

For a full description of statistical analysis methods, please refer to Section 9.

Statistical Hypotheses

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 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.

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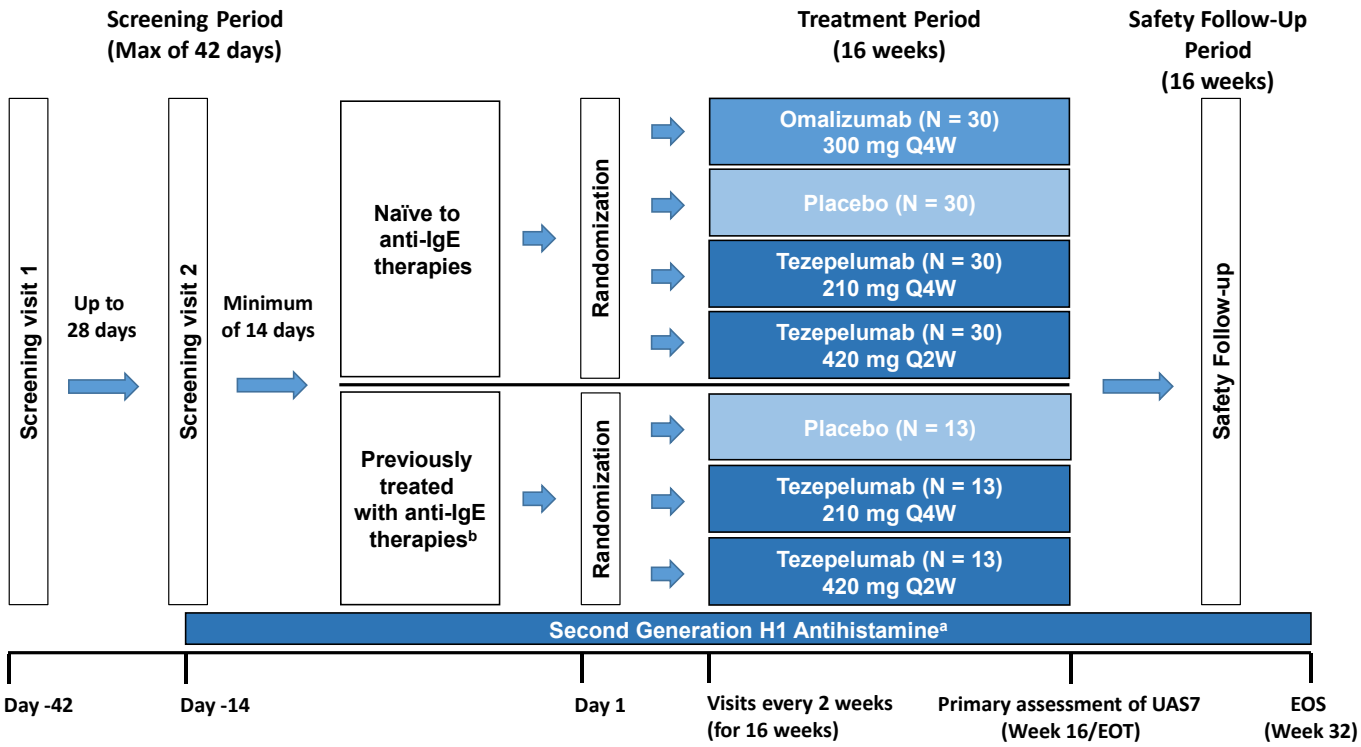
1.2 Study Schema

Figure 1-1. Study Schema



EOS = end of study; EOT = end of treatment; IgE = immunoglobulin E; Min = minimum; Q2W = once every 2 weeks; Q4W = once every 4 weeks; UAS7 = Urticaria Activity Score over 7 days.
[a] Subjects should maintain a stable dose of second generation H1-antihistamine as the background medication from screening visit 2 throughout the study until the EOS visit.
[b] Subjects previously treated with anti-IgE therapies may be intolerant to or inadequate responders to anti-IgE therapies or may have discontinued for other reason.

1.3 Schedule of Activities (SoA)

Table 1-1. Schedule of Activities

PROCEDURE	Screening Period: Visit 1 (a max of 42 days before Day 1)[a]	Screening Period: Visit 2 (min of 14 days before Day 1)[a]	Randomization: Day 1	Treatment Period: Wk 2[b]	Wk 4[b]	Wk 6[b]	Wk 8[b]	Wk 10[b]	Wk 12[b]	Wk 14[b]	EOT[b]/ ET[l]: Wk 16	Notes
GENERAL AND SAFETY ASSESSMENTS												
Informed consent	X											
[redacted]												
Verify eligibility criteria	X	X	X[c]									
Demographics	X											
Physical examination	X											
Physical measurements	X											Height and weight
Urticaria, Dermatology and Medical history	X											
Substance use history	X											Substances: drugs, alcohol, tobacco, caffeine
Vital signs	X	X	X	X	X	X	X	X	X	X	X	BP, RR, HR, and temperature
Adverse events[d]		X	X	X	X	X	X	X	X	X	X	
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	
Concomitant therapies review	X	X	X	X	X	X	X	X	X	X	X	
Tuberculosis testing	X										X	
LABORATORY ASSESSMENTS												
Serum and/or Urine pregnancy test (females of childbearing potential only)[e]	X		X		X		X		X		X	Serum testing mandatory at screening

PROCEDURE	Screening Period: Visit 1 (a max of 42 days before Day 1)[a]	Screening Period: Visit 2 (min of 14 days before Day 1)[a]	Randomization: Day 1	Treatment Period: Wk 2[b]	Wk 4[b]	Wk 6[b]	Wk 8[b]	Wk 10[b]	Wk 12[b]	Wk 14[b]	EOT[b]/ ET[l]: Wk 16	Notes
SARS-CoV-2 Antibody Test[n]												Approximately 4 weeks post-vaccination
Coagulation	X											
Hematology	X		X	X	X		X		X		X	
Chemistry	X		X				X				X	
HIV, Hepatitis B and C screening	X											
Urinalysis	X		X				X				X	
Anti-tezepelumab antibody			X		X						X	
[redacted]												
PHARMACOKINETIC ASSESSMENTS												
PK Sampling			X	X	X		X		X		X	
STUDY-SPECIFIC ASSESSMENTS (eg, DISEASE-SPECIFIC ASSESSMENTS)												
Assign eDiary device		X										
PATIENT-REPORTED OUTCOME ASSESSMENTS[m]												
eDiary[h]		Daily										

PROCEDURE	Screening Period: Visit 1 (a max of 42 days before Day 1)[a]	Screening Period: Visit 2 (min of 14 days before Day 1)[a]	Randomization: Day 1	Treatment Period: Wk 2[b]	Wk 4[b]	Wk 6[b]	Wk 8[b]	Wk 10[b]	Wk 12[b]	Wk 14[b]	EOT[b]/ ET[l]: Wk 16	Notes
UAS (daily)[h]		Daily										
AAS (daily)[h]		Daily										
sgAH questionnaire		X	X	X	X	X	X	X	X	X	X	
Sleep related outcomes (daily)[h]		Daily										
PGI-S			X	X	X	X	X	X	X	X	X	
PGI-C				X	X	X	X	X	X	X	X	
UCT	X		X		X		X		X		X	
AECT[i]			X		X		X		X		X	
CU-Q2oL			X		X		X		X		X	
AE-QoL[i]			X		X		X		X		X	
DLQI			X		X		X		X		X	
WPAI-CU			X		X		X		X		X	
STUDY TREATMENT												
sgAH dose[j]		Daily										
Document dose of sgAH and any rescue medication use		Daily										
Administration of tezepelumab, omalizumab, or placebo[k]			X	X	X	X	X	X	X	X		

AAS = Angioedema Activity Score; AECT = Angioedema Control Test; AE-QoL = Angioedema Quality of Life Questionnaire; BP = blood pressure; [redacted]; **CSU = chronic spontaneous urticaria;** CU-Q2oL = Chronic Urticaria Quality of Life Questionnaire; DLQI = Dermatology Life Quality Index; eCRF = electronic case report form; eDiary = electronic diary; EOT = end of treatment; ET = early termination; HIV = human immunodeficiency virus; HR = heart rate; IgE = immunoglobulin E; Max = maximum; Min = minimum; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic; **Q4W = every 4 weeks;** RR = respiratory rate; TSLP = thymic stromal lymphopoietin; UAS = Urticaria Activity Score; UCT = Urticaria Control Test; Wk =Week; WPAI-CU = Work Productivity and Activity Impairment Questionnaire: Chronic Urticaria

[a] Screening visit 1 can occur up to a maximum of 42 days before the first dose of investigational product on day 1. Screening visit 2 should occur a minimum of 14 days before first dose of investigational product on day 1.

[b] The window for visits is ± 3 days.

[c] Only certain inclusion criteria specified in the protocol will be re-evaluated at the day 1 visit. These criteria will be evaluated prior to any other day 1 study activities and are required to be met for dosing with investigational product.

[d] Adverse events related to study procedures observed by the investigator or reported by the subject that occur after screening visit 2.

[e] Pregnancy testing applies to females of childbearing potential only, as defined in the protocol. The pregnancy test at screening must be a serum pregnancy test. All other scheduled pregnancy tests can be urine or serum tests. Pregnancy testing should be performed before dosing. Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations. If a urine pregnancy test is positive, a confirmatory serum pregnancy test will be performed by the study center and entered into the eCRF.

[redacted]

All daily assessments should be performed at the same time every day, in the morning.

[i] AECT and AE-QoL will only be administered to subjects with angioedema.

[j] Examples of an acceptable approved sgAH include 1 tablet daily of the following: cetirizine 10 mg, desloratadine 5 mg, ebastine 10 mg, fexofenadine 120 mg, levocetirizine 5 mg, loratadine 10 mg, and rupatadine 10 mg (van den Elzen et al, 2017)

[k] Administration of study drug is the final activity performed at a visit. Subjects randomized to Q4W dosing will receive placebo at the visits between dosing with tezepelumab. Subjects will be observed for 2 hour post-treatment at the day 1 and week 2 visits. For all other visits where investigational product is administered, subjects will be observed for a period of time at the discretion of the investigator.

[l] All subjects who terminate the study early will complete an early termination visit consisting of all assessments included in the EOT (week 16) visit. In addition, an EOS visit will occur 16 weeks after the EOT visit. In the event a patient is unable to have an EOS visit, the site will attempt to contact the subject by telephone to obtain safety information.

[m] PROs are to be assessed prior to any other assessments at each visit.

[n] SARS-COV-2 serology (antibody) test will be done approximately 4 weeks after the last dose of vaccination and at a scheduled visit.

Table 1-2. Schedule of Activities

PROCEDURE	Safety Follow-up Period		Notes
	Wk 24[a]	Wk 32[a]/EOS[b]	
GENERAL AND SAFETY ASSESSMENTS			
Vital signs	X	X	BP, RR, HR, and temperature
Adverse events[c]	X	X	
Serious adverse events	X	X	
Concomitant therapies review	X	X	
LABORATORY ASSESSMENTS[n]			
Serum and/or Urine pregnancy test (females of childbearing potential only)[d]	X	X	
SARS-CoV-2 Antibody Test[h]			Approximately 4 weeks post-vaccination
Hematology	X	X	
Chemistry		X	
Urinalysis		X	
Anti-tezepelumab antibody		X	
[redacted]			
PHARMACOKINETIC ASSESSMENTS			
PK Sampling	X	X	
PATIENT-REPORTED OUTCOME ASSESSMENTS			
eDiary[e]	Daily		
UAS (daily)[e]	Daily		
AAS (daily)[e]	Daily		
sgAH questionnaire	X	X	
Sleep related outcomes (daily)[e]	Daily		
PGI-S	X	X	
PGI-C	X	X	
UCT	X	X	
AECT[f]	X	X	
CU-Q2oL	X	X	
AE-QoL[f]	X	X	
DLQI		X	
WPAI-CU		X	

PROCEDURE	Safety Follow-up Period		Notes
	Wk 24[a]	Wk 32[a]/EOS[b]	
STUDY TREATMENT			
sgAH dose[g]	Daily		
Document dose of sgAH and any rescue medication use	Daily		

AAS = Angioedema Activity Score; AECT = Angioedema Control Test; AE-QoL = Angioedema Quality of Life Questionnaire; BP = blood pressure [redacted]; **CSU = chronic spontaneous urticaria;** CU-Q2oL = Chronic Urticaria Quality of Life Questionnaire; DLQI = Dermatology Life Quality Index; eCRF = electronic case report form; eDiary = electronic diary; EOS = end of study; EOT = end of treatment; HR = heart rate; IgE = immunoglobulin E; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic; RR = respiratory rate; sgAH = second generation H1-antihistamine; TSLP = thymic stromal lymphopoietin; UAS = Urticaria Activity Score; UCT = Urticaria Control Test; Wk = Week; WPAI-CU = Work Productivity and Activity Impairment Questionnaire: Chronic Urticaria

[a] The window for visits is ± 3 days.

[b] An EOS visit will occur 16 weeks after the EOT visit. In the event a patient is unable to have an EOS visit, the site will attempt to contact the subject by telephone to obtain safety information.

[c] Adverse events related to study procedures observed by the investigator or reported by the subject that occur after screening visit 2.

[d] Pregnancy testing applies to females of childbearing potential only, as defined in the protocol. The pregnancy test at screening must be a serum pregnancy test. All other scheduled pregnancy tests can be urine or serum tests. Pregnancy testing should be performed before dosing. Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations. If a urine pregnancy test is positive, a confirmatory serum pregnancy test will be performed by the study center and entered into the eCRF.

[e] All daily assessments should be performed at the same time every day, in the morning.

[f] AECT and AE-QoL will only be administered to subjects with angioedema.

[g] Examples of an acceptable approved sgAH include 1 tablet daily of the following: cetirizine 10 mg, desloratadine 5 mg, ebastine 10 mg, fexofenadine 120 mg, levocetirizine 5 mg, loratadine 10 mg, rupatadine 10 mg (van den Elzen et al, 2017)

[h] SARS-COV-2 serology (antibody) test will be done approximately 4 weeks after the last dose of vaccination and at a scheduled visit.

2. Introduction

2.1 Study Rationale

Tezepelumab has been approved by the U.S. Food and Drug Administration (FDA) for the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma. Tezepelumab is an anti-thymic stromal lymphopoietin (TSLP) monoclonal antibody**, currently also** in development for **other potential indications including** chronic obstructive pulmonary disease, chronic rhinosinusitis with nasal polyps, chronic spontaneous urticaria (CSU)**, and additional indications**. Thymic stromal lymphopoietin is an epithelial cell-derived cytokine that is produced in response to proinflammatory stimuli (eg, infectious, allergic, and environmental stimuli) and trauma; it plays an upstream, pivotal role in the initiation of widespread allergic responses, and drives activation of a broad range of cell types including eosinophils, mast cells, T cells, dendritic cells, type 2 innate lymphoid cells, and basophils (Watson and Gauvreau, 2014), which perpetuate the T helper 2 (Th2) response. The resulting cascade of cytokines associated with this type 2 polarizing phenotype (Kaur and Brightling, 2012), have grave consequences for human health.

Tezepelumab binds with high affinity to human TSLP and inhibits the TSLP-mediated signaling initiated by the TSLP: TSLP receptor binding. It has been shown to lower blood eosinophils, total immunoglobulin (Ig) E, and Th2 pathway activity (interleukin [IL]-5, IL-13). [redacted].

There is strong preclinical and clinical evidence that TSLP plays a role in Th2-mediated pathways, and TSLP is a reasonable target for the treatment of CSU. Thymic stromal lymphopoietin has been shown to promote mast cell development and is critical in mast cell biology. A study of human skin mast cell function demonstrated TSLP receptor expression prevented apoptosis of human skin mast cells (Hazzan et al, 2019). Compared to healthy controls, the number of TSLP-positive cells is increased in both lesioned and non-lesioned skin of patients with CSU (Kay et al, 2015). Mast cell numbers are also known to be increased up to 3-fold in the lesioned and non-lesioned skin of CSU patients (Kay et al, 2015). In the skin, the production and release of TSLP is restricted to epidermal keratinocytes and mast cells (He and Geha, 2010). In addition,

TSLP is well known to act as an alarmin, and its expression and release from epithelial cells is induced in response to a broad array of stimuli, including mechanical injury, infection, and inflammatory cytokines (Allakhverdi et al, 2007; He and Geha, 2010; Roan et al, 2019).

Combined these findings support the therapeutic targeting TSLP by inhibition with tezepelumab as a strong potential candidate for treatment in patients with CSU.

This study will evaluate the safety and efficacy in the treatment of tezepelumab in patients with CSU. Qualified subjects will have documented symptoms of CSU despite treatment with H1-antihistamines. The target population will be composed of subjects who are anti-IgE naïve, and subjects previously exposed to anti-IgE therapy. Omalizumab is the only approved anti-IgE therapy for CSU. Subjects who had inadequate responses or were intolerant to anti-IgE therapy, or discontinued omalizumab for other reasons may be included in the group of subjects previously exposed to anti-IgE therapy. Two dose levels of tezepelumab (420 mg subcutaneous [SC] injection every 2 weeks [Q2W] and 210 mg SC every 4 weeks [Q4W]) were selected based on tezepelumab exposure, safety and response analysis of tezepelumab concentration, and response data collected in previous clinical trials in an asthma allergen challenge study, as well as phase 2b asthma and phase 2a atopic dermatitis clinical studies. An omalizumab treatment group will used for contextualization of study results. These subjects will serve as a positive control.

2.2 Background

2.2.1 Disease

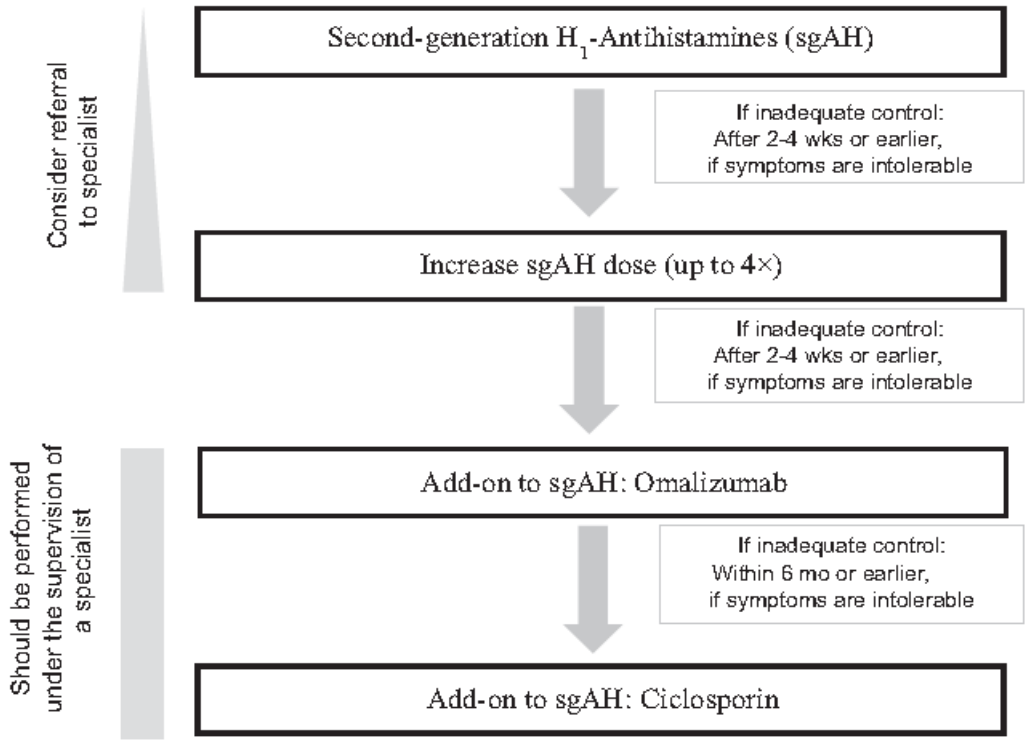
Chronic spontaneous urticaria is a common skin disease that is characterized by the spontaneous appearance of wheals, angioedema, or both for > 6 weeks as a result of known (ie, the presence of mast cell-activating autoantibodies) or unknown causes (Zuberbier et al, 2018; Bernstein et al**,** 2014).

Chronic spontaneous urticaria is highly prevalent, affecting up to 1% of the population. It primarily affects women (Vestergaard et al, 2017). It is a self-limiting disorder, persisting for 2 to 5 years in the majority of cases, although 20% of patients suffer for more than 5 years (Nebiolo et al, 2009). Beyond the visual impact of wheals and angioedema, quality of life (QoL) is substantially reduced in patients due to pruritus, interference with sleep, daily activities, social interaction, work productivity, and emotional well-being (Maurer et al, 2011).

The underlying pathophysiology for CSU involves mast cell and basophil degranulation with release of histamine, leukotrienes, prostaglandins, and other inflammatory mediators. Functional autoantibodies against the high-affinity IgE receptor have been detected in approximately one-third of patients, suggesting an autoimmune component to CSU. In addition, cytokines that promote a Th2 profile of inflammation such as IL-33, IL-25, and TSLP have been shown to be increased in CSU skin lesions, suggesting that innate pathways may play a role in the pathogenesis of CSU, perhaps by enhancing survival of mast cells in the lesioned skin (Kay et al, 2015).

According to the EAACI/GA^{2}LEN/EDF/WAO guideline for the management of urticaria, the goal of treatment is complete symptom control. Therapies aim to reduce the effect of mast cell mediators such as histamine, platelet-activating factor, cytokines, and others on target structures of the skin, including blood vessels (vasodilation and extravasation) and sensory nerves (itch). The guideline uses a stepwise treatment algorithm (Figure 2-1). First-line treatment consists of approved doses of second generation H1-antihistamines (sgAH). If there is inadequate response to treatment, higher doses (up to 4x approved doses) of sgAH are recommended. After that, omalizumab, a humanized anti-IgE monoclonal antibody, is recommended. Although omalizumab has provided advancement in treatment, 20% to 40% of patients do not respond to treatment. Those who don't respond to omalizumab may be treated with cyclosporine although it is not approved for CSU and many patients must discontinue treatment due to adverse events. Additional treatment options are needed for patients with CSU.

Figure 2-1. EAACI/GA²LEN/EDF/WAO Guideline for the Management of Urticaria



sgAH = second generation antihistamines
Source: Zuberbier et al, 2018

2.2.2 Amgen Investigational Product Background: Tezepelumab

Tezepelumab is a human recombinant monoclonal antibody of the Ig G2 subclass that specifically binds human TSLP, blocking the interaction between TSLP and its high-affinity receptor complex. Targeting TSLP may serve to inhibit multiple biologic pathways involved in CSU.

A detailed description of the chemistry, pharmacology, pharmacokinetics (PK), efficacy, and safety of tezepelumab is provided in the Investigator's Brochure.

2.2.3 Non-Amgen Investigational Product Background: Xolair® (omalizumab)

Omalizumab is a humanized anti-IgE monoclonal antibody that binds to the Fc region of free IgE and prevents it from binding to its high-affinity receptor on mast cells and basophils. As described in a boxed warning in its US prescribing information, omalizumab has been associated with anaphylaxis presented as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, as early as after the first dose, but also beyond 1 year after beginning regularly administered treatment (Xolair prescribing information).

Refer to the regional manufacturer package insert for additional information.

2.3 Risk Assessment

To date, tezepelumab has been well tolerated with no identified risks from studies in healthy volunteers, or patients with asthma, chronic obstructive pulmonary disease, and moderate to severe atopic dermatitis.

Hypersensitivity (including anaphylaxis, serious allergic reactions, and immune complex disease) is an important potential risk for tezepelumab and is considered a key safety risk. No serious allergic reactions nor anaphylactic reactions considered related to tezepelumab have been reported in the clinical program. The subject incidence of positive posttreatment antidrug antibodies observed in the phase 2 dose-ranging asthma study was low and was higher in subjects who received placebo (4.3%) than in subjects treated with tezepelumab (1.7%). No subjects developed neutralizing antibodies in that study. As part of the current study, subjects can be randomized to receive treatment with omalizumab (Xolair®), which has been associated with anaphylaxis and has a boxed warning in its US prescribing information (Xolair prescribing information). For these reasons, all visits where investigational product is administered, subjects will be observed for a period of time of 2 hours or at the discretion of the investigator as defined in Section 6.1.

Serious infections are also an important potential risk associated with tezepelumab and are considered a key safety risk. The mechanism of action of tezepelumab suggests potential inhibitory effects on immune responses mediated by Th2 cells, leading to the possibility of suppression of the host's protective immune response and impairing host defense against certain infections (eg, bacterial infections, parasitic [helminth] infections, and opportunistic infections). However, there is no clear preclinical or clinical evidence supporting such a role, and no safety signals related to infections have been detected in the tezepelumab program.

Injection site reactions are considered a potential risk for tezepelumab. Injection site reactions were balanced between the treatment groups and placebo in the phase 2b severe asthma study and no event was considered serious.

Data from preclinical, clinical, and literature sources does not currently support malignancy being considered a risk with tezepelumab; however, it is categorized as an adverse event of special interest. [redacted]

[redacted] Thymic stromal lymphopoietin literature data (ie, information on class effects, knockout mouse models, and human genetic mutations) does not indicate a potential carcinogenic concern associated with long-term tezepelumab treatment; however, malignancies will be carefully monitored in this study.

Tezepelumab binds to human TSLP and prevents its interaction with the TSLP receptor complex. There are no data on CSU and the risk of **coronavirus disease 2019 (**COVID-19**)**. Subjects will be closely monitored and the potential impact of COVID-19 on these participants will be carefully considered.

The benefit/risk assessment for tezepelumab in CSU based on the development for atopic dermatitis and asthma through phase 2 is anticipated to be favorable. The future benefit/risk assessment will largely be defined by results from the phase 3 program.

The above benefit risk assessment supports the conduct of this clinical trial. Reference should be made to the Investigator's Brochure for further data on tezepelumab.

3. Objectives and Endpoints

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 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 complete 16 weeks of study treatment. • Summary measure – **D**ifference **of mean change from baseline in UAS7 score at week 16** between tezepelumab 420 mg subcutaneous (SC) every 2 weeks	

(Q2W) or 210 mg SC every 4 weeks (Q4W) and placebo (tezepelumab 420 mg SC Q2W or 210 mg 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 tezepelumab 420 mg SC Q2W or 210 mg SC Q4W and placebo, 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 the 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).

Secondary

• To evaluate the effect of tezepelumab on improvement in itch using the Itch Severity Score over 7 days (ISS7)	• Change from baseline in ISS7 at week 16
• To evaluate the effect of tezepelumab on improvement in hives using the Hives Severity Score over 7 days (HSS7)	• Change from baseline in HSS7 score at week 16
• To evaluate the effect of tezepelumab on subjects achieving minimal residual disease using the UAS7	• UAS7 $\leq$ 6 at week 16
• To evaluate the effect of tezepelumab on subjects achieving the minimal important difference (MID) on change from baseline in the UAS7	• **Change** from baseline in UAS7 $\leq$ **-**10 at week 16
• **To evaluate the effect of tezepelumab compared with placebo in CSU subjects using the UAS7**	• **Complete response in UAS7 defined as UAS7 = 0 at week 16**
• To evaluate the effect of tezepelumab on complete resolution of itch using the ISS7	• ISS7 = 0 at week 16
• To evaluate the effect of tezepelumab on subjects achieving the MID on change from baseline in the ISS7	• **Change** from baseline in ISS7 $\leq$ **-**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	• Achieving minimal disease activity and the change from baseline of defined CSU QoL measures

measured by all patient-reported outcomes (PROs)	(DLQI, CU-Q2oL AECT, AE-QoL, WPAI-CU) 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 CU-Q2oL	• 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 AE-QoL ≤ **-**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 achieving well controlled disease using the AECT	• AECT ≥ 10 at week 16 and all other measured timepoints
• 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

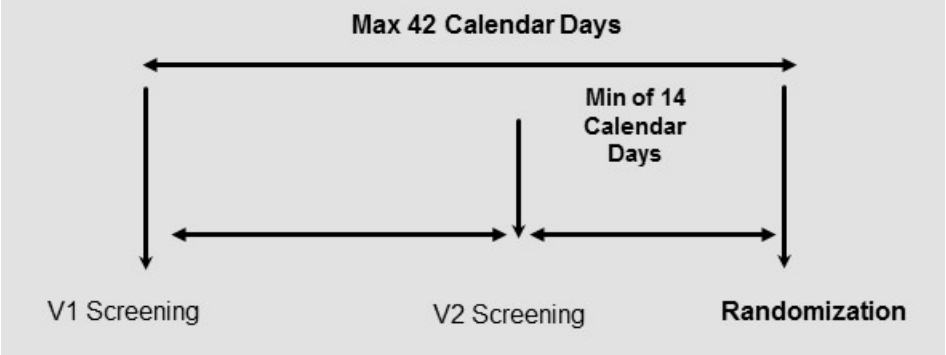
4. Study Design

4.1 Overall Design

This phase 2b study is designed to evaluate the efficacy and safety of tezepelumab in adult subjects with CSU. Eligible subjects include adults with a clinical diagnosis of CSU for ≥ 6 months at the time of screening who remain symptomatic despite treatment with sgAH (up to 4x the approved dose) and are anti-IgE naïve or subjects who are also previous users of anti-IgE therapies (symptomatic despite treatment with sgAH and are intolerant, inadequate responder, or were discontinued for other reason). The study duration is approximately 38 weeks and includes an up to 42-day screening period, a 16-week treatment period, and 16-week safety follow-up period. The screening period

consists of 2 visits and **allows** a maximum of 42 days before enrollment/randomization. At screening visit 1, the majority of screening eligibility criteria will be reviewed**,** and subjects will be asked to complete the Urticaria Control Test (UCT). At screening visit 2 (a minimum of 14 days before randomization), subjects will receive the electronic diary (eDiary). In addition, at screening visit 2, subjects will also begin a sgAH stabilization period of at least 14 days, and will be required to complete a daily Urticaria Activity Score (UAS) recording, daily Angioedema Activity Score (AAS) recording, and adverse event related to study procedures collection. Starting from screening visit 2, subjects must maintain a stable dose of sgAH during the 14 days sgAH stabilization period and continue throughout the duration of the study until the end of study (EOS) visit. Subjects who do not meet all of the screening criteria will be considered screen failures. For eligible subjects, investigational product dosing will occur on day 1 and weeks 2, 4, 6, 8, 10, 12, and 14. Primary and secondary objectives will be evaluated at the week 16 visit. After week 16, subjects will continue in the safety follow-up period for 16 weeks.

Figure 4-1. Screening and Enrollment



Note: Subjects may proceed to screening visit 2 if serologic elements related to eligibility from screening visit 1 are not yet available.

Up to 2 interim analyses will be performed: 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.

The overall study design is described by a study schema in Section 1.2. The endpoints are defined in Section 3.

4.2 Number of Subjects

Approximately **159** subjects will be **enrolled** to the anti-IgE naïve **stratum** and **the** anti-IgE experienced **stratum** with an approximate **3:1 ratio**: 120 **CSU** subjects who are symptomatic despite treatment with sgAH and are anti-IgE naïve**,** and **approximately 39** subjects who are symptomatic despite treatment with sgAH and were previously treated with anti-IgE therapies. Subjects will be randomized to either placebo, omalizumab, or 1 of 2 doses of tezepelumab in the anti-IgE naïve stratum, and placebo or 1 of 2 doses of tezepelumab in the anti-IgE experienced stratum.

Subjects in this clinical investigation shall be referred to as "subjects." For the sample size justification, see Section 9.2.

4.2.1 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study will not be replaced.

4.2.2 Number of Sites

Approximately 80 investigative sites in Europe, the Americas, and Asia will be included in the study. Sites that do not enroll subjects within 6 months of site initiation may be closed.

4.3 Justification for Investigational Product Dose

The tezepelumab dose of 210 mg Q4W has been shown to have efficacy in the treatment of asthma and an impact on mast cell related biomarkers including IL-5 (60% reduction), eosinophils (50% reduction), and IgE (20%). Although the impact of tezepelumab on CSU endpoints has not been previously evaluated, since in CSU like in asthma, eosinophils, mast cells, and IgE play an important role in the pathophysiology, this dose of tezepelumab has the potential to show efficacy. Reports suggest higher active TSLP and cytokine levels in lesioned skin in CSU; hence, this study is also evaluating a higher dose (420 mg Q2W) (Kay et al, 2015). The tezepelumab 420 mg Q2W dose has exposure levels higher than what was observed at 280 mg Q2W (PATHWAY highest dose in the phase 2b asthma and phase 2a atopic dermatitis studies) and trough concentrations close to 700 mg intravenously Q4W in the asthma allergen challenge study, which demonstrated improvement in physiologic measurements in subjects with mild atopic asthma (Gauvreau et al, 2014). Tezepelumab 420 mg Q2W will allow for the further evaluation of tezepelumab efficacy and impact on skin mast cells at higher nonoverlapping drug concentrations with 210 mg Q4W. Inclusion of the 420 mg Q2W dose will also allow for exposure-response analysis to further inform dose selection for future CSU studies.

Preclinical data supporting the safety of a tezepelumab 420 mg SC Q2W dose are based on a no-observed adverse effect level for 6-month toxicology studies of 300 mg/kg SC weekly, [redacted]. Additionally, predicted steady state exposures (C_{max} and AUC) from the tezepelumab 420 mg SC Q2W dosing regimen are also within the range of the exposures in previous tezepelumab clinical studies which were deemed safe.

4.3.1 Justification for Non-Amgen Investigational Product Dose

The maximum approved dose for omalizumab in the treatment of chronic idiopathic urticaria is 300 mg SC Q4W, thus, that is the dose that will be evaluated in this study. The omalizumab group will be used as the internal active control for the evaluation of treatment effect of tezepelumab. Per urticaria treatment guidelines, use of omalizumab is third line after higher off-label antihistamine use has failed to provide an adequate response (Zuberbier et al, 2018).

4.4 End of Study

4.4.1 End of Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receive**d** an intervention **to collect** final data for the primary endpoint(s). The primary completion date **for this study** is the date when the last subject has completed the assessments for week 16.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination [ET] of the study), then the primary completion will be the date when the last subject is assessed or received an intervention for evaluation in the study (ie, last subject last visit).

End of Study: The EOS date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable. The EOS date is the date when the last subject has an opportunity to complete the assessments for week 32.

4.4.2 Study Duration for Subjects

For an individual subject, the length of participation includes a 2-visit screening period of a maximum of 42 days, including an H1-antihistamine stabilization period of at least 14 days, a 16-week treatment period, and an EOS visit that occurs 18 weeks after the final dose of study drug (16 weeks after the end of treatment [EOT] visit).

4.5 Patient Input on Study Design

Patient input was not obtained.

5. Study Population

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidates (eg, date of screening). This log may be completed and updated via an Interactive Response Technology (IRT).

Eligibility criteria will be evaluated during screening. Each subject should meet all the inclusion criteria and none of the exclusion criteria for this study in order to be randomized. Under no circumstances can there be exceptions to this rule. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions will not be provided. Subjects who consent to participate in the study but are not subsequently randomized are considered screen failures.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 11.3).

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

101 Subject has been informed about study procedures and medications and has provided informed consent prior to initiation of any study-specific activities/procedures

102 Subject is able to communicate with the investigator, and understands and complies with the requirements of the study

103 Age ≥ 18 to ≤ 80 years of age at screening

104 Chronic spontaneous urticaria diagnosis for ≥ 6 months at the time of screening visit 1

105 CSU inadequately controlled by sgAH at enrollment, as defined by all of the following:

- The presence of itch and hives for ≥ 6 consecutive weeks at any time prior to screening visit 2
- Failure to respond to an sgAH (up to 4 times the approved dose)

- Urticaria Activity Score over 7 days (UAS7) (range 0-42) ≥ 16 and Hives Severity Score over 7 days (HSS7) (range 0-21) ≥ 8 during the 7 days prior to enrollment

106 Subject must have been on a sgAH at approved or increased doses (up to 4x the approved dose) for treatment of CSU for at least 3 consecutive days immediately prior to the day -14 screening visit (screening visit 2) and must have documented current use on the day of screening visit 1

107 This is only applicable for anti-IgE experienced subjects. Subject with CSU who discontinued, is intolerant to, or was an inadequate responder to anti-IgE therapies despite being treated with omalizumab 300 mg Q4W for 6 months or higher doses of omalizumab > 2 months (or per local country treatment standards) or another anti-IgE therapy.

5.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

Disease Related

201 Urticaria is solely due to inducible urticaria

202 Active dermatologic diseases (or conditions) other than chronic urticaria, with urticaria wheals or angioedema symptoms such as urticarial vasculitis, erythema multiforme, cutaneous mastocytosis (urticaria pigmentosa) and hereditary or acquired angioedema (eg, due to C1 inhibitor deficiency)

203 Any other active skin disease associated with chronic itching that might influence, in the investigator's opinion, the study evaluations and results (eg, atopic dermatitis, dermatitis herpetiformis, senile pruritus, etc.)

204 History of a clinically significant infection within 28 days prior to day 1 that, in the opinion of the investigator or medical monitor, might compromise the safety of the subject in the study, interfere with evaluation of the investigational product, or reduce the subject's ability to participate in the study. Clinically significant infections are defined as either of the following:

- 1) a systemic infection; or
- 2) a serious skin infection requiring parenteral antibiotic, antiviral, or antifungal medication

205 Diagnosis of a helminth parasitic infection within 6 months prior to screening visit 1 that had not been treated with or had failed to respond to standard of care therapy

206 Documented medical history of chronic alcohol or drug abuse within 12 months prior to screening visit 1

207 Evidence of active liver disease at screening, including jaundice or aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase greater than twice the upper limit of normal (ULN)

208 Subjects who, in the opinion of the investigator, have evidence of active tuberculosis (TB), either treated or untreated, or a positive purified protein derivative (PPD) or QuantiFERON-tuberculosis Gold Plus (QFT-Plus) test for TB during screening. Subjects with an indeterminate QFT-Plus may be enrolled if they have ALL of the following:

- No symptoms of TB: productive, prolonged cough (> 3 weeks); coughing up blood; fever; night sweats; unexplained appetite loss; unintentional weight loss
- No evidence of active TB on chest radiograph within 3 months prior to the first dose of investigational product. Note: Chest radiograph is not part of screening procedure and will be the responsibility of the Investigator as this is outside the scope of this protocol

Note: If required, QFT-plus test can be repeated. Subjects with the repeated indeterminate QFT-plus should be excluded from the study.

209 History of malignancy, except for basal cell carcinoma or in situ carcinoma of the cervix treated with apparent success with curative therapy ≥ 12 months prior to screening or other malignancies treated with apparent success with curative therapy ≥ 5 years prior to screening visit 1

210 Subject is unable to complete an electronic patient diary or complete questionnaires, or does not meet the required level of compliance with the eDiary during the 14 days sgAH stabilization period

- Completion of UAS (daily) for < 11 of 14 days prior to randomization, or
- Completion of AAS (daily) for < 11 of 14 days prior to randomization

Other Medical Conditions

211 Medical examination or laboratory findings that suggest the possibility of decompensation of co-existing conditions for the duration of the study. Any items that are cause for uncertainty must be reviewed and approved by the Medical Monitor

212 History or evidence of severe depression, schizophrenia, previous suicide attempts, or suicidal ideation

Prior/Concomitant Therapy

213 Treatment with any biologic products (eg, omalizumab, ligelizumab) within 4 months or 5 half-lives (whichever is longer) prior to screening visit 1

214 Routine (daily or every other day for 5 or more consecutive days) use of systemic corticosteroids within 30 days prior to screening visit 1

215 Routine (daily or every other day for 5 or more consecutive days) use of systemic hydroxychloroquine within 30 days prior to screening visit 1

216 Routine (daily or every other day for 5 or more consecutive days) use of methotrexate, cyclosporine A, cyclophosphamide, tacrolimus, azathioprine, and mycophenolate mofetil within 30 days prior to screening visit 1

217 Undergone plasmapheresis within 30 days prior to screening visit 1

218 Major surgery within 8 weeks prior to screening visit 1 or planned inpatient surgery or hospitalization during the study period

219 Receipt of Ig or blood products within 30 days prior to screening visit 1

220 Regular (daily or every other day) treatment with oral doxepin within 14 days prior to screening visit 1

221 Vaccination with a live or attenuated vaccine within 30 days prior to screening visit 1. Receipt of **COVID-19 vaccines and** inactive/killed vaccinations

(eg, inactive influenza) **are** allowed, provided the vaccinations are not administered within 7 days before or after any study dosing visit

222 Known hypersensitivity, including severe hypersensitivity reactions and/or history of anaphylactic shock, to omalizumab or any ingredient of Xolair

223 History of or known hypersensitivity, including severe hypersensitivity reactions, and/or history of anaphylactic shock, to any biologic therapy, to any of the products or components to be administered during dosing or to products of similar chemical classes (ie, to murine, chimeric, or human antibodies)

Prior/Concurrent Clinical Study Experience

224 Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending the previous non-biologic clinical study, or less than 4 months or 5 half-lives (whichever is longer) since ending the treatment on another biologic clinical study.

Diagnostic Assessments

225 Any clinically meaningful abnormal finding in physical examination, vital signs, hematology, clinical chemistry, or urinalysis during the run-in period, which in the opinion of the investigator, may put the subject at risk because of participation in the study, or may influence the results of the study, or the subject's ability to complete the entire duration of the study

226 Positive hepatitis B surface antigen and Hepatitis B core antibody (if a country requirement), or hepatitis C antibody serology. Subjects with a history of hepatitis B vaccination without a history of hepatitis B can enroll in the study.

227 Positive human immunodeficiency virus (HIV) test at screening or the subject is taking antiretroviral medications, as determined by medical history, prior medications, and/or the subject's verbal report

Other Exclusions

228 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for 16 weeks after the last dose of any protocol-required therapy. Females of childbearing potential should only be enrolled in the study after a negative highly sensitive serum pregnancy test

229 Female subjects of childbearing potential unwilling to use 1 highly effective method of contraception during treatment and for 16 weeks after the last dose of any protocol-required therapy. Refer to Section 11.5 for additional contraceptive information

230 Female subjects of childbearing potential with a positive pregnancy test assessed at screening and/or day 1 by a serum pregnancy test.

231 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, patient-reported outcome [PRO] Assessments) to the best of the subject and investigator's knowledge

232 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion

5.3 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see Section 11.3).

The subject or subject's legally acceptable representative must personally sign and date the IRB/IEC approved informed consent before commencement of study-specific procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (at the time of signing the informed consent) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by IRT. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened. This number will not necessarily be the same as the randomization number assigned for the study.

The sponsor will monitor the study population baseline characteristics during enrollment. If necessary, the sponsor may restrict enrollment of certain populations in order to ensure the appropriate distributions of subject characteristics.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized into the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Refer to Section 8.1.1.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen failure. Screen failure subjects may be eligible for

rescreening once. Subjects who fail to meet inclusion criterion #105 relating to disease severity at baseline as reported in the eDiary after the 2-week sgAH stabilization period (UAS7 score [range: 0 to 42] ≥ 16 and HSS7 [range: 0 to 21] ≥ 8 during the 7 days prior to randomization) will not be eligible for rescreening.

5.5 Antihistamine Stabilization Period

A minimum of 14 days sgAH stabilization period is required prior to randomization. Each subject should maintain a stable dose of the sgAH (up to 4x approved dose) prescribed by their treating physician for at least 14 days prior to determination of eligibility for enrollment as described in Section 6.4.1.

Subjects who do not meet the inclusion criteria #105 of UAS7 and HSS7 at baseline after the sgAH stabilization period and/or satisfy the daily eDiary completion compliance criteria for UAS and AAS (Exclusion #210) will not be eligible to enroll into the study.

Subjects should maintain a stable dose of sgAH as the background medication from screening visit 2 throughout the study treatment and follow-up period, up to the EOS visit.

Rescue medication is permitted up to 4x the approved dose of the same sgAH used as the background medication, if necessary, for worsening of urticaria symptoms (eg, daily UAS maximum score of 6, angioedema).

6. Treatments

Study treatment is defined as any investigational product(s), non-investigational product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment shown in Table 6-1 below. Information on

preparation, handling, storage, accountability, destruction, or return of the investigational product during the study are provided in the IPIM.

6.1 Treatment(s) Administered

6.1.1 Investigational Products

The quantity of investigational product administered, dose start date/time, and box number are to be recorded on each subject's CRF. The site's unblinded pharmacist/administrator will prepare the appropriate dose of the investigational product (tezepelumab, omalizumab, or placebo) as per the randomization schedule for each subject. The unblinded administrator will provide the appropriate treatment for each subject.

Table 6-1. Study Treatments

Study Treatment Name	Amgen Investigational Product:[a] Tezepelumab	Placebo	Non-Amgen Investigational Product:[b] Omalizumab (Xolair®)
Dosage Formulation	[redacted] mg/mL in [redacted] mM acetate, [redacted] % weight/volume L-proline, [redacted] % weight/volume polysorbate 80, pH [redacted]	[redacted] % weight/volume sodium carboxy methyl cellulose in [redacted] mM acetate, [redacted] mM L-proline, [redacted] % weight/volume polysorbate 80, pH [redacted]	150 mg/mL in a pre-filled syringe (PFS) (Xolair)
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	Each subject will receive 2 injections per visit. For subjects randomized to 210 mg Q4W and 420 mg Q2W, volumes for injections from vials will be detailed in the IPIM. Subjects randomized to Q4W dosing will receive placebo at intervening visits, such that all subjects receive an injection Q2W.	Each subject will receive 2 injections per visit. For subjects randomized to placebo, volumes for injections from vials provided will be detailed in the IPIM. Subjects will receive placebo dosing Q2W.	Each subject will receive 2 injections per visit. For subjects randomized to 300 mg Q4W, volumes for injections from PFS will be detailed in the IPIM. Subjects randomized to Q4W dosing will receive placebo at intervening visits, such that all subjects receive an injection Q2W.
Route of Administration	SC injection	SC injection	SC injection
Accountability	The quantity, dose start date/time, and box number of investigational product are to be recorded on each subject's CRF(s).	The quantity, dose start date/time, and box number of investigational product are to be recorded on each subject's CRF(s).	The quantity, dose start date/time, and box number of investigational product are to be recorded on each subject's CRF(s).
Dosing Instructions	Investigational product will be administered by qualified study center personnel as the final activity for each study visit. The window for study visits is ± 3 days. Injection sites are to be rotated. Subjects will be observed for 2 hours post-treatment at the day 1 and week 2 visits. For all other visits where investigational product is administered, subjects will be observed for a period of time at the discretion of the Investigator.	Investigational product will be administered by qualified study center personnel as the final activity for each study visit. The window for study visits is ± 3 days. Injection sites are to be rotated. Subjects will be observed for 2 hours post-treatment at the day 1 and week 2 visits. For all other visits where investigational product is administered, subjects will be observed for a period of time at the discretion of the Investigator.	Investigational product will be administered by qualified study center personnel as the final activity for each study visit. The window for study visits is ± 3 days. Injection sites are to be rotated. Subjects will be observed for 2 hours post-treatment at the day 1 and week 2 visits. For all other visits where investigational product is administered, subjects will be observed for a period of time at the discretion of the Investigator.

CRF = case report form; IPIM = Investigational Product Instruction Manual; PFS = prefilled syringe; SC = subcutaneous; Q2W = every 2 weeks; Q4W = every 4 weeks
[a] Tezepelumab will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.
[b] Omalizumab will be manufactured and packaged by Novartis Pharmaceuticals Corporation and/or Genentech, Inc. and distributed using Amgen (or designee) clinical study drug distribution procedures.

6.1.2 Non-Amgen Investigational Products

Not applicable.

6.1.3 Medical Devices

The following non-Amgen investigational combination product provided by Amgen for use in this study is Omalizumab (Xolair®) with prefilled syringe (Table 6-1).

Non-Amgen investigational combination product Xolair® with prefilled syringe is a single-use, disposable, handheld, mechanical "spring-based" device for fixed dose subcutaneous injection of 150 mg/mL.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-investigational medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.1.4 Other Protocol-required Therapies

A stable dose of sgAH is required daily throughout the entire duration of the study from screening visit 2 to the EOS visit. See Section 6.1.5.1.

6.1.5 Other Treatment Procedures

6.1.5.1 Background Medication

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.

Examples of an acceptable approved sgAH include 1 tablet daily of the following: cetirizine 10 mg, desloratadine 5 mg, ebastine 10 mg, fexofenadine 120 mg, levocetirizine 5 mg, loratadine 10 mg, and rupatadine 10 mg (van den Elzen et al, 2017). The investigator should instruct the subject to notify the study site of any new medications he/she takes after enrollment into the study. All medications and procedures administered after the subject was enrolled into the study must be recorded

on the respective CRF pages. The therapy name, indication, dose, unit, frequency, route, start date, and stop date should be recorded. Background sgAH medication will be sourced locally. Subjects will record daily use in the eDiary.

6.1.5.2 Rescue Medication

The same sgAH that the subject is on at screening visit 2 will be allowed as a rescue medication at up to 4x the approved dose. A switch of the rescue medication for an individual subject is not permitted. Subjects should be directed to use rescue medication dosing only if there is worsening of urticaria symptoms (eg, a daily UAS score of 6 or angioedema). All sgAH rescue medication will be sourced locally. Use of rescue medication (number of tablets taken over the past 24 hours) will be recorded daily in the subject's eDiary. The dose per day of rescue medication will be calculated as the additional daily number of tablets. The dose per week will be calculated as the sum of the dose per day (daily dose plus rescue medication), over 7 days.

All subjects are to be encouraged to complete the schedule of study visits and assessments whether or not they complete study treatment or receive rescue treatment.

6.1.6 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any investigational product(s), device(s) or combination product(s) provisioned and/or repackaged/modified by Amgen.

Any product complaint(s) associated with an investigational product(s), non-investigational products(s), devices(s), or combination product(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

6.1.7 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

Initiation of the following classes of treatments is NOT allowed after the start of screening (visit 1).

- anti-IgE therapy
- systemic corticosteroids
- systemic hydroxychloroquine

- methotrexate, cyclosporine A, cyclophosphamide, tacrolimus, azathioprine, and mycophenolate mofetil
- H2 antagonists (H2 blockers)
- leukotriene receptor antagonists (LTRAs)

  Note: For LTRAs and H2 blockers, if they are used for the conditions other than CSU and a stable dose was maintained at least 4 weeks prior to visit 1, and no dose change during the study, they are not prohibited from use.
- intravenous or intramuscular IgG
- plasmapheresis
- doxepin (oral)
- live attenuated vaccines

Each concomitant drug must be individually assessed against all exclusion criteria. If in doubt, the investigator should contact the sponsor or delegate before randomizing a subject or allowing a new medication to be started.

If the prohibited treatment was inadvertently used during the study for an indication other than CSU, the subject must immediately discontinue use of the prohibited treatment if he/she wishes to continue in the study. Medication should be assessed for adherence to the indication and other inclusion/exclusion criteria.

Systemic corticosteroids (SCS) and anti-inflammatory medications are not recommended for the treatment for CSU, and are prohibited medications for this study.

If a subject uses SCS during the treatment period, the event will be handled as an intercurrent event. The subject may continue IP treatment if no safety concerns judged by the investigator and the sponsor. Any marketed or investigational biologics (eg, dupilumab and omalizumab) are not allowed within 4 months or 5 half-lives (whichever is longer) prior to visit 1, during study period and 4 months or 5 half-lives (whichever is longer) after last dose of investigational product.

All subjects are to complete the schedule of study visits and assessments whether or not they complete study treatment or receive rescue medication.

6.2 Dose Modification

6.2.1 Dose-cohort Study Escalation/De-escalation and Stopping Rules

There are no dose-cohort study escalation/de-escalation and/or stopping rules in this study.

6.2.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

6.2.2.1 Amgen Investigational Product: Tezepelumab

The reason for dose change of tezepelumab is to be recorded on each subject's CRF(s). No dose changes are permitted for tezepelumab.

An individual subject may be discontinued at the discretion of the investigator and/or the sponsor due to clinically significant events.

Subjects who receive rescue medications may continue treatment with study drug, per the instructions outlined in Section 6.1.5.2.

6.2.2.2 Non-Amgen Investigational Product(s): Omalizumab

The reason for dose change of omalizumab is to be recorded on each subject's CRF(s). No dose changes are permitted for omalizumab.

Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of omalizumab. Anaphylaxis has occurred after the first dose of omalizumab but also has occurred beyond 1 year after beginning treatment. Closely observe patients for an appropriate period of time after omalizumab administration and be prepared to manage anaphylaxis and have them seek immediate medical care should symptoms occur. Additional information on risks associated with omalizumab will be found in the local medical health authority approved product information.

Subjects experiencing a severe hypersensitivity reaction to study drug must discontinue treatment.

6.2.3 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 11.7 for details regarding drug-induced liver injury (DILI) guidelines, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

6.3 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product during the study are provided in the IPIM.

6.4 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Method of Treatment Assignment

After meeting all randomization requirements described in Section 4.1, subjects who are symptomatic despite treatment with a sgAH and are anti-IgE naïve will be randomized in

a 1:1:1:1 allocation ratio to 1 of 2 tezepelumab treatment groups, omalizumab, and placebo, respectively. Subjects who are symptomatic despite treatment with a sgAH and are anti-IgE experienced (intolerant, inadequate responder, or discontinued for other reason), will be randomized in a 1:1:1 ratio to 1 of 2 tezepelumab treatment groups and placebo, respectively.

The randomization will be stratified by:

1. anti-IgE naïve versus anti-IgE experienced
2. [redacted]
3. disease severity (UAS7 at baseline $\geq$ 28 versus $<$ 28)

The randomization will be performed by the IRT system. The randomization number will be provided to the site through an IRT. [redacted]

The randomization date is to be documented in the subject's medical record and on the enrollment CRF.

6.4.2 Blinding

Treatment assignment will be blinded to all subjects, site personnel (with the exception of the pharmacist and study drug administrator), and Amgen as described below.

6.4.2.1 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment is to only be unblinded by the investigator when knowledge of the treatment is essential for the further management of the subject on this study or may potentially impact the safety of the subject. Unblinding at the study site, by anyone other than the unblinded pharmacist and the unblinded study drug administrator, for any other reason will be considered a protocol deviation. It is encouraged that the Amgen Trial Manager and the Amgen Medical Monitor be notified before the blind is broken unless the investigator believes that identification of the study treatment is required for a medical emergency. If this is not possible, the Amgen Trial Manager and Amgen Medical Monitor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation. An unblinded pharmacist and unblinded study drug administrator will have access to the treatment based on the randomization list from the IRT. A description of how responsible investigators will access treatment information, in the event that there is a need to break the blind will be detailed in the IPIM.

6.4.2.2 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information is not to be distributed to the study team, investigators, or subjects prior to the study being formally unblinded (eg, the formal unblinding may occur at the final analysis rather than during the primary analysis) except as specified (eg, Section 6.4.2.1).

Pre-identified members of the team may be unblinded following the Primary Analysis; however, the investigators, subjects, and members of the study team who interact with sites or are involved in decision making on the conduct of the study will not have access to unblinding information until the study is formally unblinded at the Final Analysis. Any member of the clinical study team that is unblinded at the Primary Analysis must be replaced by a blinded team member.

Staff from Clinical Supply Chain, Biological Sample Management, Clinical Pharmacology Modeling and Simulation, Computational Biology, Clinical Immunology, Clinical Biomarkers and Diagnostics, and Global Biostatistical Sciences departments who are responsible for tracking, assaying, or analyzing biological samples during the conduct of this study are considered unblinded to the treatment assignments in this study. These individuals will not to have access to subject level clinical data apart from the samples they are assaying and analyzing during the course of the study.

If interim analysis and/or exposure-response analysis is performed, the interim analysis team and/or exposure-response analysis team, including Clinical Pharmacology Modeling and Simulation, Global Biostatistics Sciences, and Biostatistical programming, who are independent of the study team, may be unblinded. The analysis plan and data integrity document for the exposure-response analysis will detail the analyses and describe the timing for unblinding according to Amgen's standard operating procedure.

6.5 Treatment Compliance

Subjects will receive the SC doses of investigational product at the study centers. The doses will be administered by qualified study personnel for the duration of the study. All efforts should be made to administer investigational product within the defined study windows. In the case of an out of window visit, investigational product can be administered within 1 week of the target visit day (ie, calculated from the day 1 visit). If investigational product cannot be administered within 1 week of the target visit date, the dose is considered missed. If a subject arrives for a visit and investigational product was

administered within < 1 week prior, the dose should not be administered, but all other study procedures should be conducted and administration of investigational product should occur as soon as possible at least 1 week after the previous administration.

6.6 Treatment of Overdose

There is currently no specific treatment in the event of overdose of tezepelumab and the effects of overdose of this product are not known. An overdose with associated adverse events is recorded as the adverse event diagnosis/symptoms on the relevant adverse event modules in the Event CRF.

6.7 Prior and Concomitant Treatment

6.7.1 Prior Treatment

Prior therapies that were being taken/used from 5 years prior to screening through the first dose of investigational product will be collected.

For all prior therapies, therapy name, indication, dose, unit, frequency, route, start date and stop date, specifically prior CSU therapies, should be collected.

6.7.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.1.7.

Concomitant therapies are to be collected from the first dose of investigational product through the EOS. Therapy name, indication, dose, unit, frequency, route, start date and stop date should be collected.

Allowed concomitant treatments and directions pertaining to rescue therapy are outlined in Section 6.1.5.2.

7. Discontinuation Criteria

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 7.1, 7.2.1, and 7.2.2.

7.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (SoA) (Table 1-1) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 11.3.

Reasons for early removal from protocol-required investigational product(s) or procedural assessments may include any of the following:

- Decision by Sponsor
- Lost to follow-up
- Death
- Ineligibility determined
- Protocol deviation
- Non-compliance
- Adverse event
- Subject request
- Pregnancy or breastfeeding
- Disease flare requiring treatment not allowed in the protocol

7.2 Discontinuation From the Study

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is

unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study, and must document the subject's decision to withdraw in the subject's medical records.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Section 11.6 for further details). Refer to the SoA (Table 1-1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.2.1 Reasons for Removal From Washout Period, Run-in Period, or Invasive Procedures

Not applicable to this study.

7.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- Decision by sponsor
- Withdrawal of consent from study
- Death
- Lost to follow-up

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

- For subjects who are lost to follow-up, the investigator can search publicly available records where legally permitted to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

8. Study Assessments and Procedures

Study procedures and their time points are summarized in the SoA (see Table 1-1).

As protocol waivers or exemptions are not allowed if a randomized subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Telemedicine and home healthcare visits may be implemented at randomization/day 1 onward, where circumstances outside the subject's, site's, and sponsor's control (eg, pandemic) result in study visits being unable to be conducted. The sponsor must authorize use of these approaches in advance of each visit and this approach may only be used where allowable by local health authorities, ethics committees, and healthcare provider guidelines (eg, hospital policies). The minimum possible number of visits should occur outside the clinic, and visits should return to "in-clinic" at the earliest possible opportunity.

8.1 General Study Periods

8.1.1 Screening, Enrollment and/or Randomization

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the ICF, the site will register the subject in the IRT and screen the subject in order to assess eligibility for participation. The screening window is a maximum of 42 days.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, (see Section 5.4) as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen failure. Screen failure subjects may be eligible for rescreening once. Subjects who fail to meet inclusion criteria related to disease severity

at baseline as reported in the eDiary after the 2 week sgAH stabilization period (UAS7 score [range: 0 to 42] ≥ 16 and HSS7 [range: 0 to 21] ≥ 8 during the 7 days prior to randomization) will not be eligible for rescreening.

Rescreen subjects must first be registered as screen failures in IRT and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 42-day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 30 days after the original signing of the ICF, all screening procedures, including informed consent, must be repeated.

8.1.2 Treatment Period

Visits will occur per the SoA (Table 1-1). The window for study visits is ± 3 days. The date of the first dose of investigational product is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Administration of investigational product is to occur following completion of all other study activities for each visit.

8.1.3 Safety Follow-up

The safety follow-up period begins after the week 16 visit and continues through week 32. Safety follow-up visits will occur at weeks 24 and week 32/EOS (Table 1-2). All subjects who terminate the study early will complete an ET visit consisting of all assessments included in the EOT (week 16) visit. In addition, safety follow-up visits will occur at 8 weeks and 16 weeks after the EOT visit. In the event a patient is unable to have a safety follow-up visit, the site will attempt to contact the subject by telephone to obtain safety information.

8.1.4 End of Study

The EOS visit will occur 16 weeks after the EOT visit at week 16 (at week 32/18 weeks after the final dose of investigational product) (Table 1-2).

8.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required timepoints.

8.2.1 General Assessments

8.2.1.1 Informed Consent

All subjects must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed.

8.2.1.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study the impact on biomarkers variability and PK of the protocol-required therapies.

8.2.1.3 Medical History

The investigator or designee will collect a complete medical history that started within 5 years prior to enrollment through informed consent. Medical history will include information on the subject's concurrent medical conditions, specifically CSU history and medication use. Record all findings on the medical history CRF. In addition to the medical history above, CSU history, including information on prior use of anti-IgE therapy for subjects in the anti-IgE experienced stratum, must date back to the original diagnosis.

8.2.1.4 Physical Examination

Physical examination will be performed as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

8.2.1.5 Physical Measurements

Height in centimeters should be measured without shoes. Weight in kilograms should be measured without shoes.

8.2.1.6 Substance Abuse History

Obtain a detailed history of prior and/or concurrent use of drugs, alcohol, tobacco, and caffeine.

8.2.2 Efficacy Assessments

8.2.2.1 Patient-Reported Outcomes (PRO)

At each timepoint, as indicated in Table 1-1, PROs are to be assessed prior to any other assessments.

8.2.2.1.1 Electronic Diary (eDiary)

The eDiary, which includes certain PRO measures, will be completed by the subject at home each morning using an electronic device according to the SoA (Table 1-1) 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. The subject should bring the eDiary to each study visit.

8.2.2.1.2 Urticaria Activity Score (UAS)

The UAS is a CSU-specific PRO measure mainly used to assess CSU activity/severity and treatment response. It contains 2 components: the **Hives 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-hour**s**, and the summed result **of daily HSS and ISS** gives a daily UAS score **(**range: 0 to 6 points/day**)**. **The daily UAS** score summed over a **7-day period gives** a weekly **UAS score (UAS7) (**range**:** of 0 to 42 points**)** (Mathias et al, 2012a).

0	Itch and hive free — indicative of no symptoms of CSU and considered a full 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

The HSS component of the UAS assigns a score of 0, 1, 2, or 3 points for no wheals, $<$ 20 wheals, 20 to 50 wheals, and $>$ 50 wheals per day, respectively (Hawro et al, 2018). The minimal important difference (MID) for UAS7 is between 9.5 and 10.5 points (equivalent to 10 points). The UAS is the current standard for measuring signs and symptoms, as well as disease activity in CSU and is used in clinical care and trials (Zuberbier et al, 2018; Hawro et al, 2018). Once daily UAS is recommended by treatment guidelines (Zuberbier et al, 2018) and is what will be used in this study.

8.2.2.1.3 Angioedema Activity Score (AAS)

The AAS is a prospective 5-item PRO measure used to determine angioedema activity (Weller et al, 2013). Subjects document, as part of the daily diary, each morning, the presence or absence of angioedema during the past 24 hours. If angioedema was present, subjects score 5 key factors (duration, physical discomfort, impact on daily activities, impact on appearance, and overall severity) each with 0 to 3 points. The AAS daily score ranges from 0 to 15 points. The daily AAS scores are summed for 7 days to form the Angioedema Activity Score over 7 days (AAS7). The MID for AAS7 is 8 points

(Weller et al, 2013). The AAS will be measured once daily according to the SoA (Table 1-1).

8.2.2.1.4 Sleep Related Outcomes

The sleep related outcomes consist of 4 daily items: 1 sleep interference score and 3 items on sleep quality. 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 sleep quality items consist of 3 questions: falling asleep, wakefulness, and feeling rested in the morning. These are adapted from the chronic urticaria quality of life questionnaire (CU-Q2oL) sleep items (Baiardini et al, 2011; Baiardini et al, 2005).

Details on the questions are as follows:

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

   Response options range from 0 to 3, where:
   0 = No difficulty
   1 = A little difficulty
   2 = Moderate difficulty
   3 = A lot of difficulty

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

   Response options range from 0 to 3, where:
   0 = Not at all
   1 = Rarely
   2 = Occasionally
   3 = Quite often

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

   Response options range from 0 to 3, where:
   0 = Not at all

1 = Slightly

2 = Moderately

3 = Very much

Each diary item will be summed to generate a weekly score (range: 0 to 21). **The order of item 3 response will be reversed in the analysis so that a** higher score indicates poorer sleep quality/greater sleep interference.

8.2.2.1.5 Patient Global Impression of Severity (PGI-S)

The Patient Global Impression of Severity (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 to very severe symptoms). The PGI-S will be completed by the subject at the study center according to the SoA (Table 1-1).

8.2.2.1.6 Patient Global Impression of Change (PGI-C)

The Patient Global Impression of Change (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. The PGI-C will be completed by the subject at the study center according to the SoA (Table 1-1).

8.2.2.1.7 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). The UCT will be completed by the subject at the study center according to the SoA (Table 1-1).

8.2.2.1.8 Angioedema Control Test (AECT)

This PRO measure is only applicable for subjects with angioedema. The Angioedema Control Test (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, 2020a). Subjects answer the 4 questions with 5 answer options based on their symptoms over the last 3 months. The results of the validation of the AECT have been validated (Weller et al, 2020b). Angioedema control test scores range from 0 to 16 points. A cutoff value of $\geq$ 10 points is used to identify well-controlled disease and $<$ 10 points is used to identify poorly controlled disease (Weller et al, 2020b). The MID has not been established (Weller et al, 2020a). The AECT will be completed by the subject at the study center according to the SoA (Table 1-1).

8.2.2.1.9 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 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). A study by Kulthanan et al suggests that the minimal clinically important difference 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 SoA (Table 1-1).

8.2.2.1.10 Angioedema Quality of Life Questionnaire (AE-QoL)

This PRO measure is only applicable for subjects with angioedema. The Angioedema Quality of Life Questionnaire (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, 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 minimal clinically important difference 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 SoA (Table 1-1).

8.2.2.1.11 Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index (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 dermatology-related symptoms and feelings (embracement), impacts on daily activities, leisure, work or school, personal relationships, and the side effects of treatment. 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 (Basra et al, 2008). The DLQI is validated in CSU and the established MID is 2.24 (Shijkar et al, 2005). The DLQI will be completed by the subject at the study center according to the SoA (Table 1-1).

8.2.2.1.12 Work Productivity and Activity Impairment Questionnaire: Chronic Urticaria (WPAI-CU)

The Work Productivity and Activity Impairment Questionnaire: Chronic Urticaria (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 SoA (Table 1-1).

8.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the SoA see (Table 1-1).

8.2.3.1 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF. Record all measurements on the vital signs CRF.

8.2.3.2 Vital Status

Vital status must be obtained for all subjects within the limits of local law. This includes subjects who may have discontinued study visits with or without withdrawing consent and should include interrogation of public databases, if necessary. If deceased, the date and reported cause of death should be obtained.

8.2.4 Adverse Events and Serious Adverse Events

Treatment-emergent adverse events are events categorized as adverse events starting or worsening on or after the first dose of investigational product as determined by "did the event start before the first dose of investigational product" equal to "No" or missing on the events CRF and up to the EOS date.

8.2.4.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

8.2.4.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the Amgen Standard Grading Scale, and is described in Section 11.4. The investigator is responsible for ensuring that any adverse events related to study procedures that were observed by the investigator or reported by the subject that occur after screening visit 2 through the EOS/safety follow-up or 18 weeks after the last administration of investigational product are collected and reported using the Event CRF. In addition, the investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after the first dose of investigational product are collected and reported using the Event CRF.

8.2.4.1.2 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the EOS visit are reported using the Event CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours of the investigator's knowledge of the event, as indicated in Section 11.4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available. It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix 4 (Section 11.4). An AE of severe intensity need not necessarily be considered serious unless it meets the criteria shown in Appendix 4 (Section 11.4).

8.2.4.1.3 Serious Adverse Events After the Protocol-required Reporting Period

If the investigator becomes aware of serious adverse events after the protocol-required reporting period is complete, these serious adverse events will be reported to Amgen (regardless of causality). The investigator will report serious adverse events to Amgen within 24 hours following the investigator's awareness of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product.

If further safety related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.

The method of recording, evaluating, and assessing causality of adverse events, and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Section 11.4.

8.2.4.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

8.2.4.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 11.4.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

8.2.4.4 Regulatory Reporting Requirements for Serious Adverse Events

If subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities. Aggregate analyses may also be unblinded by the Safety Assessment Team, as appropriate. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

8.2.4.5 Safety Monitoring Plan

Subject safety will be routinely monitored as defined in Amgen's safety surveillance and signal management processes.

8.2.4.6 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects or the female partner of a male subject, will be collected after the start of study treatment and through 16 weeks after the last dose of any protocol required therapy.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in

Section 11.5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Section 11.5.

8.2.4.7 Adverse Events of Interest

An adverse event of interest is an event of scientific and medical interest towards improving the understanding of the investigational product. An adverse event of interest may be serious or non-serious. For this study, 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

Please refer to the section of the important Key Safety Information or additional information regarding adverse events of interest in the current active Investigator's Brochure.

8.2.5 Clinical Laboratory Assessments

Refer to Section 11.2 for the list of clinical laboratory tests to be performed and to the SoA (Table 1-1) for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event CRF. The investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

All protocol-required laboratory assessments, as defined in Section 11.2, must be conducted in accordance with the laboratory manual and the SoA (Table 1-1).

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded. Total

IgE, and eosinophils on complete blood count and differential are considered unblinding data for this study. Pharmacokinetic and anti-drug antibody (ADA) testing and results should always be blinded until end of study. Additional details regarding potentially unblinding data and study personnel are provided in Section 6.4.2.2.

8.2.5.1 Tuberculosis Testing

All subjects must receive either a purified protein derivative (PPD) or QuantiFERON test at screening and EOT/ET.

The PPD test must be read by a trained healthcare professional 48 to 72 hours after the test is placed. The PPD reader must be identified on the delegation of authority for this responsibility.

If a subject does not receive a PPD test, they must have QuantiFERON testing. Refer to the laboratory manual for instructions on sample collection, processing, and shipping of samples.

8.2.5.2 Pregnancy Testing

A highly sensitive serum pregnancy test should be completed at screening and a highly sensitive urine test should be completed at the day 1 visit for females of childbearing potential.

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Form, see Figure 11-2). Refer to Section 11.5 for contraceptive requirements.

Additional pregnancy testing should be performed Q4W during treatment with protocol-required therapies and at weeks 24 and 32 (18 weeks after the last dose of protocol-required therapies).

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

8.2.6 SARS-CoV-2 Serology (Antibody) Testing

For subjects who received COVID-19 (SARS-CoV-2) vaccination, a SARS-CoV-2 serology (antibody) test will be done approximately 4 weeks after the last dose of vaccination and at a scheduled visit. Instructions for sample collection, processing, storage, and shipment will be included in a separate laboratory manual provided to the sites.

8.2.7 Pharmacokinetic Assessments

All subjects randomized to treatment with tezepelumab will have PK samples assessed. Whole blood samples of approximately 5 mL will be collected for measurement of serum concentrations of tezepelumab as specified in the SoA (Table 1-1). A maximum of 2 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.2.8 Pharmacodynamic Assessments

Venous blood samples will be collected for measurement of [redacted], and [redacted] at time points specified in the SoA (Table 1-1).

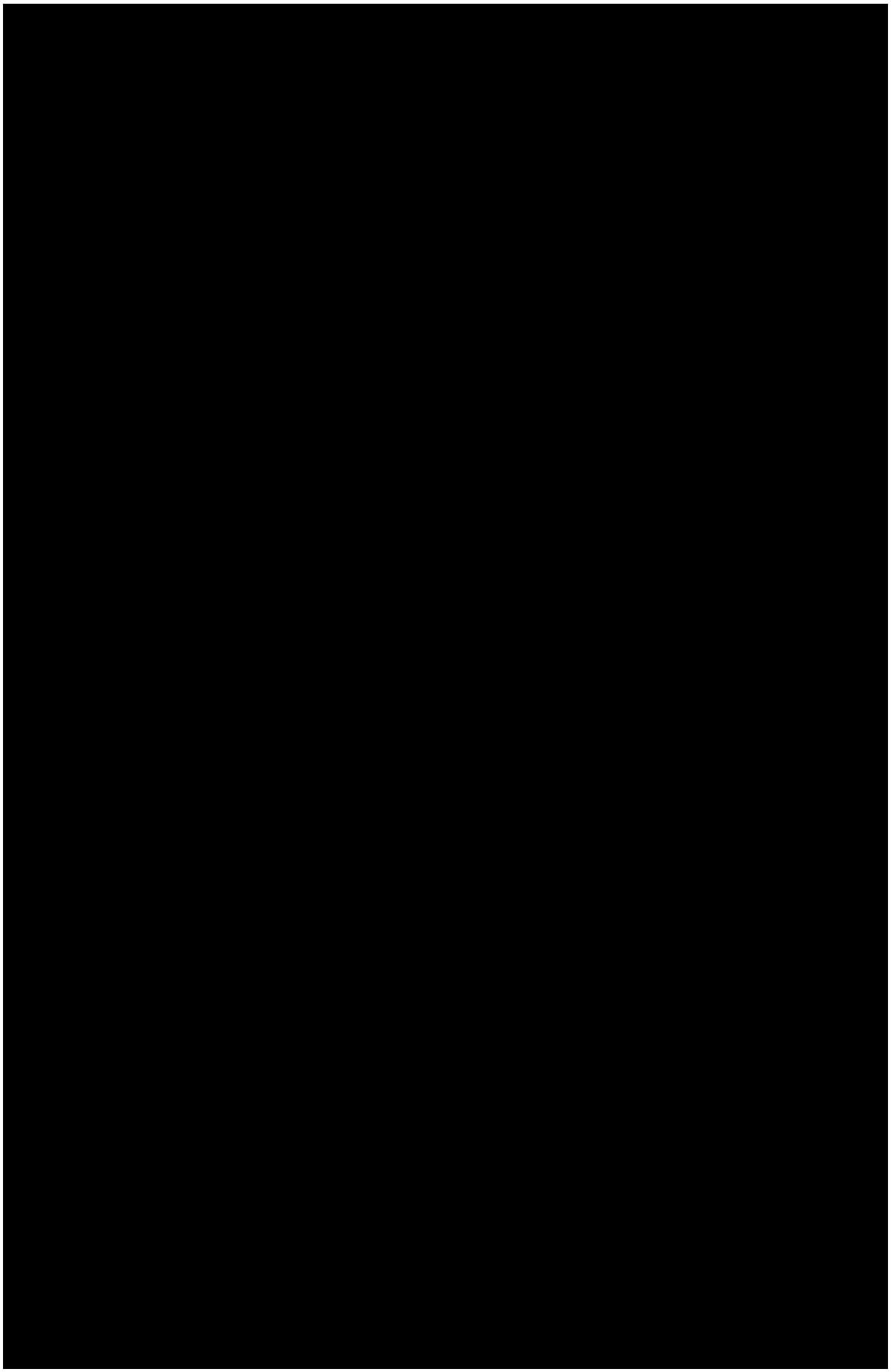
[redacted]

8.2.10 Anti-drug Antibody Testing Procedures

Blood sample(s) for anti-drug antibody testing are to be collected according to the time points specified in the SoA (Table 1-1). Antibody testing will only be conducted if there is unexplained loss of exposure to tezepelumab or a potentially antibody-related safety concern. Samples testing positive for binding antibodies may be further characterized.

Refer to the laboratory manual for detailed collection and handling instructions.

[redacted]



9. Statistical Considerations

9.1 Statistical Hypotheses

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, tezepelumab 420 mg SC Q2W and 210 mg SC Q4W compared to placebo **in the overall and** the anti-IgE naïve **population** will be tested **sequentially** using the Bonferroni procedure to control for the type 1 error rate **adjusting** for **covariates specified in Section 9.3.2**.

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.

9.2 Sample Size Determination

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**i**s 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].

9.3 Analysis Sets, Subgroups, and Covariates

9.3.1 Analysis Sets

9.3.1.1 All Subjects Randomized

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

9.3.1.2 Full Analysis Set (FAS)

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 as a randomized treatment group as intent-to-treat (ITT) concept.

9.3.1.3 Safety Analysis Set (SAS)

The SAS will consist of all randomized subjects who received at least 1 dose of investigational product and analyzed as treated. All safety analyses will be based on the SAS.

9.3.1.4 Pharmacokinetic Analysis Set

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.

9.3.2 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 analysis of other endpoints will be adjusted for the following covariates **as appropriate**:

- Baseline score of endpoint
- Stratification factors:
  - Anti-IgE naïve versus anti-IgE experienced
  - Disease severity (UAS7 at baseline $\geq$ 28 versus $<$ 28)

Additional covariates may be considered and will be described in the statistical analysis plan (SAP).

9.3.3 Subgroups

Two types of subgroup analyses will be conducted: 1) to explore the internal consistency of the detected overall treatment effect on the primary efficacy variable; and 2) to explore a treatment effect in the prespecified subpopulation (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.**

To explore the consistency of treatment effect, subgroup analyses by age, gender, race, baseline disease characteristics, type of background medication, comorbidities, region, and baseline biomarkers may be performed as appropriate. The detailed list of variables and cutoff for subgroup analyses will be described in the SAP. The study is not powered to draw conclusions from the first type of subgroup analysis. The second subgroup

analysis will be conducted as secondary hypotheses on the primary endpoint as described in Section 9.4.2.2 below.

9.3.4 Handling of Missing and Incomplete Data

Missing data for continuous efficacy endpoints will be analyzed 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 considered as nonresponder in efficacy analysis.

9.4 Statistical Analyses

The details of the statistical analyses will be developed in a separate SAP and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the EOS, as defined in Section 4.4.1.

9.4.1 Planned Analyses

9.4.1.1 Interim Analysis and Early Stopping Guidelines

Up to 2 interim analyses will be performed: 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.

The interim analysis will be performed by the internal interim analysis team 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 interim analysis charter and a separate statistical analysis plan.

9.4.1.2 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.

9.4.1.3 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.

9.4.2 Methods of Analyses

9.4.2.1 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. For categorical endpoints, the descriptive statistics will contain frequency and percentage. For continuous endpoints, the descriptive statistics will include the number of observations, mean, standard error, standard deviation, median, first quartile, third quartile, minimum, and maximum.

[redacted]

[redacted]

9.4.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary endpoint of change from baseline in UAS7 at week 16 will be analyzed using a **repeated measure model**. The **repeated measure** model will include treatment, study week, and treatment-by-week interaction, baseline UAS7 score and stratification factor (prior anti-IgE status). Multiple imputation and baseline observation carried forward (BOCF) may be considered for sensitivity analysis for missing data.
Secondary	**The binary secondary endpoint of response rate (eg, UAS7, HSS7, ISS7, AAS7) will be analyzed with generalized estimating equations (GEE). The GEE model will include treatment, study week, and treatment by week interaction, baseline score, and stratification factor (prior anti-IgE status). Multiple nonresponder imputation may be considered for sensitivity analysis.** The continuous secondary endpoints of change from baseline in ISS7, HSS7, AAS7, UCT, CU-Q2oL, DLQI, AE-QoL, AECT, WPAI-CU, and sleep related outcomes will be analyzed using a **repeated measure model** that includes terms for treatment, study week, and treatment-by-week interaction, **baseline continuous value of the endpoint** and stratification factors (prior anti-IgE therapy status). Cumulative frequency of H1-antihistamine rescue medication use and cumulative number of weeks with complete response will be analyzed using a generalized linear model that includes terms for treatment, prior anti-IgE therapy status, and baseline disease severity.
Exploratory	Exploratory endpoints will be described in the SAP finalized before database lock

The efficacy analyses of primary, secondary, and some exploratory endpoints will be performed for all FAS subjects, then for anti-IgE naïve and anti-IgE experienced subjects, respectively, by excluding the stratification factor of prior anti-IgE treatment status from the model.

9.4.2.3 Safety Analyses

9.4.2.3.1 Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies,

and significant treatment-emergent adverse events will also be provided. Subject adverse events of interest, will be tabulated by system organ class and preferred term.

9.4.2.3.2 Laboratory Test Results

Laboratory parameters will be summarized descriptively by treatment group. Mild, moderate, or severe, as defined by the Amgen Standard Grading Scale will be presented for each laboratory parameter, when available.

9.4.2.3.3 Vital Signs

The analyses of vital signs will include summary statistics over time by treatment group. Shifts in vital sign values between the baseline and the worst on-study value will be tabulated by treatment group.

9.4.2.3.4 Physical Measurements

Height and weight will be summarized descriptively as baseline summaries.

9.4.2.3.5 Exposure to Investigational Product

Exposure to investigational product will be summarized by treatment group. Additional details will be provided in the SAP.

9.4.2.3.6 Exposure to Non-investigational Product

Descriptive statistics will be produced to describe the exposure to omalizumab by treatment group. Additional details may be provided in the SAP.

9.4.2.3.7 Exposure to Other Protocol-required Therapy

Descriptive statistics will be produced to describe the exposure to investigational product by treatment group.

9.4.2.3.8 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 will be summarized and analyzed. Details of the analysis will be described in the SAP.

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11. Appendices

11.1 Appendix 1. List of Abbreviations and Definitions of Terms

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
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0\text{-}7d}$	area under the concentration-time curve from day 0 to day 7
$AUC_{0\text{-}28d}$	area under the concentration-time curve from day 0 to day 28
BIL	bilirubin
BOCF	baseline observation carried forward
CFR	U.S. Code of Federal Regulations
C_{max}	maximum observed serum concentration
CMH	Cochran-Mantel-Haenszel
COVID-19	**coronavirus disease 2019**
CRF	case report form
CRO	contract research organization
CSU	chronic spontaneous urticaria
CU-Q2oL	Chronic urticaria Quality of Life Questionnaire
DILI	drug induced liver injury
DLQI	Dermatology Life Quality Index
eDiary	electronic diary
EDC	electronic data capture
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
End of Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Study (primary completion)	defined as the date when the last subject is assessed or receive**d** an intervention **to collect** final data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early
End of Study (end of trial)	defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable

End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
Enrollment	A subject is considered enrolled once the subject is randomized and has received investigational product
EOS	end of study
EOT	end of treatment
ET	early termination
Exposure-Response Analysis	mechanism-based modeling & simulation and statistical analyses based on individual pharmacokinetic (PK) exposure (eg, population pharmacokinetic modeling) and response, which may include biomarkers, pharmacodynamic (PD) effects, efficacy and safety endpoints.
FAS	full analysis set
FDA	**U.S. Food and Drug Administration**
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GEE	**generalized estimating equations**
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
HSS	**Hives Severity Score**
HSS7	Hives Severity Score over 7 days
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IL	interleukin
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IRT	interactive response technology that is linked to a central computer in real time as an interface to collect and process information
ISS	**Itch Severity Score**
ISS7	Itch Severity Score over 7 days
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimal important difference
NCT	National Clinical Trials
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetics

PPD	purified protein derivative
PRO	patient-reported outcome
Q2W	every 2 weeks
Q4W	every 4 weeks
QFT-Plus	QuantiFERON-tuberculosis Gold Plus
QoL	quality of life
Randomization	A subject will undergo randomization upon meeting all eligibility criteria at the day 1 randomization visit
SAP	statistical analysis plan
SAS	Safety Analysis Set
sgAH	second generation antihistamines
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
SC	subcutaneous
SoA	schedule of activities
Study day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
TB	tuberculosis
TBL	total bilirubin
Th2	T helper 2
TSLP	thymic stromal lymphopoietin
UAS	Urticaria Activity Score
UAS7	Urticaria Activity Score over 7 days
UCT	Urticaria Control Test
ULN	upper limit of normal
WHODRUG	World Health Organization Drug Dictionary
WPAI-CU	Work Productivity and Activity Impairment Questionnaire: Chronic Urticaria

11.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 11-1 will be performed by the central laboratory and/or by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 5.1 and 5.2 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 11-1. Analyte Listing

Central Laboratory: Chemistry	Central Laboratory: Coagulation	Central Laboratory: Urinalysis	Central Laboratory: Hematology	Other Labs
Sodium Potassium Chloride Bicarbonate Total protein Albumin Calcium Adjusted calcium Magnesium Phosphorus Glucose BUN or Urea Creatinine Uric acid Total bilirubin Direct bilirubin ALP LDH AST (SGOT) ALT (SGPT) Cholesterol HDL LDL Triglycerides	PT/INR PTT/APTT	Specific gravity pH Blood Protein Glucose Bilirubin WBC RBC Epithelial cells Bacteria Casts Crystals	RBC Nucleated RBC Hemoglobin Hematocrit MCV MCH MCHC RDW Reticulocytes Platelets WBC Differential • Total neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes • Myeloblasts • Promyelocytes • Myelocytes • Metamyelocytes • Atypical lymphocytes	Central Laboratory: Antibodies [redacted] Hep B surface antigen Hep B core antigen[a] Hep C antibody HIV[b] [redacted] IgE Serum pregnancy PPD or QuantiFERON Gold Plus [redacted] SARS-CoV-2 anti body Local Laboratory: Urine Pregnancy

ALP = alkaline phosphatase; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; [redacted] HDL = high density lipoprotein; Hep = hepatitis; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IgE = immunoglobulin E; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PPD = purified protein derivative; PT = prothrombin time; RBC = red blood cell count; RDW = Red cell distribution width; SGOT = serum glutamic-oxaloacetic transaminase; SGPT - serum glutamic-pyruvic transaminase; WBC = white blood cell count

[a] If a country requirement.

[b] HIV assessment is recommended.

[redacted]

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

11.3 Appendix 3. Study Governance Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable ICH laws and regulations

The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and ICF must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the U.S. Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Recruitment Procedures

Recruitment and retention of patients is fundamental to a successful study. We will implement modern innovative methods such as reaching out to social networks and patient advocacy groups.

Informed Consent Process

An initial sample ICF is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the sample ICF are to be communicated formally in writing from the Amgen Trial Manager to the investigator. The written ICF is to be prepared in the language(s) of the potential patient population.

The investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study unless it is a local requirement. The investigator shall then inform the primary care physician. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the ICF is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 7.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

The original signed ICF is to be retained in accordance with institutional policy, and a copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional future research. The investigator or authorized designee will explain to each subject the objectives of the future research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for future research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the Case Report Form (CRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed ICFs) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors must qualify for authorship, and all those who qualify are to be listed. Each author must have participated sufficiently in the work to take public

responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- A recognized expert in the therapeutic area
- An Investigator who provided significant contributions to either the design or interpretation of the study
- An Investigator contributing a high number of eligible subjects

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research and Development Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Retention of study documents will be governed by the Clinical Trial Agreement.

Source Documents

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the interactive response technology (IRT) system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRFs, ICFs, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable
- Non-investigational product(s), and/or medical device(s) or combination product(s) documentation, as applicable

Retention of study documents will be governed by the Clinical Trial Agreement.

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination (ET) and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

11.4 Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure. • Note: Treatment-emergent adverse events will be defined in the statistical analysis plan (SAP).

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an adverse event or serious adverse event.

Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of

the other outcomes listed in the above definition. These events are typically to be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event/serious adverse event information in the Event case report form (CRF).
- The investigator must assign the following adverse event attributes:
  - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Severity (or toxicity defined below);
  - Assessment of relatedness to investigational product, other protocol-required therapies; and
  - Action taken.
- If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Event CRF.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor/responsible contract research organization (CRO) in lieu of completion of the Event CRF page.
- If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity

The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on:

Grade	Definition
MILD	Aware of sign or symptom, but easily tolerated
MODERATE	Discomfort enough to cause interference with usual activity
SEVERE[a]	Incapacitating with inability to work or do usual activity

[a] An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of a serious adverse event, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product protocol-required therapies and/or study-mandated procedure and each occurrence of each adverse event/serious adverse event.
- Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.
- There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.
- The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event

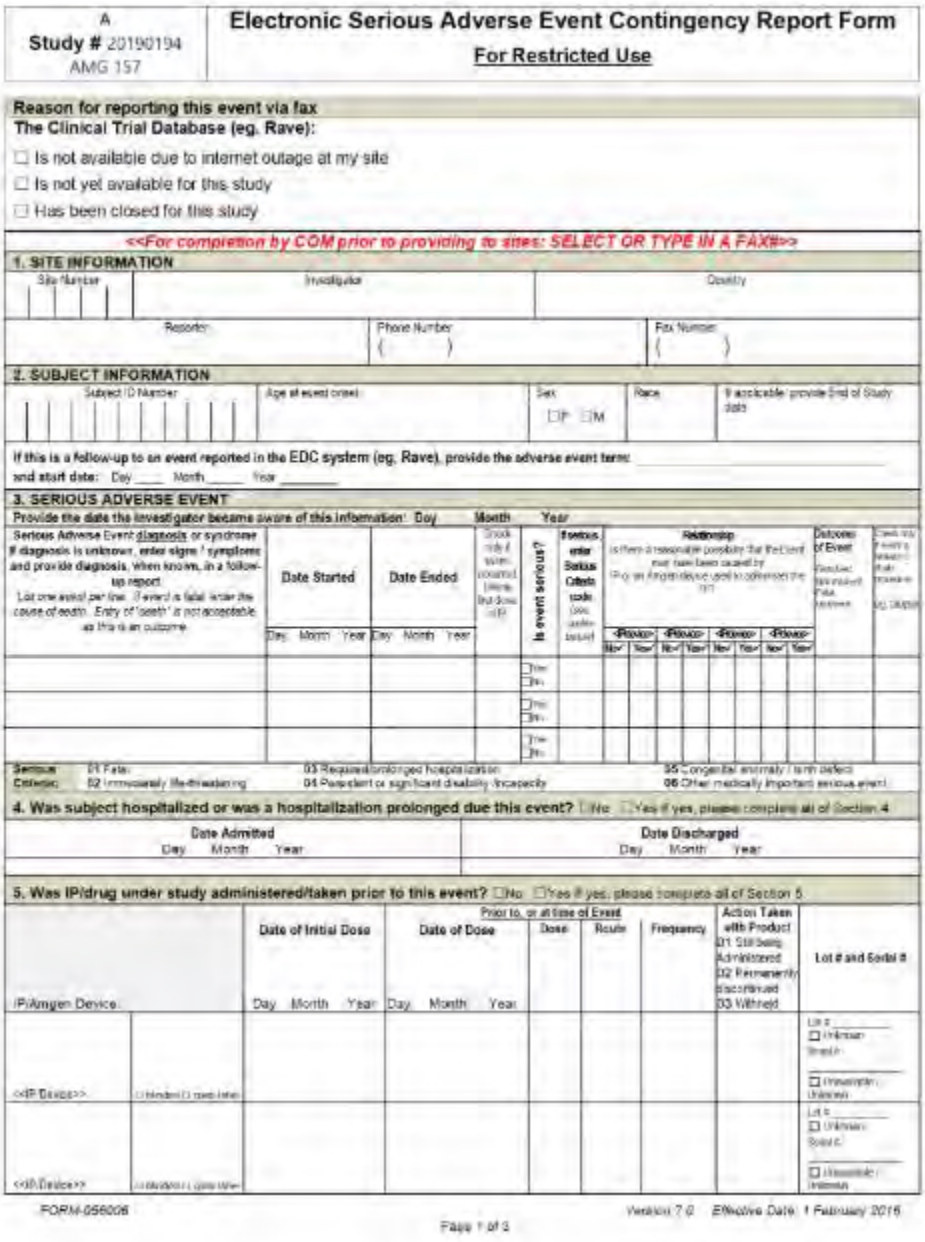
- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed Event CRF.
- The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool

- The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system via the Safety Report Form.
- If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using an electronic Serious Adverse Contingency Report Form (see Figure 11-1) within 24 hours of the investigator's knowledge of the event.
- The site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on a paper Serious Adverse Event Report Form (see Figure 11-1).

Figure 11-1. Sample Electronic Serious Adverse Event Contingency Form



A
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AMG 157

Electronic Serious Adverse Event Contingency Report Form
For Restricted Use

Reason for reporting this event via fax
The Clinical Trial Database (eg. Rave):
☐ Is not available due to internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

<<For completion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION
Site Number | Investigator | Country
Reporter | Phone Number ( ) | Fax Number ( )

2. SUBJECT INFORMATION
Subject ID Number | Age at event onset | Sex ☐F ☐M | Race | If applicable: provide End of Study date

If this is a follow-up to an event reported in the EDC system (eg. Rave), provide the adverse event term: _____
and start date: Day ____ Month _____ Year _____

3. SERIOUS ADVERSE EVENT
Provide the date the investigator became aware of this information: Day Month Year

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report. List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.	Date Started (Day Month Year)	Date Ended (Day Month Year)	Check only if term recurred. Leave blank if first time occurred	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship (Is there a reasonable possibility that the Event may have been caused by the IP, an Amgen device used to administer the IP?) <Primary> No / Yes; <Primary> No / Yes; <Primary> No / Yes; <Primary> No / Yes	Outcome of Event	Check only if Event is Ongoing at Data Cutoff
				☐Yes ☐No				
				☐Yes ☐No				
				☐Yes ☐No				

Serious: 01 Fatal; 03 Required or prolonged hospitalization; 05 Congenital anomaly / birth defect
Criteria: 02 Immediately life-threatening; 04 Persistent or significant disability /incapacity; 06 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted (Day Month Year)	Date Discharged (Day Month Year)

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Amgen Device		Date of Initial Dose (Day Month Year)	Prior to, or at time of Event: Date of Dose (Day Month Year)	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
<<IP Device>>	☐Masked ☐Open-label							Lot # _____ ☐Unknown Serial # _____ ☐Unavailable / Unknown
<<IP Device>>	☐Masked ☐Open-label							Lot # _____ ☐Unknown Serial # _____ ☐Unavailable / Unknown

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A **Study #** 20190194 AMG 157	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Subject ID Number

8. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete.

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete.

Date (Day Month Year)	Test											
	Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete

Date (Day Month Year)	Additional Tests	Results	Units

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A **Study #** 20190194 AMG 157	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale

Signature of Investigator or Designee -	Title	Date
I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.		

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11.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for females of childbearing potential pediatric are outlined in Section 5.2.

Female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant during treatment and for a period of relevant systemic exposure after the last dose of protocol-required therapies.

Additional medications given during the study may alter the contraceptive requirements. These additional medications may require female subjects to use highly effective methods of contraception and/or for an increased length of time. In addition, male subjects may also be required to use contraception. The investigator must discuss these contraceptive changes with the subject.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy;
  - Documented bilateral salpingectomy; or
  - Documented bilateral oophorectomy.

  Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.
- Premenarchal female
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

Note: Failure rate of < 1% per year when used consistently and correctly.

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device
- Intrauterine hormonal-releasing system
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 16 weeks after the last dose of any protocol-required therapy.
- Information will be recorded on the Pregnancy Notification Form (see Figure 11-2). The form must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 16 weeks after the last dose of protocol-required therapy. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal

complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.

- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 11.4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 7.1 for details).

Male Subjects with Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for 16 weeks after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 11-2) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies and for 16 weeks after the last dose of any protocol-required therapy.
- Information will be recorded on the Lactation Notification Form (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 228.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and

complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 16 weeks after discontinuing protocol-required therapies.

Figure 11-2. Pregnancy and Lactation Notification Forms

Amgen Proprietary Confidential

AMGEN® Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: _20190194_____

Study Design: ☒ Interventional ☐ Observational (If Observational ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):** ____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd__/ yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details: _____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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Amgen Proprietary Confidential

AMGEN Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ais-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20190194

Study Design: ☒ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):** ____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details: _____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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11.6 Appendix 6. Sample Storage and Destruction

Any blood eg, biomarker, pharmacokinetics (PK), pharmacogenetic sample collected according to the SoA (Table 1-1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the inflammatory conditions, the dose response and/or prediction of response to tezepelumab, characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of [redacted] or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood or tissue samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the

request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality.

11.7 Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR, and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Non-alcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (eg, rhabdomylosis, hemolysis)

If investigational product(s) is/are withheld, the subject is to be followed for possible drug-induced liver injury (DILI) according to recommendations in the last section of this appendix.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

Table 11-2. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3x ULN at any time	> 2x ULN
		OR
INR	--	> 1.5x (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8x ULN at any time > 5x ULN but < 8x ULN for ≥ 2 weeks > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule > 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values > 3x ULN (when baseline was < ULN)
	OR	
ALP	> 8x ULN at any time	--

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal

Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then Amgen investigational product and other protocol-required therapies, as appropriate is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 11-2) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation, according to the criteria specified in the above, require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate Case Report Form (CRF) (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 11.4.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 11-2 or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (BIL) (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin (Ig) G, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels
- A more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting, and fever
    - Prior and/or concurrent use of alcohol, recreational drugs, and special diets
    - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms

- Viral serologies
- Creatine phosphokinase, haptoglobin, lactate dehydrogenase, and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic (PK) analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in the corresponding CRFs.

Amendment 2

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

Amgen Protocol Number: 20190194

EudraCT Number: 2020-002759-39

NCT Number: NCT04833855

Amendment Date: 26 April 2022

Rationale:

This protocol is being amended mainly to reduce the number of anti-immunoglobin E (IgE) experienced subjects since there are limited sources of these subjects. Applicable sections of the protocol are being modified to clarify that approximately 39 subjects will be randomized to the anti-IgE experienced strata. In addition, interim analysis 2 is being added for administrative decision making purposes. This interim analysis will be performed when the 120 subjects in the anti-IgE naïve stratum complete week 16. [redacted] Changes including, but not limited to, the following were incorporated into the protocol:

- Added language to study rationale to include the tezepelumab brand name, TEZSPIRE™, and to clarify that the U.S. Food and Drug Administration (FDA) has approved tezepelumab as an add-on maintenance treatment for adult and pediatric patients aged 12 years and older with severe asthma
- Updated number of subjects (ie, in synopsis, number of subjects, and sample size determination sections) recruited for the anti-IgE experienced cohort to approximately 39 subjects (approximately 13 per arm) due to limited source of subjects

- Updated objectives and endpoints language (ie, in synopsis and objectives and endpoints sections) to modify the summary measure language of the first estimand of the primary objective, to delete exploratory endpoints measured at end of treatment (EOT) and language on time to first event of subjects receiving H1 antihistamine recue medication, and to relocate the key secondary objective and endpoint to be part of the secondary objectives and endpoints. This change is being made in response to regulatory advice regarding Hives Severity Scores over 7 days (HSS)7 and Itch Severity Score over 7 days (ISS7) assessments. In addition, Urticaria Activity Score over 7 days (UAS7) ≤ 6 and minimal import difference (MID) are also clinical meaningful endpoints.
- Updated exclusion criteria 221 to clarify that coronavirus disease 2019 (COVID-19) vaccines are allowed provided that the vaccination is not administered within 7 days before or after any study dosing visit
- Updated language in urticaria activity score (UAS) section to clarify that subjects are required to document both Hives Severity Scores (HSS) and Itch Severity Scores (ISS) daily with a recall period over 24 hours, and to define that a weekly UAS score represents the sum over a period of 7 days
- Updated statistical considerations sections to accommodate changes in number of subjects, and to relocate the key secondary endpoints to the secondary endpoints section, as well as changes to the multiple testing strategy
- Administrative and editorial changes have been made throughout the protocol for clarification

Amendment 1

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

Amgen Protocol Number (tezepelumab) 20190194

EudraCT Number: 2020-002759-39

Amendment Date:	01 September 2021
Superseding Amendment Date:	30 September 2021

Rationale:

The following changes were made to the protocol, dated September 01st, 2021, to incorporate regulatory authority recommendations, to align with international treatment guidelines, to reduce patient burden and improve study experience by reducing the frequency of select eDiary data collection and eliminate USS, and to clarify/correct other items in the protocol.

Target patient population changes include:

- Updated overall design (Section 4.1) to clarify second generation H1-antihistamines (sgAH) requirements.
- Updated inclusion criterion #105 to clarify which subjects are considered inadequately controlled by sgAH.
- Updated exclusion criterion #210 to clarify the sgAH stabilization period.
- Updated antihistamine stabilization period (Section 5.5) to clarify sgAH requirements.
- Updated background medication (Section 6.1.5.1) and rescue medication (Section 6.1.5.2) to clarify sgAH requirements

Patient Reported Outcomes (PRO) changes include:

- Updated schedule of activities (Section 1.3) to reduce the frequency of chronic urticaria quality of life questionnaire, dermatology life quality index assessment, and work productivity and activity impairment questionnaire (chronic urticaria).
- Removed the urticaria severity score (Section 8.2.2.1.11), and from the schedule of activities (Section 1.3), objectives and endpoints (Section 3), and throughout the protocol.

Reduction of washout period for prior use of biologics changes include:

- Updated exclusion criterion #213 to 4 months or 5 half-lives (whichever is longer) prior to screening visit 1 based on the half-life of biological products.
- Updated exclusion criterion #224 to clarify timeframe for non-biologic clinical studies, and biological clinical studies or treatment based on the half-life of biological products.

Systemic corticosteroid changes include:

- Updated excluded treatments, medical devices, and/or procedures (Section 6.1.7) to clarify the use of systemic corticosteroids.

Leukotriene receptor antagonist and H2-blocker changes include:

- Updated excluded treatments, medical devices, and/or procedures (Section 6.1.7) to exclude H2 antagonists and leukotriene receptor antagonists as classes of treatment during the study.

Statistical changes include:

- Updated primary objectives and endpoints (Section 3) to clarify the definition of intercurrent events under the first estimand of primary and key secondary objectives.
- Updated primary objectives and endpoints (Section 3) to add a secondary objective evaluating the effect of tezepelumab on subjects achieving complete control of angioedema disease.
- Updated objectives and endpoints (Section 3) to clarify the minimal residual disease endpoints.
- Updated adverse events (Section 8.2.4.1.1) to replace common terminology criteria for adverse events with Amgen's standard grading scale for AE intensity.
- Updated covariates (Section 9.3.2) to clarify the analysis of the primary and key secondary endpoints using the baseline score of endpoint.
- Updated handling of missing and incomplete data (Section 9.3.4) to clarify addressing missing data in binary efficacy endpoints.
- Updated efficacy analyses (Section 9.4.2.2) to clarify statistical analysis methods to be used for primary, key secondary, and secondary endpoints.

Other changes include:

- Updated exclusion criterion #208 to clarify QFT-plus test requirements.
- Updated exclusion criterion #226 to clarify Hepatitis B core antibody testing, only where required by local country or region.
- Updated laboratory test results (Section 9.4.2.3.2) to utilize Amgen's standard grading scale for AE intensity.
- Updated assessment of severity for evaluating adverse events and serious adverse events (Appendix 4, Section 11.4) to replace common terminology criteria for adverse events with Amgen's standard grading scale for AE intensity.
- Updated template safety language.
- Administration, typographical and formatting changes were made throughout the protocol.

On 30 September 2021, the protocol Amendment 1 was superseded to rectify the error in study schema

Amendment 1

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

Amgen Protocol Number (tezepelumab) 20190194

EudraCT Number: 2020-002759-39

Amendment Date: 01 September 2021

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