A Phase IV, Randomized, Double-Blind, Placebo-Controlled Exploratory Study of Xolair (Omalizumab) for Treatment of Idiopathic Angioedema in Patients Who Remain Symptomatic Despite Current Therapy

Authors:	E. A. Schwantes, MS
Principle or Coordinating Investigator:	R. K. Viswanathan, MD and S.K. Mathur, MD, PhD

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
b.i.d.	twice a day
CRF	Case Report/Record Form
CRD	Clinical Research and Development
CPO	Country Pharma Organization
CRO	Contract Research Organization
CSR	Clinical Study Report
ECG	Electrocardiogram
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMS	Integrated Medical Safety
i.v.	intravenous(ly)
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
o.d.	once a day
p.o.	oral(ly)
REB	Research Ethics Board
SAE	serious adverse event

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Medication number	A unique identifier on the label of each medication package in studies that dispense medication using an IVR system
Patient number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study.
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later
Study drug	Any drug administered to the patient as part of the required study procedures; includes investigational drug and any control drugs
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

Protocol synopsis

Title of study: A Phase IV, Randomized, Double-Blind, Placebo-Controlled Exploratory Study of Xolair (Omalizumab) for Treatment of Idiopathic Angioedema in Patients Who Remain Symptomatic Despite Current Therapy

Purpose and rationale: The overall hospitalizations for a diagnosis of angioedema doubled from the year 2000 to 2009. Although some of the cases represented hereditary angioedema or ace-inhibitor induced angioedema, the majority of episodes were idiopathic. Idiopathic Angioedema (IAE) can be life-threatening especially when affecting tissues within the respiratory tract. No clear guidelines exist for management of this important condition for clinicians. Current therapies typically include avoidance of potential triggers and use of medications either for prophylaxis or for acute events, such as antihistamines, corticosteroids, and epinephrine. There remains a critical need for therapeutic options to provide more effective prophylaxis.

Objectives:

Primary objective: To estimate the effect of omalizumab in reducing the severity of angioedema episodes in patients with IAE.

Secondary objectives:

To estimate the effect of omalizumab in improving quality of life in IAE subjects.

To estimate the effect of omalizumab in reducing frequency, duration of angioedema episodes, need for rescue medication/corticosteroids, and need for unscheduled clinic/urgent care/ER visits.

To assess the safety of omalizumab usage in patients with IAE.

To assess the effect of omalizumab on biomarkers previously implicated in the pathogenesis of IAE.

Population: Forty adults (age 18 or older) with 2 or more episodes of Idiopathic Angioedema (IAE) in the past 6 months, despite current therapy will enter the treatment period.

Inclusion/Exclusion criteria:

Inclusion criteria

1) Adults or adolescents who are 18 years or older with physician diagnosis of IAE.

2) Minimum of two episodes of IAE in the past 6 months.

3) Management with a stable treatment plan for the prior 6 months.

4) Complement profile (C1 Esterase inhibitor panel) within normal reference values.

5) If a woman is of child-bearing potential, she must agree to a reliable form of birth control including: abstinence, oral contraceptives (birth control pills), Depo-provera, an IUD (intrauterine device), or double-barrier contraception (partner using condom and subject using diaphragm, contraceptive sponge or cervical cap, and spermicidal).

Exclusion criteria

1) Diagnosis of HAE, Acquired Angioedema, or Ace-inhibitor associated angioedema, which are forms of angioedema with known mechanisms and alternate treatment options.

2) Chronic Urticaria (itching and/or hives) with or without Angioedema which are known mast cell mediated processes previously shown to be responsive to the use of omalizumab.

3) Previous usage of omalizumab in the last 3 months which can affect the patient-related outcomes and biomarker assessments if not "washed out" of the system.

4) Patients, who in the judgment of the investigator, have a history or condition that might compromise patient safety or compliance, interfere with evaluations, or preclude completion of the study.

Investigational and reference therapy:

Treatment Arm	# of Patients Entered Treatment	Type of Study Drug	Compound	Min Dose	Max Dose	Frequency	Admin. Route
Treatment Arm	20	Investigational	Xolair (omalizumab)	300mg		every 4 weeks x 24 weeks	Subcutaneous
Placebo Arm	20	Placebo	Matching placebo			every 4 weeks x 24 weeks	Subcutaneous

Study design: This study is a randomized, double-blind, placebo-controlled, parallel group trial which will study the effects of omalizumab on patients with 2 or more episodes of Idiopathic Angioedema (IAE) in the past 6 months, despite current therapy. This study has three periods; screening, treatment, and follow-up. Subjects in the screening period will be consented and screened for eligibility criteria. 40 qualified individuals will enter the treatment period. Individuals will be randomized to either every 4 weeks subcutaneous administration of omalizumab 300mg (20 subjects) versus every 4 weeks placebo injection (20 subjects) in addition to their previously prescribed management plan for a total of 24 weeks. Individuals will then enter a follow-up period of 4 months. Study visits will occur every 4 weeks during the treatment period for update of clinical status and administration of omalizumab/placebo injection. After, the treatment period individuals will be seen twice for follow-up. The entire study will consist of 10 study visits and will last approx. 10 months.

Efficacy assessments:

- Changes in the patient-related outcome measure of Angioedema Activity Score (AAS7, (Weller et al., 2013))

Other assessments:

- Changes in the quality of life of idiopathic angioedema patients as determined by the Angioedema QoL Questionnaire (AE-QoL, Weller et al., Allergy 2012)
- Changes in the severity of angioedema episodes in the past 4 weeks will be determined using changes in the patient-related outcome measure of Angioedema Activity Score (AAS28, (Weller et al., 2013))
- Frequency, duration of IAE episodes (hours), rescue medication or corticosteroid usage, and number of unscheduled clinic/urgent care/ER visits will be based on monthly recall with questionnaires performed at each study visit.

- Visual analog score for IAE severity will be determined at each study visit.
- We will identify any reported AE during the course of the study.
- We will examine changes in basophil flow cytometry (CD63 and CD203 expression), tryptase, bradykinin and its degradation products, and platelet activating factor (PAF).

Data analysis:

The primary analysis will estimate the effect of treatment, compared to placebo, on the change in Angioedema Activity Score (AAS7) from baseline to the end of the treatment period using analysis of covariance (ANCOVA) with treatment group and baseline AAS7 as covariates. Longitudinal comparisons of the repeated (monthly) AAS7 measurements will also be examined using linear mixed effect models in a secondary analysis. For the secondary outcomes, a similar strategy will be used, adjusting for the baseline value of the outcome where possible, using similar linear models or generalized linear models including count regression for frequency outcomes and logistic regression for categorical outcomes. Participants will be compared as-randomized using the intention-to-treat principle. Missing data will be addressed using multiple imputations.

1 Background

Angioedema (AE) refers to the rapid swelling of the deep dermis, submucosal and subcutaneous tissue while urticaria involves swelling in the upper dermis. It occurs as a result of a transient extravasation of fluid into the interstitium due to the release of vasoactive substances. Angioedema can involve various tissues and regions of the body including face, lip, tongue, mouth, throat, larynx, extremities, abdomen, and genitalia. Angioedema can be life-threatening especially when affecting tissues within the respiratory tract. Several different types of AE have been recognized over the years including most notably hereditary angioedema (HAE), ACE-inhibitor induced angioedema (ACEI-AE), acquired angioedema (AAE), and an idiopathic form (IAE) that could be either histaminergic or nonhistaminergic in etiology. IAE is defined as angioedema episodes that occur without any clear identifiable etiology and not associated with HAE (hereditary angioedema), ACE-inhibitor induced angioedema, acquired angioedema, and angioedema associated with chronic urticaria.

The time course of the angioedema episode is variable lasting anywhere from 1-4 days with the nonhistaminergic forms taking longer to resolve. HAE can start to present early in childhood and worsen around puberty with symptoms involving the abdominal wall, extremities, face and upper airway and can last about 24-48 hours. Recurrent abdominal pain usually prompts its evaluation. ACEI-AE has an incidence of approximately 0.1-0.7% with symptoms targeting the face, lips, tongue, larynx and pharynx. It is characteristically associated with the usage of an ACE-I. Acquired angioedema is an adult onset form often associated with the presence of a lymphoproliferative disorder with symptoms targeting the face, upper airways and abdomen. Idiopathic angioedema is poorly characterized and symptoms involve the extremities, face, and upper airways with a lower preponderance for the abdomen. While involvement of the larynx and pharynx has been reported, it involves the respiratory tract much less frequently.

It is important to establish or exclude an appropriate etiology for AE as the therapeutic algorithms for management varies. HAE subtypes (Type I and II) are well characterized forms of AE with known defects in the SERPING1 gene resulting in depressed complement profiles (low C4) including abnormal C1 inhibitor level and/or function. An evaluation of complement profiles and C1 inhibitor level and function can help to delineate these entities. A new subtype of HAE (Type III) has been recently described with a normal complement profile and C1 inhibitor panel that occurs as a result of mutations in the Factor XII gene. It has a more characteristic association to estrogen exposure. Acquired angioedema has a similar complement profile to HAE Type I with one distinguishing feature- a low C1q level. No known genetic mutations are associated with AAE. ACEI-AE has a normal complement profile and is associated with ACE-I usage. Idiopathic angioedema also has a normal complement profile, but some of the distinguishing features of the above are lacking. Mechanistically, increased levels of bradykinin and degradation products appear to play a role in all forms of angioedema with some forms having a mast-cell mediated component that is responsive to antihistamine therapy.

2 Purpose and rationale

Treatment guidelines are clearly established for the management of HAE I and II for prophylactic and abortive purposes, and avoidance of ACE-I is recommended for ACEI-AE. However, no clear guidelines exist for the diagnosis or management of IAE. Current therapies typically include avoidance of potential triggers and use of medications either for prophylaxis or for acute events, such as antihistamines, corticosteroids, and epinephrine. There remains a critical unmet need for therapeutic options to provide more effective prophylaxis and possible disease-modification effects for patients with IAE. For example, there are some patients using chronic prophylactic antihistamine therapy and for any acute episode of IAE, they may take additional on demand medications such as additional doses of antihistamine and/or corticosteroid. There are others who may not use any chronic prophylaxis and only use on demand antihistamines and/or corticosteroids with acute episodes of IAE.

Omalizumab recently garnered FDA-approval for chronic urticaria with or without angioedema. Evidence from trials performed in chronic urticaria suggests that omalizumab is efficacious in controlling both urticarial flares and concurrent angioedema episodes. However, omalizumab has not yet been well investigated for IAE, though there have been some case reports that suggest efficacy for IAE (Azofra et al., 2015; Ozturk and Kocaturk, 2014; Sands et al., 2007; Weller et al., 2013)

With the efficacy observed in urticaria patients, it is clear that omalizumab can suppress mast cell activity, although the mechanisms for the benefit remain somewhat unclear. The kinetics of omalizumab effects, especially in the context of chronic spontaneous urticaria, suggests that sequestration of IgE molecules is not the complete answer. Given the likely role of mast cells in the majority of IAE, ***we hypothesize that omalizumab will have potential disease modifying effects in reducing the severity and frequency of IAE***.

3 Objectives

3.1 Primary objectives

To estimate the effect of omalizumab in reducing the severity of angioedema episodes in patients with IAE.

3.2 Secondary objectives

To estimate the effect of omalizumab in improving quality of life in IAE subjects.

To estimate the effect of omalizumab in reducing frequency, duration of angioedema episodes, need for rescue medication/corticosteroids, and need for unscheduled clinic/urgent care/ER visits.

To assess the safety of omalizumab usage in patients with IAE.

To assess the effect of omalizumab on biomarkers previously implicated in the pathogenesis of IAE.

4 Study design

This study is a randomized, double-blind, placebo-controlled, parallel group trial which will study the effects of omalizumab on patients over the age of 18 with 2 or more episodes of Idiopathic Angioedema (IAE) in the past 6 months, despite current therapy. This study has three periods; screening, treatment, and follow-up. Subjects in the screening period will be consented and screened for eligibility criteria. If subjects have not had a complement profile within the normal reference range (C1 Esterase inhibitor panel), subjects will be asked to return for a second screening visit to assess their complement profile. Subjects in the screening period will also undergo a 24-hour urine collection for mast cell mediators (such as n-methyl histamine, 11β- PGF2α, and PGD2 testing) and a blood draw for chronic urticaria index testing in addition to the C1 esterase inhibitor panel. If under the subject's current care guidelines, they are taking prednisone or other immunomodulator episodically (on demand usage) we will collect baseline test after a 14 day washout period has occurred. If there is no such window or they are taking daily medication, we will proceed with the baseline measurements despite the use of an immunomodulatory or prednisone. 40 qualified individuals will enter the treatment period. Individuals will have a baseline assessment and be randomized to either every 4 week subcutaneous administration of omalizumab 300mg (20 subjects) versus every 4 week placebo injection (20 subjects) in addition to their previously prescribed management plan for a total of 6 months. Individuals will then enter a follow-up period of 4 months. Study visits will occur every 4 weeks during the treatment period for update of clinical status and administration of omalizumab/placebo injection. After the treatment period individuals will be seen twice for follow-up, 4 weeks and 12 weeks post treatment. The entire study will consist of 10 study visits and will last approx. 10 months (see Table 4-1). The blind will be maintained for the full 10 months of the study.

Table 4-1 Study design

Study Periods	Screening		Treatment						Follow-Up	
Visit Number	1A	1B	2	3	4	5	6	7	8	9
Time of Visit	Screen	Screen	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 36
Visit window	-3 to -6 wks	-1 to -3 wks		±7days	±7days	±7days	±7days	±7days	±7days	
Inclusion/Exclusion	x									
Informed consent	x									
Physical examination	x									x
Dispense AAS28		x (7 days)	x	x	x	x	x	x	x (12 weeks)	
Collect AAS28			x (7 days)	x	x	x	x	x	x	X (12 weeks)
In clinic questionnaires (Ae-Qol and VAS)			x	x	x	x	x	x	x	x
Administer study medication			x	x	x	x	x	x		
Laboratory test*		x	x			x			x	x
Urine pregnancy test		x	x	x	x	x	x	x	x	x
Adverse events				x	x	x	x	x	x	x
Concomitant Meds	x	x	x	x	x	x	x	x	x	x

* Laboratory testing study grid in Appendix 4

5 Population

Forty adults (age 18 or older) with 2 or more episodes of Idiopathic Angioedema (IAE) in the past 6 months, despite being on recommended therapy for the past 6 months will enter the treatment period at the University of Wisconsin-Madison Allergy and Asthma Clinical Research Unit. Once an individual enters the treatment phase they will be counted as 1 of the 40 subjects, and they will not be replaced. It is anticipated that we will need to screen 60 subjects in order to obtain 40 qualified participants.

Subjects will primarily be recruited by Drs. Mathur and Viswanathan from their clinics. Subjects who are seen in their clinics for a diagnosis of idiopathic angioedema will be asked if they are interested in participating in this study. If yes, their contact information will be given to the Allergy Research Staff to do a follow up call for a phone screen. The following information will be faxed to the allergy research staff: name, phone number, alternate phone number, and email address. If no, their information will not be shared with the Allergy Research Staff.

Additionally, we will use UW Health Electronic Medical Record system (HealthLink) to send out recruitment letters. Letters will be sent to those individuals (age 18 or older) who have ICD 9/10 code for angioedema with no history of drug-induced angioedema, hereditary angioedema, or a history of urticaria. The letters will invite them to participate in the study and notify them that they will receive a follow up phone call regarding the study.

Letters will be also be sent out to local allergists notifying them of the study. The letter will include a second letter which can be given to their patients they feel would qualify for the study. In addition, advertisements will be placed

around the local hospital and clinics.

This study recruitment and treatment is expected to last 5 years, from the recruitment of the first subject, with anticipated end date of 12/2021. Study analysis is expected to last an additional year.

5.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria:

- Adults or adolescents who are 18 years or older at the time of screening with physician diagnosis of IAE.
- Minimum of two episodes of IAE in the past 6 months at the time of screening.
- Management of IAE with a stable controller treatment plan for the prior 6 months at the time of screening, which will include patients managed using the following approaches:
  -No prophylaxis and only use of on demand medications for episodes of IAE
  -Use of prophylactic medications and additional on demand medications for episodes of IAE
- Complement C1 esterase inhibitor panel within normal reference ranges.
- If a woman is of child-bearing potential, she must agree to a reliable form of birth control including: abstinence, oral contraceptives (birth control pills), Depo-provera, an IUD (intrauterine device), or double-barrier contraception (partner using condom and subject using diaphragm).

5.2 Exclusion criteria

Patients who meet any of the following criteria will be excluded from study entry: Safety

Exclusion Criteria

- Unable to give informed written consent, unable to adhere to the outlined visit schedule or unable to tolerate the procedures required for participation in this trial.
- Unable, in the judgment of the investigator, to comply with study procedures and/ or directions.
- Treatment with an investigational agent within 30 days of the screening visit.
- Medical examination or laboratory findings that may suggest neoplasms, malignancies, or a history of malignancies.
- Nursing mothers, pregnant women, or women of childbearing potential who are planning a pregnancy during the course of the study.
- Any history of life-threatening angioedema which affects breathing requiring intubation in the past 2 years and prior to angioedema treatment.
- Patients, who in the judgment of the investigator, have a history or condition that might compromise patient safety or compliance, interfere with evaluations, or preclude completion of the study.

Baseline Exclusion Criteria

- Diagnosis of HAE, Acquired Angioedema, or Ace-inhibitor associated angioedema, which are forms of angioedema with known mechanisms and alternate treatment options.
- Chronic Urticaria with or without Angioedema which are known mast cell mediated processes previously shown to be responsive to the use of omalizumab.
- Previous use of omalizumab in the last 3 months which can affect the patient-related outcomes and biomarker assessments if not “washed out” of the system.

6 Treatment

6.1 Investigational and control drugs

Omalizumab is a sterile, white, preservative-free, lyophilized powder, contained in a single-use vial that will be reconstituted with sterile water for injection (SWFI), USP, and administered as a subcutaneous injection. Each omalizumab vial contains 202.5 mg of omalizumab, 145.5 mg sucrose, 2.8 mg L-histidine hydrochloride monohydrate, 1.8 mg L-histidine, and 0.5 mg polysorbate 20. Each vial is designed to deliver 150 mg of omalizumab in 1.2 mL after reconstitution with 1.4 mL SWFI, USP.

Placebo will be provided by drug supply management

6.2 Treatment arms

Patients will be assigned to one of the following 2 treatment arms in a ratio of 1:1

- Arm 1: Omalizumab: 300mg subcutaneous injection every 4 weeks for 24 weeks. Total dose will be divided into two 150mg/1.2mL injections.
- Arm 2: Placebo Group: two 1.2mL subcutaneous injections every 4 weeks for 24 weeks.

6.3 Treatment assignment

Randomization will be completed by the University of Wisconsin Hospital and Clinics Pharmaceutical Research Center using a forced block design. Once a subject has been cleared for initial treatment, the next ascending sequential randomization number (and corresponding treatment) will be assigned.
Subjects will be enrolled and randomized to one of two treatment arms in a 1:1 ratio.

6.4 Treatment blinding

All subjects and research staff will be blinded to treatment assignment; study drug will be administered by a single unblinded research nurse (who will not be evaluating patients or collecting data). Double blinded treatment will be maintained until the conclusion of the study. Randomization and treatment preparation will be handled by the unblinded Hospital Pharmacy. Unblinding of the investigators, statisticians and research team will occur at the conclusion of data analysis.

Subjects will remain blinded until analysis of the trial has been completed. At the conclusion of the study analysis, participants will be notified through written notification from Drs. Mathur or Viswanathan of their treatment assignment.

6.5 Treating the patient

6.5.1 Patient numbering

Patients will be assigned a Subject ID# upon screening; Randomization Number (and treatment) will be assigned prior to first treatment, but after subject has been cleared for treatment.

6.5.2 Dispensing the study drug

Once randomized to a study treatment, the product will be prepared by unblinded staff in the UW hospital pharmacy.

Omalizumab-assigned subjects

- Reconstitution:
    - Using a 1 inch, 18g needle and 3mL syringe, draw up 1.4mL of Sterile Water for Injection (SWFI), USP

- Slowly add the SWFI to the wet the powder, do not shake
- Gently swirl the upright vial for 5-10 seconds approximately every 5 minutes until dissolved; generally, takes 20 minutes to dissolve completely
- Continue to swirl gently until no gel-like particles are visible; do not use if contents are not completely dissolved after 40 minutes
- Resulting solution is 150mg/1.2mL

- Drawing up the dose
  - Invert the vial for 15 seconds so the solution drains toward the stopper
  - Remove all of the solution in the vial by inserting a new 3mL syringe with a 1inch, 18g needle into the inverted vial
  - Expel any air or bubbles or excess solution to obtain the 1.2mL dose.
  - Remove needle and cap with a sterile rubber tip.
  - Expiration = 4 hours if stored at room temperature and 8 hours if stored under refrigeration.

Placebo-assigned subjects

- Drawing up the dose
  - Draw up 1.2mL placebointo a 3mL syringe.
  - Expel any air or bubbles or excess solution to obtain the 1.2mL dose.
  - Remove needle and cap with a sterile rubber tip.
  - Expiration = 4 hours if stored at room temperature and 8 hours if stored under refrigeration.

6.5.3 Study drug supply, storage and tracking

Omalizumab will be provided in 150mg single use vials containing sterile, white, Preservative-Free, lyophilized powder. Vials will be stored under refrigeration at 2^{o} to 8^{o} (36^{o} to 46^{o} F).

Matching placebo will be supplied by Novartis. Vials will be stored at room temperature: 20^{o} to 25^{o} (68^{o} to 77 ^{o}F); that results in a mean kinetic temperature calculated to be not more than 25^{o}; and that allows for excursions between 15^{o} and 30^{o} (59^{o} and 86^{o}F).

All study provided products must be received at the study site by a designated individual, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated staff have access. Storage conditions must be adequately monitored and appropriately documented as source information. Investigator or designee must maintain an accurate record of the shipment and dispensing of study drug and all supplies are to be used only for subjects on this protocol and not for any other purposes. Study drug will be supplied from Novartis in 3 shipments, 6 months apart.

6.5.4 Instructions for prescribing and taking the study drug

Each study drug dose (Omalizumab 300mg or Placebo) will consist of two syringes; each containing 1.2 mL total volume. Due to the viscosity of Omalizumab, study drug must be administered by an unblinded Research Nurse. Active omalizumab may take a total of 5 to 10 seconds to administer and the placebo significantly less time; as such the Research Nurse will slowly administer the placebo at a rate of 0.5 ml per sec. The unblinded Research Nurse will continue to maintain the blind for both active and placebo subjects.

Study drug injections will be repeated every 4 weeks +/- 7 days for a total of 24 weeks under protocol stipulations. Administer only under direct medical supervision and observe patient for a minimum of 2 hours following administration of any dose given for the first three visits, and then 30 minutes for any subsequent doses.

6.5.5 Permitted study drug dose adjustments and interruptions

No dosage modification of study drug will be allowed during this study.

If a subject misses a dose of medication by more than a week (7 days), that dose will be skipped. If a subject misses more than two subsequent doses in the dosing series the subject will no longer receive study medication, but will remain in the study and be labeled SDD (study drug discontinuation).

6.5.6 Rescue medication

Study drug must be administered in a location with ready access to emergency medication (epinephrine) and supplies in the event of serious hypersensitivity reaction. Study drug administration will occur in the Clinical Research Unit North, Allergy Research offices. The allergy research Investigator on-call staff will be available for any emergent situations. Emergency supplies must include those as needed for airway management and resuscitation. Subjects must be observed for a minimum of 2 hours before being discharged to home after the first three administrations, or 30 min after subsequent doses.

6.5.7 Study drug discontinuation and premature patient withdrawal

Study drug must be discontinued if the subject becomes pregnant.

The investigator has the right to discontinue a patient from study treatment for any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues on study treatment, noncompliance (e.g. missed 2 consecutive visits or 3 total visits) or an anaphylactic reaction to study drug. Every effort will be made to continue to follow patients who discontinue from study treatment.

6.5.8 Emergency unblinding of treatment assignment

Subjects will not be unblinded prior to the final analysis of study data. If subjects have an anaphylactic reaction to study medication or an idiopathic trigger, they will be treated appropriately and will no longer receive study medication. Subjects will be labeled SDD, study drug discontinuation.

7 Visit schedule and assessments

Table 7-1 lists all of the assessments and indicates with an "x" the visits when they are performed.

Table 7-1 Assessment schedule

Study Periods	Screening		Treatment						Follow-Up	
Visit Number	1A	1B	2	3	4	5	6	7	8*	9*
Time of Visit	Screen	Screen	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 36
Visit window	-3 to -6 wks	-1 to -3 wks		±7days	±7days	±7days	±7days	±7days	±7days	
Inclusion/Exclusion	x									
Informed consent	x									
Physical examination	x									x
Dispense AAS28		x (7 days)	x	x	x	x	x	x	X (12 weeks)	
Collect AAS28			x (7 days)	x	x	x	x	x	x	X (12 weeks)
In clinic questionnaires (Ae-Qol and VAS)			x	x	x	x	x	x	x	x
Administer study medication			x	x	x	x	x	x		
Laboratory test*		x	x			x			x	x
Urine pregnancy test		x	x	x	x	x	x	x	x	x
Adverse events				x	x	x	x	x	x	x
Concomitant Meds	x	x	x	x	x	x	x	x	x	x

SDD = Study drug discontinuation
PPW = Premature patient withdrawal
*These assessments are still performed after SDD if the subject is willing.

7.1 Information to be collected on screening failures

At the screening visits the following information will be collected on all subjects: assessment for frequency, duration of IAE episodes (hours), rescue medication or corticosteroid usage, complement profiles (C1 Esterase inhibitor panel*),* Chronic Urticaria Index Urine mast cell mediators (such as n-methyl histamine, 11β- PGF2α, PGD2), AAS7 and 28 and Ae-QOL questionnaire responses, and number of unscheduled clinic/urgent care/ER visits in the past year.

Screen failures may be rescreened at the discretion of the investigator and will keep the same screening ID number.

7.2 Patient demographics/other baseline characteristics

At the screening visits the following information will be collected on all subjects: assessment for frequency, duration of IAE episodes (hours), rescue medication or corticosteroid usage, complement profiles (C1 Esterase inhibitor panel*),* Chronic Urticaria Index, Urine mast cell mediators (such as n-methyl histamine, 11b-PGF2a, PGD2), AAS7, 28 and Ae-QOL questionnaire responses, and number of unscheduled clinic/urgent care/ER visits in the past year.

At the baseline visit, we will also examine basophil flow cytometry (CD63 and CD203 expression), tryptase, bradykinin and bradykinin degradation products, and platelet activating factor (PAF).

Complement profiles will be collected for the purposes of study inclusion, C1 Esterase inhibitor panel must be within normal reference values.

7.3 Treatment exposure and compliance

Questionnaires such as AAS and Ae-QOL will be collected during treatment visits every 4 weeks.

Additionally, assessment for frequency, duration of IAE episodes (hours), rescue medication or corticosteroid usage, visual analog score for IAE severity and number of unscheduled clinic/urgent care/ER visits in the previous month will be collected.

Every 12 weeks, at the treatment visits and at the conclusion of the trial, we will also examine changes in basophil flow cytometry (CD63 and CD203 expression), tryptase, bradykinin and its degradation products, and platelet activating factor (PAF).

7.4 Efficacy

All subjects will be given a paper questionnaire by the research nurses to assess their angioedema disease activity. Each patient will be given a quiet room to complete the questionnaire. Patients will report their disease activity on an Angioedema Activity Score (AAS, Appendix 1, (Weller et al., 2013)), at baseline and during all study visits. The Angioedema Activity Score is a validated disease specific patient- reported outcomes questionnaire. The AAS consists of 5 questions plus yes/ no questions for disease presence days. A categorical score between 0 and 3 has been assigned each answer. The question scores are summed up to an AAS day sum score, 7 AAS day sum scores to an AAS week sum score (AAS7) (primary outcome), and 4 ASS week sum scores may be summed up to an AAS 4-week sum score (AAS28) per the scoring template.
Accordingly, the minimum and maximum possible AAS scores are 0-15 (AAS day sum score), 0-105 (AAS7), and 0-420 (AAS28).

7.4.1 Efficacy assessment 1

The Urticaria Activity Score, UAS7, is a widely accepted for its usage in individuals with Urticaria, and has been used in previous omalizumab (Xolair) trials, however given the focus of this trial on angioedema, the AAS is more relevant. The AAS is a validated, published angioedema tool (Weller et al., 2013).

7.5 Safety

All subjects will be assessed for the incidence and severity of adverse events, using an adverse event reporting guidelines at each study visit. Data safety monitoring will be completed by the UW Madison ICTR data and safety monitoring board (DSMB). We plan to utilize the UW ICTR Data Monitoring Committee (DMC) to oversee the study, and function as an external DSMB. Study progress and safety will be reviewed annually (and more frequently if needed) by the DMC. The UW ICTR DMC is comprised of experienced members (core plus ad hoc) with expertise required to oversee this study. The DMC members will review protocol-specific reports created by statisticians using data pulled from the ICTR OnCore clinical research management system. Progress reports, including patient recruitment, retention/attrition, and AEs will be provided to the Data Monitoring Committee following each of the annual reviews. The DMC members will review protocol-specific reports created by statisticians that serve a non-voting member role on the DMC using data extracted from the ICTR OnCore-CRM system. These standard reports will include an overview of study objectives, a review of actual and projected accrual rates, an evaluation of subject demographics, a summary of the number and seriousness of adverse events. An interim analysis of study results may be performed and source documents may be reviewed to allow the DMC to independently judge whether the overall integrity and conduct of the protocol remain acceptable based on data provided and reported by the Principal Investigator. The DMC will make recommendations to the Principal Investigator that could include actions of continuation, modification, suspension, or termination.

7.5.1 Physical examination

Participants will be assessed by a trained medical professional for changes in vital signs.

7.5.2 Pregnancy and assessments of fertility

Pregnancy tests will be administered at the screening visit 1B and all subsequent visits on all pre-menopausal female patients by the clinical research staff. Additionally, all pre-menopausal women must agree to maintain a reliable form of birth control though out their participation of the study.

7.6 Other assessments

7.6.1 Health-related Quality of Life

Angioedema QoL Questionnaire (AE-QoL, Appendix 2 (Weller et al., 2012)) is a validated symptom specific questionnaire. The AE-QoL can be completed at any time during the study visits and subjects will be given a quiet room to answer all written questions. Research coordinator will administer and grade the written questionnaires. Each questionnaire consists of validated questions pertaining to functioning, fatigue/mood, fears/shame and nutrition. The AE-QoL will produce individual's scores for each assessment as a profile instrument and for a total score as an index instrument. The minimum sum for each assessment is 1 point per question and the maximum is 5 points per question and scores are calculated using the following formula (Σ items - min Σ items) // (max Σ items - min Σ items) x 100. Scores are linear in value and reported as a percent, with 0% being the lowest score and 100% being the highest. If more than one question is missed, the score is not valid and will not be included in the analysis.

Visual analog scores, Appendix 3 will be collected on all subjects, by a trained research coordinator. At the screening visit, the participant will be asked to rate their overall health state at their most recent angioedema event. The rating will be done on a scale of 0-100 with 100 increments, with 100 being the best imaginable state, and 0 being the worst imaginable state. This data will be collected by giving the subject a scale which will be printed on a sheet of paper, the subject will then draw a line where they feel best describes their health state at the indicated time. The research coordinator will then report the value (as 000) closest to the line drawn. Participants will then repeat this value at each subsequent visit if they have had an angioedema event since the previous visit. The lowest possible score will be 0 and the highest possible score will be 100.

7.6.2 Other Biomarkers

At screening (V1B), venipuncture will be performed for 1-3mL plain red tube and 1-8.5mL serum separator tube. The collected tubes will be for analysis of complement C1 Esterase inhibitor panel and Chronic Urticaria Index Instruction for urine collection will be sent home with subject (V1A) for 24 hour urine collection, urine will be returned at V1B. Urine will be tested for mast cell mediators such as n-methyl histamine, 11βPGF2α, and PGD2. Blood for C1 Esterase Inhibitor pane and urine will be sent to UWHC central core lab for processing. Blood for CUI will be processed by research lab and frozen for batch testing at time of study analysis. Subjects will be off prednisone for 2 weeks at V1B, unless prednisone is used as daily therapy.

At baseline (V2), every 12 weeks (V5, 8) during study treatment, and at 12 weeks post treatment (V9) all subjects regardless of study treatment will have a venipuncture. Collection of blood will be performed prior to receiving study treatment. Venipuncture will be performed under standard procedures, and 60 ml of blood will be drawn (2-10 ml Serum Separator Tubes, 1-5 ml red top tube, 2- 10 ml EDTA tubes and 1- 4ml EDTA tube). All samples will be processed for serum and plasma by centrifuging at 1500 RPM for 10 min, supernatant will be collected and aliquoted in 0.5 ml/ aliquot and immediately frozen at -80 degrees in cryotubes. The additional sample drawn at the University of Wisconsin-Madison for basophil flow cytometry method is described below.

Serum and plasma will be analyzed by commercial ELISA at the conclusion of the study for the following: tryptase, bradykinin and it degradation products, and platelet activating factor (PAF).

Basophil flow cytometry for CD63 and CD203 expression will be performed on 4 ml of EDTA blood. The buffy coat will be collected by spinning the samples at 700g for 15 min and collecting the cell population in between the erythrocyte layer and the plasma layer. Once the buffy coat (leukocytes) has been collected, the cells will be washed in a solution of HEPES-heparin buffered solution (HBE) by centrifugation at 400 g for 10 min. Finally,

pelleted cells with be re-suspended in 5 ml of HBE. Cells with then undergo either no activation, activation by FMLP, activation by IgE or activation by calcium ionophore A23187. Cells will then be stained, and have flow cytometry performed using CD63 and CD203 as markers of basophil activation (Chirumbolo et al., 2008).)

8 Safety monitoring

8.1 Adverse events

Definition of an AE: Any untoward medical occurrence in a subject administered a pharmaceutical product temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE 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 medicinal (investigational) product. Anticipated day-to-day fluctuations of the disease under study that do not represent a clinically significant exacerbation or worsening do not need to be considered an adverse event, unless they:

1. fulfill the definition of a serious adverse event, or
2. have worsened and are clinically significant requiring medical intervention other than the use of the rescue medication, or
3. result in discontinuation of subject from the study.

Investigational Medicinal Product (IMP) includes the drug under evaluation and the comparator drug(s) if specified as part of the research objective, given at any time during the study. Medical conditions/ diseases present before starting the drug of interest are only considered adverse events if they worsen after starting the drug of interest. Beginning at visit 3 and throughout the study, the Investigator and study staff will record all adverse events on an adverse event form to be maintained in the subject's research chart, regardless of the severity or relationship to investigational product or procedure. The form will include observation date and resolution date.

All adverse events will be graded by severity using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, May 28, 2009 listed below:

Grade 1= Mild adverse event

Grade 2= Moderate adverse event

Grade 3= Severe and undesirable adverse event

Grade 4= Life threatening or disabling adverse event

Grade 5= Death

Assessment of Causality

The principal or co-investigator will assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product will be considered and investigated.

The relationship between as adverse event and the investigational product will be recorded on the study adverse event form. The NCI-CTCAE provides the following descriptors and definitions for assigning relationship. This NCI nomenclature will be used but causality will be judged by the investigators in the context of asthma.

Code	Descriptor	Definition
1	Unrelated	The event is clearly not related to the investigational product
2	Unlikely	The adverse event is doubtfully related to the investigational product
3	Possible	The adverse event may be related to the investigational product
4	Probable	The adverse event is likely related to the investigational product
5	Definite	The adverse event is clearly related to the investigational product

Study Related Non-serious and Unexpected or Expected Adverse Event Reporting

All non-serious and unexpected adverse events will be kept in an adverse event log and reported annually to the study DSMC until the completion of the study. Other adverse events, for any study procedures or use of investigational product, that are both not serious and expected will not be reported to the study DSMC. These are the expected adverse events listed in the protocol and consent as possible results from a study procedure. The investigator will meet all local reporting requirements as dictated by the UW IRB.

The most common adverse events associated with study drug administration include allergic reaction to the study medication, nausea, headache, swelling of the inside of the nose, throat or sinuses, cough, joint pain, and upper respiratory infections.

8.2 Serious adverse event reporting

A serious adverse event (SAE) or reaction is defined (21 CFR 312.32 (a)) as any adverse event occurring at any dose that suggests a significant hazard, contraindication, side effect or precaution. This includes, but may not be limited to any of the following events:

- Death: A death occurring during the study or which comes to the attention of the Investigator during the protocol-defined follow-up after the completion of therapy, whether or not considered treatment-related, must be reported.
- Life-threatening: Any adverse therapy experience that places the participant or participant, in the view of the Investigator, at immediate risk of death from the reaction as it occurred.
- Hospitalization or prolongation of existing hospitalization.
- Persistent or significant disability/incapacity.
- Congenital anomaly/birth defect.
- An event that required intervention to prevent permanent impairment or damage.

An important medical event that does not meet the criteria listed above may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether reporting is appropriate in other situations. These situations might include an important medical event 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 one of the other outcomes listed in the above definition.

Timelines: All serious adverse events (SAEs) from interventional clinical trials must be reported by the sites to Novartis and UW Madison DSMB within 24 hours of occurrence of the SAE. The timelines for investigator initiated trials reporting to Novartis will be done as per Third Party Study/Investigator Initiated Trial Agreement.

8.2.1 Adverse Event of Special Interest

Adverse Events of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the Product. Special interest AEs will be collected and reported to the Sponsor per SAE guidelines.

The XOLAIR® (omalizumab) Events of Special Interest are:

- Anaphylaxis
- Drug-induced liver injury
- Suspected transmission of an infectious agent by the study drug

8.2.2 Follow-up reports

SAEs will be followed until resolution or until it is judged to be permanent, and an assessment will be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the drug of interest, the interventions required to treat it, and the outcome.

The Sponsor shall support Novartis in the following-up of all SAEs so that complete information is available to maintain patient safety and also as part of any commitments by Novartis to any Health authority OR specific Health authority follow-up requests for the product under investigation.

We will use the UW-ICTR for local data monitoring oversight. This plan includes the use of the ICTR OnCore clinical research management (OnCore-CRM) system which allows more efficient tracking of protocols and protocol subjects. ICTR OnCore-CRM is a secure, web-based, customizable information system that addresses issues related to the costs and complexities associated with conducting clinical trials. It provides fully integrated clinical data management, study administration, and financial management capabilities for a portfolio of clinical trials. The ICTR OnCore-CRM system is specifically designed to improve the efficiency and effectiveness of clinical research at large research centers by facilitating core activities such as study setup and activation, accrual, clinical data collection and analysis, data and safety monitoring, financial management, and regulatory compliance.

Safety Review Plan – We plan to utilize the UW ICTR Data Monitoring Committee (DMC) to oversee the study. Study progress and safety will be reviewed annually (and more frequently if needed) by the DMC. The UW ICTR DMC is comprised of experienced members with expertise required to oversee this study. The DMC members will review protocol-specific reports created by statisticians using data pulled from the ICTR OnCore clinical research management system. Progress reports, including patient recruitment, retention/attrition, and AEs will be provided to the Data Monitoring Committee following each of the annual reviews. The DMC members will review protocol-specific reports created by statisticians that serve a non-voting member role on the DMC using data extracted from the ICTR OnCore-CRM system. These standard reports will include an overview of study objectives, a review of actual and projected accrual rates, an evaluation of subject demographics, a summary of the number and seriousness of adverse events. An interim analysis of study results may be performed and source documents may be reviewed to allow the DMC to independently judge whether the overall integrity and conduct of the protocol remain acceptable based on data provided and reported by the Principal Investigator. The DMC will make recommendations to the Principal Investigator that could include actions of continuation, modification, suspension, or termination.

8.2.3 Individual and Overall Study Stopping Rules

Based upon the definition of Serious Adverse Event as described in 21 CFR 312.32.

Individual Safety Stopping Rules

Individuals will be stopped from the study if the following events occur:

a. If anaphylaxis or hypersensitivity AEs occur within 2 hours of administration of study drug.
b. If anaphylaxis or hypersensitivity AEs occur within 8 hours of study drug on consecutive administrations.
c. If SAE of angioedema or severe allergic reaction, e.g. anaphylaxis, involves hospitalization.

Anaphylaxis to drug will be distinguished from Angioedema activity primarily by clinical evaluation of symptoms and timing of reaction. Anaphylaxis often involves multiple organ systems whereas Angioedema will only be skin without

hives. Anaphylaxis to drug will occur soon after administration (unlikely more than 2 hours later) whereas Angioedema can occur at any time.

Overall Safety Stopping Rules

The study will be stopped if:

a. A research related death occurs in any subject.
b. An event occurs that the investigator feels warrants halting of the study.
c. If >25% enrolled subjects (after at least 8 subjects enrolled) experience study drug-related AEs.
d. The same or similar serious and unexpected adverse event associated with the investigational product that occurs in at least two subjects. This may include a potentially life-threatening event, event requiring hospitalization, or any event that may potentially result in serious harm to other research subjects.
e. For non-serious adverse events, if more than 25% of research subjects meet the

8.3 Pregnancies

To ensure patient safety, each pregnancy in a patient (or a patients' partner) on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy will be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

REPRODUCTIVE RISKS
Pregnancy ***Category B***

Female who become pregnant during the study or males whose partner becomes pregnant during the study, must immediately inform the study doctor. The doctor will discuss the risks of continuing with the pregnancy and the possible effects on the fetus. The subject's doctor should monitor until the conclusion of the pregnancy.

9 Data review and database management

9.1 Data collection

Data Quality and Management
1. Description of Plan for Data Quality and Management– The PI, or study staff, will review all data collection forms on an ongoing basis for data completeness and accuracy as well as protocol compliance. When possible, data will be collected using programs that allow direct transfer to a spreadsheet, in order to avoid human error. When data must be manually entered, double-entry will be used to allow accuracy checks. Accuracy checks will be performed by a different individual than those involved in data entry.
2. Frequency of Data Review for these Studies – The frequency of data review for this study will include annual review of subject accrual (adherence to protocol regarding demographics, inclusion/exclusion), adverse event rates (injuries), and out of range (non-clinically significant) laboratory data. The PI and Data Monitoring Committee will review these data annually.

9.2 Database management and quality control

Data will be maintained in a REDCap and Oncore database, and it will be the responsibility of the database manager to ensure data is entered in a timely manner and to perform routine quality control checks of the database.The REDCap server is housed in a state-of-the-art data center managed by the UW SMPH network staff. The levels of security for the server are fivefold and include: 1) Physical Security: server is located in a secure data center under control of UW School of Medicine and Public Health (SMPH) ITS, which is a dedicated computer machine room (passkey access only) containing emergency backup power, an uninterruptible power supply (UPS), and an automatic fire detection and suppression system. SMPH ITS does not have access to the

DOM RedCap server; 2) Access controls: Data access is limited to DOM Faculty and staff approved individuals; 3) Domain access restrictions: access to DOM computing resources, including the DOM RedCap Server, is restricted to individuals with a logon ID for the DOM Domain. Logon IDs are issued only upon approval of the Administrator or Data Custodian (PI); 4) Authentication: Password protection is used at the network level for all transactions that allow entry and editing of data, provide access to EPHI data, or administrative activities, and; 5) Firewall: located behind UW-Madison SMPH firewall.

We will use the UW-ICTR for local data monitoring oversight. This plan includes the use of the ICTR OnCore clinical research management (OnCore-CRM) system which allows more efficient tracking of protocols and protocol subjects. ICTR OnCore-CRM is a secure, web-based, customizable information system that addresses issues related to the costs and complexities associated with conducting clinical trials. It provides fully integrated clinical data management, study administration, and financial management capabilities for a portfolio of clinical trials. The ICTR OnCore-CRM system is specifically designed to improve the efficiency and effectiveness of clinical research at large research centers by facilitating core activities such as study setup and activation, accrual, clinical data collection and analysis, data and safety monitoring, financial management, and regulatory compliance.

The PI, or study staff, will review all data collection forms on an ongoing basis for data completeness and accuracy as well as protocol compliance. When possible, data will be collected using programs that allow direct transfer to a spreadsheet, in order to avoid human error. When data must be manually entered, double-entry will be used to allow accuracy checks. Accuracy checks will be performed by a different individual than those involved in data entry.

The frequency of data review for this study will include annual review of subject accrual (adherence to protocol regarding demographics, inclusion/exclusion), adverse event rates (injuries), and out of range (non-clinically significant) laboratory data. The PI and Data Monitoring Committee will review these data annually.

10 Data analysis

10.1 Populations for analysis

Data will be analyzed in the following treatment groups

1.) An intent-to-treat analysis of all randomized individuals, omalizumab vs. placebo
2.) A per-protocol analysis of all individuals who received at least 4 study doses, omalizumab vs. placebo

Interim analysis may be conducted at the discretion of the study's statistician and principal investigators.

10.2 Patient demographics/other baseline characteristics

Due to the small sample size, patient demographics will not be used in the data analysis of this study, however for the purposes of publication and reporting we will report the distribution per group of the following: gender, age, race, and ethnicity.

The following baseline characteristics will also be assessed for distribution, AAS 7 scores, AeQoL score, visual analog scores, and other laboratory data (Urine n-methyl histamine, Urine 11β-PGF2α, Urine PGD2, and Chronic urticaria index). Chronic urticaria index will only be deemed usable if the participant has not taken prednisone within 14 days of testing.

10.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Due to the small sample size, at this time the data will not be analyzed for individual rescue medications, however the usage of rescue medication by individuals will be reported.

Study drug and compliance will not be analyzed, other than general reporting.

10.4 Analysis of the primary objective(s)

10.4.1 Variable

The primary outcome is the change in the 7-day Angioedema Activity Score (AAS7) from baseline to end of treatment period.

10.4.2 Statistical hypothesis, model, and method of analysis

The primary analysis will estimate the effect of treatment, compared to placebo, on the change in Angioedema Activity Score (AAS7) from baseline to the end of the treatment period using analysis of covariance (ANCOVA) with treatment group and baseline AAS7 as covariates. The goal of this analysis is to obtain an estimate and 95% confidence interval for the mean treatment effect.

10.4.3 Handling of missing values/censoring/discontinuations

Missing data due to missed visits or early study withdrawal will be addressed using multiple imputation of missing data and results from the multiply-imputed data sets combined using the Rubin method.
Treatment groups will be compared as-randomized using the intention-to-treat principle.

10.4.4 Supportive analyses

The mean treatment effect estimate with 95% CI will also be reported from the model without baseline AASS7 covariate. Departures from a normal distribution will be addressed using data transformations such as the logarithm, square root, or other power transformation, and nonparametric regression methods will also be considered. Analyses of longitudinal AAS measurements obtained monthly during the treatment period and at the 9 month follow up visit will be examined using linear mixed effect models.

10.5 Analysis of secondary objectives

10.5.1 Efficacy (secondary)

The effect of treatment compared to placebo on the change in IAE severity from baseline to the end of the treatment period as recorded on a 0-100 visual analog scale will be estimated using ANCOVA with treatment group and baseline AAS severity as covariates. The treatment effect on the change in AE-QoL will be estimated using similar models with treatment group and baseline AE-QoL as covariates. The change in frequency of IAE episodes and their total duration in hours (frequency x duration) will be
compared using similar baseline-adjusted models. The occurrence (any vs none) and frequency of urgent care visits, ER visits, rescue medication and corticosteroid use will be compared using similar baseline- adjusted generalized linear models including logistic regression for occurrence and count regression such as Poisson or negative binomial regression for frequency variables as appropriate. Laboratory measurements including CD63 and CD203 basophil expression, tryptase, bradykinin and its degradation products, and platelet activating factor (PAF) will be compared using similar baseline-adjusted models.
Measurements obtained longitudinally during the treatment period and at the 9 month follow up visit will be compared between groups using (generalized) linear mixed effect models.

10.6 Sample size calculation

Based on estimated (Weller et al. Allergy 2013) AAS7 standard deviations at baseline and at 6 months of 9.5 and a correlation of 0.5 between them, we estimate the standard deviation for the baseline to 6 month change as $(2 \times 9.5^2 \times (1-0.5))^{1/2} = 9.5$. Under this assumption, enrolling 20 subjects per group will provide an estimate of the size of the treatment effect- the difference in the baseline to 6 month change between treatment and placebo groups- with a margin of error (half-width of 95% CI) of 6.1. Based on a chart review of patients followed for a diagnosis in the UW Health Allergy Clinics, we estimate 100 patients will meet inclusion criteria. Given the additional 988 patients seen in non-Allergy clinics, we expect the recruitment of 40 subjects is feasible.

10.7 Power for analysis of critical secondary variables

Assuming an IAE severity (0-100 visual analog scale) change from baseline standard deviation of 13.8 (Cicardi, M et al, 2010), we estimate enrolling 20 participants per group will provide an estimate of the treatment effect with a margin of error of 8.8. Assuming an AE-QoL change from baseline standard deviation of 15 (Weller et al Allergy 2012), we estimate enrolling 20 participants per group will provide an estimate of the treatment effect with a margin of error of 9.6.

11 Ethical considerations

11.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.
Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.3 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation.

11.4 Publication of study protocol and results

The University of Wisconsin-Madison study team will be responsible for all study data and its analysis. The PIs, Dr. Viswanathan and Dr. Mathur, reserve the right to prepare all manuscripts, and scientific presentations of the data at the conclusion of the study. All manuscripts and any form of presentation will be sent to Novartis for pre-approval prior to public dissemination.

This study is required by law to be listed on the clinicaltrials.gov website for the entire trial, and for the investigators involved to abide by all of the site rules and regulations for dissemination of results and data.

12 Protocol adherence

12.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB. Only amendments that are required for patient safety may be implemented prior to IRB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol.

13 References

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Appendix 1:

Angioedema Activity Score

AAS

(Angioedema Activity Score)

Angioedema activity documentation

Patient name: _____

Date questionnaire completed (dd mm yyyy): ____ ____ _____

Week 1:

Instructions: Please document your symptoms retrospectively once a day. Refer to the last 24 hours in each case. Please answer all questions as fully as possible

		Day						
		1	2	3	4	5	6	7
Have you had a swelling episode in the last 24 hours?	no							
	yes							
⇩ **Please answer the questions below about this swelling episode during the last 24 hours. If you did not have a swelling episode, leave them blank.**								
At what time(s) of day was this swelling episode(s) present? (please select all applicable times)	midnight – 8 a.m.							
	8 a.m. – 4 p.m.							
	4 p.m. - midnight							
How severe is / was the physical discomfort caused by this swelling episode(s) (e.g., pain, burning, itching?)	no discomfort							
	slight discomfort							
	moderate discomfort							
	severe discomfort							
Are / were you able to perform your daily activities during this swelling episode(s)?	no restriction							
	slight restriction							
	severe restriction							
	no activities possible							
Do / did you feel your appearance is / was adversely affected by this swelling episode(s)?	no							
	slightly							
	moderately							
	severely							
How would you rate the overall severity of this swelling episode?	negligible							
	mild							
	moderate							
	severe							

AAS

(Angioedema Activity Score)

Angioedema activity documentation

Week 2:

Instructions: Please document your symptoms retrospectively once a day. Refer to the last 24 hours in each case. Please answer all questions as fully as possible

		Day						
		1	2	3	4	5	6	7
Have you had a swelling episode in the last 24 hours?	no							
	yes							
⇩ **Please answer the questions below about this swelling episode during the last 24 hours. If you did not have a swelling episode, leave them blank.**								
At what time(s) of day was this swelling episode(s) present? (please select all applicable times)	midnight – 8 a.m.							
	8 a.m. – 4 p.m.							
	4 p.m. - midnight							
How severe is / was the physical discomfort caused by this swelling episode(s) (e.g., pain, burning, itching?)	no discomfort							
	slight discomfort							
	moderate discomfort							
	severe discomfort							
Are / were you able to perform your daily activities during this swelling episode(s)?	no restriction							
	slight restriction							
	severe restriction							
	no activities possible							
Do / did you feel your appearance is / was adversely affected by this swelling episode(s)?	no							
	slightly							
	moderately							
	severely							
How would you rate the overall severity of this swelling episode?	negligible							
	mild							
	moderate							
	severe							

AAS

(Angioedema Activity Score)

Angioedema activity documentation

Week 3:

Instructions: Please document your symptoms retrospectively once a day. Refer to the last 24 hours in each case. Please answer all questions as fully as possible

		Day						
		1	2	3	4	5	6	7
Have you had a swelling episode in the last 24 hours?	no							
	yes							
⇩ **Please answer the questions below about this swelling episode during the last 24 hours. If you did not have a swelling episode, leave them blank.**								
At what time(s) of day was this swelling episode(s) present? (please select all applicable times)	midnight – 8 a.m.							
	8 a.m. – 4 p.m.							
	4 p.m. - midnight							
How severe is / was the physical discomfort caused by this swelling episode(s) (e.g., pain, burning, itching?)	no discomfort							
	slight discomfort							
	moderate discomfort							
	severe discomfort							
Are / were you able to perform your daily activities during this swelling episode(s)?	no restriction							
	slight restriction							
	severe restriction							
	no activities possible							
Do / did you feel your appearance is / was adversely affected by this swelling episode(s)?	no							
	slightly							
	moderately							
	severely							
How would you rate the overall severity of this swelling episode?	negligible							
	mild							
	moderate							
	severe							

AAS

(Angioedema Activity Score)

Angioedema activity documentation

Week 4:

Instructions: Please document your symptoms retrospectively once a day. Refer to the last 24 hours in each case. Please answer all questions as fully as possible

		Day						
		1	2	3	4	5	6	7
Have you had a swelling episode in the last 24 hours?	no							
	yes							
⇩ **Please answer the questions below about this swelling episode during the last 24 hours. If you did not have a swelling episode, leave them blank.**								
At what time(s) of day was this swelling episode(s) present? (please select all applicable times)	midnight – 8 a.m.							
	8 a.m. – 4 p.m.							
	4 p.m. - midnight							
How severe is / was the physical discomfort caused by this swelling episode(s) (e.g., pain, burning, itching?)	no discomfort							
	slight discomfort							
	moderate discomfort							
	severe discomfort							
Are / were you able to perform your daily activities during this swelling episode(s)?	no restriction							
	slight restriction							
	severe restriction							
	no activities possible							
Do / did you feel your appearance is / was adversely affected by this swelling episode(s)?	no							
	slightly							
	moderately							
	severely							
How would you rate the overall severity of this swelling episode?	negligible							
	mild							
	moderate							
	severe							

AAS

(Angioedema Activity Score)

Scoring Template

The AAS consists of 5 questions as well as an opening question. A score between 0 and 3 is assigned to every answer field. The question scores are summed up to an AAS day sum score, 7 AAS day sum scores to an AAS week sum score (AAS7), and 4 ASS week sum scores may be summed up to an AAS 4-week sum score (AAS28). Accordingly, the minimum and maximum possible AAS scores are 0-15 (AAS day sum score), 0-105 (AAS7), and 0-420 (AAS28).
The opening question may be used to count the number of angioedema affected days during the AAS documentation period but has no score.

Days of week 1						
1	**2**	**3**	**4**	**5**	**6**	**7**
n	n	n	n	n	n	n
y	y	y	y	y	y	y
1	1	1	1	1	1	1
1	1	1	1	1	1	1
1	1	1	1	1	1	1
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
Day sum scores						
Week sum score						

Days of week 2						
1	**2**	**3**	**4**	**5**	**6**	**7**
n	n	n	n	n	n	n
y	y	y	y	y	y	y
1	1	1	1	1	1	1
1	1	1	1	1	1	1
1	1	1	1	1	1	1
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
Day sum scores						
Week sum score						

Days of week 3						
1	**2**	**3**	**4**	**5**	**6**	**7**
n	n	n	n	n	n	n
y	y	y	y	y	y	y
1	1	1	1	1	1	1
1	1	1	1	1	1	1
1	1	1	1	1	1	1
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
Day sum scores						
Week sum score						

Days of week 4						
1	**2**	**3**	**4**	**5**	**6**	**7**
n	n	n	n	n	n	n
y	y	y	y	y	y	y
1	1	1	1	1	1	1
1	1	1	1	1	1	1
1	1	1	1	1	1	1
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
Day sum scores						
Week sum score						

4-Week sum score

AAS

(Angioedema Activity Score)

Scoring Template

Example for AAS scoring:

Days of week 1						
1	2	3	4	5	6	7
n	n	X	X	X	X	X
X	X	y	y	y	y	y
1	X	1	1	1	1	1
X	X	1	1	1	1	1
X	X	1	1	1	1	1
0	0	0	0	0	0	0
1	1	1	1	1	1	1
X	X	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
X	X	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
X	X	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
X	X	2	2	2	2	2
3	3	3	3	3	3	3

Day sum scores						
9	10	0	0	0	0	0
Week sum score						
19						

Days of week 2						
1	2	3	4	5	6	7
X	n	n	n	X	X	X
y	X	X	X	y	y	y
1	1	X	X	1	1	1
1	1	X	X	1	1	1
1	X	X	1	1	1	1
0	0	0	0	0	0	0
1	1	1	X	1	1	1
2	X	X	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	X	1	1	1
2	X	X	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	X	2	2	2
3	X	X	3	3	3	3
0	0	0	0	0	0	0
1	1	1	X	1	1	1
2	X	X	2	2	2	2
3	3	3	3	3	3	3

Day sum scores						
0	10	12	7	0	0	0
Week sum score						
29						

Days of week 3						
1	2	3	4	5	6	7
X	X	X	X	X	X	X
y	y	y	y	y	y	y
1	1	1	1	1	1	1
1	1	1	1	1	1	1
1	1	1	1	1	1	1
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3

Day sum scores						
0	0	0	0	0	0	0
Week sum score						
0						

Days of week 4						
1	2	3	4	5	6	7
X	n	n	n	X	X	X
y	X	X	X	y	y	y
1	1	X	X	1	1	1
1	X	X	1	1	1	1
1	X	X	1	1	1	1
0	0	0	0	0	0	0
1	1	X	X	1	1	1
2	X	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	X	0	0	0
1	1	1	1	1	1	1
2	2	X	2	2	2	2
3	X	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	X	1	1	1
2	2	X	2	2	2	2
3	X	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	X	1	1	1
2	2	X	2	2	2	2
3	X	3	3	3	3	3

Day sum scores						
0	13	10	4	0	0	0
Week sum score						
27						

4-Week sum score
75

AAS

(Angioedema Activity Score)

Scoring Template

The AAS consists of 5 questions as well as an opening question. A score between 0 and 3 is assigned to every answer field. The question scores are summed up to an AAS day sum score, 7 AAS day sum scores to an AAS week sum score (AAS7), and 4 ASS week sum scores may be summed up to an AAS 4-week sum score (AAS28). Accordingly, the minimum and maximum possible AAS scores are 0-15 (AAS day sum score), 0-105 (AAS7), and 0-420 (AAS28).
The opening question may be used to count the number of angioedema affected days during the AAS documentation period but has no score.

Days of week 1						
1	**2**	**3**	**4**	**5**	**6**	**7**
n	n	n	n	n	n	n
y	y	y	y	y	y	y
1	1	1	1	1	1	1
1	1	1	1	1	1	1
1	1	1	1	1	1	1
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3

Days of week 2						
1	**2**	**3**	**4**	**5**	**6**	**7**
n	n	n	n	n	n	n
y	y	y	y	y	y	y
1	1	1	1	1	1	1
1	1	1	1	1	1	1
1	1	1	1	1	1	1
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3

Days of week 3						
1	**2**	**3**	**4**	**5**	**6**	**7**
n	n	n	n	n	n	n
y	y	y	y	y	y	y
1	1	1	1	1	1	1
1	1	1	1	1	1	1
1	1	1	1	1	1	1
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3

Days of week 4						
1	**2**	**3**	**4**	**5**	**6**	**7**
n	n	n	n	n	n	n
y	y	y	y	y	y	y
1	1	1	1	1	1	1
1	1	1	1	1	1	1
1	1	1	1	1	1	1
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3

Day sum scores						
Week sum score						

Day sum scores						
Week sum score						

Day sum scores						
Week sum score						

Day sum scores						
Week sum score						

4-Week sum score

AAS

(Angioedema Activity Score)

Scoring Template

Example for AAS scoring:

Days of week 1						
1	2	3	4	5	6	7
n	n	X	X	X	X	X
X	X	y	y	y	y	y
1	X	1	1	1	1	1
X	X	1	1	1	1	1
X	X	1	1	1	1	1
0	0	0	0	0	0	0
1	1	1	1	1	1	1
X	X	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
X	X	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
X	X	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
X	X	2	2	2	2	2
3	3	3	3	3	3	3
Day sum scores						
9	10	0	0	0	0	0
Week sum score						
19						

Days of week 2						
1	2	3	4	5	6	7
X	n	n	n	X	X	X
y	X	X	X	y	y	y
1	1	X	X	1	1	1
1	1	X	X	1	1	1
1	X	X	1	1	1	1
0	0	0	0	0	0	0
1	1	1	X	1	1	1
2	X	X	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	X	1	1	1
2	X	X	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	X	2	2	2
3	X	X	3	3	3	3
0	0	0	0	0	0	0
1	1	1	X	1	1	1
2	X	X	2	2	2	2
3	3	3	3	3	3	3
Day sum scores						
0	10	12	7	0	0	0
Week sum score						
29						

Days of week 3						
1	2	3	4	5	6	7
X	X	X	X	X	X	X
y	y	y	y	y	y	y
1	1	1	1	1	1	1
1	1	1	1	1	1	1
1	1	1	1	1	1	1
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	1	1	1	1
2	2	2	2	2	2	2
3	3	3	3	3	3	3
Day sum scores						
0	0	0	0	0	0	0
Week sum score						
0						

Days of week 4						
1	2	3	4	5	6	7
X	n	n	n	X	X	X
y	X	X	X	y	y	y
1	1	X	X	1	1	1
1	X	X	1	1	1	1
1	X	X	1	1	1	1
0	0	0	0	0	0	0
1	1	X	X	1	1	1
2	X	2	2	2	2	2
3	3	3	3	3	3	3
0	0	0	X	0	0	0
1	1	1	1	1	1	1
2	2	X	2	2	2	2
3	X	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	X	1	1	1
2	2	X	2	2	2	2
3	X	3	3	3	3	3
0	0	0	0	0	0	0
1	1	1	X	1	1	1
2	2	X	2	2	2	2
3	X	3	3	3	3	3
Day sum scores						
0	13	10	4	0	0	0
Week sum score						
27						

4-Week sum score
75

Instructions for evaluation of the AAS

AAS scoring system:

The Angioedema Activity Score (AAS) consists of only 5 questions. The AAS scoring system is very easy. A score between 0 and 3 is assigned to every field that can be ticked by the completing patient. The fields ticked by the patient are summed up to a total score. Accordingly, the minimum and maximum possible AAS scores are 0 and 15. The answer to the first question does not get any points and is not included in the computation of the AAS score. Please find the score for each field in the template below. This template is only meant to be used for the AAS score calculations. The patients must not see this template.

AAS scoring template:

		Day						
		1	2	3	4	5	6	7
Did you experience a swelling during the last 24 hours?	no							
	yes							
⇩ **Please answer the questions below only in case you did experience a swelling during the last 24 hours!**								
In which period(s) did you have the swelling(s)? (please choose all applicable periods)	midnight - 8 a.m.	1	1	1	1	1	1	1
	8 a.m. – 4 p.m.	1	1	1	1	1	1	1
	4 p.m. - midnight	1	1	1	1	1	1	1
How strong is or was the physical discomfort caused by the swellings (e.g. pain, burning, itching)?	none	0	0	0	0	0	0	0
	mild	1	1	1	1	1	1	1
	moderate	2	2	2	2	2	2	2
	severe	3	3	3	3	3	3	3
Did you experience any limitations regarding your normal daily activities because of the current swelling(s)?	no limitations	0	0	0	0	0	0	0
	slight limitations	1	1	1	1	1	1	1
	strong limitations	2	2	2	2	2	2	2
	daily activities not possbile	3	3	3	3	3	3	3
Do or did you feel disfigured because of the current swelling(s)?	no	0	0	0	0	0	0	0
	mild	1	1	1	1	1	1	1
	moderate	2	2	2	2	2	2	2
	severe	3	3	3	3	3	3	3
As how strong would you overall rate the current swelling(s)?	negligible	0	0	0	0	0	0	0
	mild	1	1	1	1	1	1	1
	moderate	2	2	2	2	2	2	2
	severe	3	3	3	3	3	3	3

Appendix 2:

Angioedema Quality of Life Scores

AE-QoL

Quality of Life Questionnaire for Patients with Recurrent Swelling Episodes

Patient name: _____

Date questionnaire completed (dd mmm yyyy): _____ _____ _____

Instructions: This questionnaire asks a number of questions. Please read each question carefully and choose from the five answers the one that fits best for you. Please do not think too long about the questions; be sure to answer all of the questions and to give only one answer to each question, i.e., to check only one box for each question.

Indicate how often within the **last 4 weeks** you have been restricted in the areas of your daily life listed below because of swelling episodes (angioedema). (regardless of whether or not you have actually experienced swelling episodes during that time period)	**Never**	**Rarely**	**Occasionally**	**Often**	**Very often**
1. Work	☐	☐	☐	☐	☐
2. Physical activity	☐	☐	☐	☐	☐
3. Leisure time	☐	☐	☐	☐	☐
4. Social relations	☐	☐	☐	☐	☐
5. Eating and drinking	☐	☐	☐	☐	☐
In the following questions we would like to get more details about the difficulties and problems that may be associated with your recurrent swelling episodes (angioedema) (during the **last 4 weeks**)	**Never**	**Rarely**	**Occasionally**	**Often**	**Very often**
6. Do you have difficulty falling asleep?	☐	☐	☐	☐	☐
7. Do you wake up during the night?	☐	☐	☐	☐	☐
8. Are you tired during the day because you are not sleeping well at night?	☐	☐	☐	☐	☐
9. Do you have trouble concentrating?	☐	☐	☐	☐	☐

	Never	Rarely	Occasionally	Often	Very often
10. Do you feel depressed?	☐	☐	☐	☐	☐
11. Do you have to limit your choices of food or beverages?	☐	☐	☐	☐	☐
12. Do the swelling episodes place a burden on you?	☐	☐	☐	☐	☐
13. Are you afraid that a swelling episode could occur suddenly?	☐	☐	☐	☐	☐
14. Are you afraid that the frequency of the swelling episodes might increase?	☐	☐	☐	☐	☐
15. Are you ashamed to go out in public because of the swelling episodes?	☐	☐	☐	☐	☐
16. Do the swelling episodes make you embarrassed or self-conscious?	☐	☐	☐	☐	☐
17. Are you afraid that the treatment of the swelling episodes could have negative long-term effects for you?	☐	☐	☐	☐	☐

AE-QoL

Quality of Life Questionnaire for Patients with Recurrent Swelling Episodes

Instructions for evaluation of the AE-QoL (German Version)

The structure of AE-QoL

The German version of AE-QoL consists of four dimensions and a total score:

Dimensions	Item
Functioning	1. Impairment of work
	2. Impairment of physical activity
	3. Impairment of spare time activities
	4. Impairment of social relations
Fatigue/Mood	6. Difficulties of falling asleep
	7. Waking up during the night
	8. Feeling tired during the day
	9. Difficulties in concentrating
	10. Feeling downhearted
Fears/Shame	12. Feeling burdened at having swellings
	13. Fear of new suddenly appearing swellings
	14. Fear of increased frequency of swellings
	15. Ashamed to visit public places
	16. Embarrassed by the apppearence of swellings
	17. Fear of long term negative drug effects
Nutrition	5. General limitations in foods and eating
	11. Limitations in the selection of food and beverages
Total Score	Items 1 to 17

The AE-QoL scale scores as well as the AE-QoL total score are calculated by using the following formula:

(Σ items – min Σ items / max Σ items – min Σ items) x 100

For example: Scale “Functioning”:
Item 1: answer 3
Item 2: answer 2
Item 3: answer 4
Item 4: answer 5
Σ items: (3+2+4+5) = 14
min Σ items: (1+1+1+1) = 4
max Σ items: (5+5+5+5) = 20
Enter values in formula: (14 - 4 / 20 – 4) x 100 = 62.5%

The AE-QoL scale scores correspond to the mean of the items within each scale. If some items are missing, the total of the items within the scale is divided by the number of the non missing items. The same holds for the AE-QoL total score.

An AE-QoL scale score should not be calculated if more than one item is missing in that dimension. The AE-QoL total score should not be calculated if more than 25% of items (>4 items) are missing.

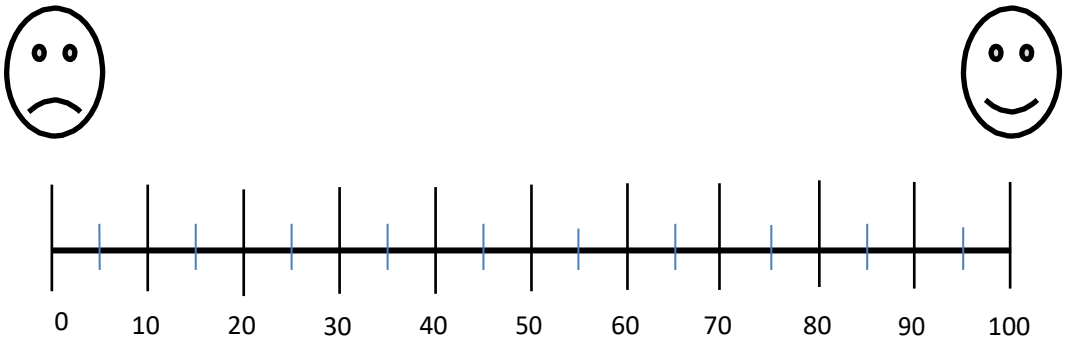
Please not that only calculating the raw scale scores (mean of the item scores within each scale) and the raw total score score (mean of all item scores) would be easier than the above described procedure. However, in case of missing answers, an interindividual as well as an intraindividual comparison of AE-QoL results would be limited. The above described linear transformation of all raw scores into percentage scores (indicating the location of the raw scores in relation (in percent) to its maximum possible score) solves this problem and makes it possible to judge and compare AE-QoL results even when single items are missing. The linear transformation of raw scores results in minimal and highest possible scale and total scores of 0 and 100, respectively.

Appendix 3:

Visual Acuity Score

Visual Acuity Score
Subject Number:
Visit Number
Date:
Read By:

Draw a line where you feel best describes your overall health state at your most recent angioedema event with 100 being the best imaginable state, and 0 being the worst imaginable state.



Appendix 4:
Laboratory Testing Study Grid

Laboratory Testing Study Grid

Study Periods	Screening		Treatment							Follow-Up
Visit Number	1A	1B	2	3	4	5	6	7	8	9
C1 Esterase Inhibitor Panel- if needed (UWHC)		x								
Chronic Urticaria Index (Research lab)		x								
Urine Mast Cell Meditators (UWHC)		x								
CD63/CD203 (Research lab)			x			x			x	x
Tryptase (Research lab)			x			x			x	x
Bradykinin (Research lab)			x			x			x	x
PAF (Research lab)			x			x			x	x