Statistical Analysis Plan

Multinational, Multicenter, Randomized, Double-Blind Study to Evaluate the Efficacy, Pharmacokinetics, Pharmacodynamics, Safety, Tolerability, and Immunogenicity of TEV-45779 Compared to Omalizumab (XOLAIR®) in Patients With Chronic Idiopathic Urticaria/Chronic Spontaneous Urticaria who Remain Symptomatic Despite Antihistamine (H1) Treatment

Study Number TV45779-IMB-30086

NCT04976192

SAP Approval Date: 02 January 2024

STATISTICAL ANALYSIS PLAN

TITLE PAGE

Study Number TV45779-IMB-30086

A Multinational, Multicenter, Randomized, Double-Blind Study to Evaluate the Efficacy, Pharmacokinetics, Pharmacodynamics, Safety, Tolerability, and Immunogenicity of TEV-45779 Compared to Omalizumab (XOLAIR) in Patients With Chronic Idiopathic Urticaria/Chronic Spontaneous Urticaria who Remain Symptomatic Despite Antihistamine (H1) Treatment

Final Version 1 with Amendment 1: Jan 2, 2024

TABLE OF CONTENTS **PAGE**

DECLARATION

I, the undersigned, declare that I have prepared the statistical analysis plan along with TLF mockups and that to the best of my knowledge this document is internally consistent with protocol and scientifically rational.

Prepared by:

[redacted]

I, the undersigned declare that I have reviewed the statistical analysis plan along with TLF mockups and that to the best of my knowledge the document is internally consistent with protocol and scientifically rational.

Reviewed by:

[redacted]

Sign & Date (MMM DD, YYYY)

AUTHORIZATION: I, the undersigned, declare that I have reviewed the statistical analysis plan along with TLF mock-ups and that to the best of my knowledge the document accurately reflects the protocol objectives.

Authorized by:

[redacted]

Teva

REVISION HISTORY

Version	Date	Author	Reasons
Draft 1	Jan 25, 2021	[redacted]	Initial Version
Draft 2	Feb 15, 2021	[redacted]	Updated based on feedback from Teva team
Draft 3	Feb 17, 2021	[redacted]	Additional feedback from Teva team and protocol update
Draft 4	Dec 1, 2021	[redacted]	Update due to Protocol Amendments 1 and 2
Amendment 1	Jan 2, 2024	[redacted]	Corrected confidence level for the penalization analysis

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	Anti-Drug Antibodies
ATC	Anatomic-therapeutic-chemical
BMI	Body Mass Index
CI	Confidence Interval
CIU	Chronic Idiopathic Urticaria
COVID-19	Coronavirus disease 2019
CRSwNP	Chronic rhinosinusitis with nasal polyp
CS	Clinically Significant
CSR	Clinical Study Report
CSU	Chronic spontaneous urticaria
DBL	Database Lock
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EoS	End of Study
EU	European Union
FCS	Fully Conditional Specifications
FDA	Food and Drug Administration
HEENT	head, eyes, ears, nose, and throat
IgE	immunoglobulin E
IgG1	immunoglobulin G1
IMP	investigational medicinal product
ISS7	weekly itch severity score (sum of the daily itch severity score for 7 days)
ITT	intent-to-treat
LTRA	leukotriene receptor antagonist
MAA	Marketing Authorisation Application

Abbreviation or special term	Explanation
mAb	monoclonal antibody
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important difference
mITT	modified intent to treat
mITT1	modified intent to treat 1
MMRM	Mixed model for repeated measures
MNAR	Missing not at random
NCS	Not Clinically Significant
NRS	Numeric Rating Scale
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred term
RTSM	Randomization and Trial Supply Management
SAP	Statistical Analysis Plan
sc	Subcutaneous
SD	Standard Deviation
SOC	System Organ Class
TITT	transition intent-to-treat
TmITT	transition modified intent-to-treat
UAS	urticaria activity score
UAS7	weekly urticaria activity score (sum of the daily number of wheals score and itch severity score over 7 days)
US	United States
WHO-DRL	World Health Organization Drug Reference List

1 INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods and data handling methods to be followed during the final reporting and analyses of data collected for the study Protocol TV45779-IMB-30086 "A Multinational, Multicenter, Randomized, Double Blind Study to Evaluate the Efficacy, Pharmacokinetics, Pharmacodynamics, Safety, Tolerability, and Immunogenicity of TEV 45779 Compared to Omalizumab (XOLAIR®)in Patients With Chronic Idiopathic Urticaria/Chronic Spontaneous Urticaria who Remain Symptomatic Despite Antihistamine (H1) Treatment".

This SAP should be read in conjunction with the study protocol. This version of the plan has been developed using the protocol with Amendment 2 dated 23 Nov 2021.

TEV-45779 is a humanized immunoglobulin G1 (IgG1)/kappa monoclonal antibody (mAb) directed against immunoglobulin E (IgE). TEV-45779 is being developed by the sponsor as a biosimilar candidate to omalizumab, which is licensed under the trade name XOLAIR® for the treatment of allergic asthma, chronic idiopathic urticaria (CIU), and nasal polyps in the United States (US) and allergic asthma, chronic spontaneous urticaria (CSU), and chronic rhinosinusitis with nasal polyps (CRSwNP) in the European Union (EU).

2 STUDY DETAILS

2.1 Study Objectives and Endpoints

The primary and secondary study objectives and endpoints are:

Objectives	Endpoints
The **primary objective** of the study is to demonstrate biosimilar efficacy of TEV-45779 300 mg compared to XOLAIR 300 mg as determined by change in itch severity score of chronic idiopathic urticaria (CIU)/chronic spontaneous urticaria (CSU) in patients who remain symptomatic despite antihistamine (H1) treatment.	The primary efficacy endpoint is: • Change from baseline in the weekly itch severity score (ISS7; sum of the daily itch severity score for 7 days) at Week 12, TEV-45779 300 mg compared to XOLAIR 300 mg
The **co-primary objective** (for the FDA submission only) of the study is to demonstrate relative potency of TEV-45779 compared to XOLAIR as determined by change in itch severity score of CIU/CSU in patients who remain symptomatic despite antihistamine (H1) treatment.	The co-primary efficacy endpoint is: • Relative potency of 2 dose levels (300 mg and 150 mg) of TEV-45779 and XOLAIR as measured by ISS7 at Week 12 using a 4-point assay, ie, TEV-45779 300 mg, TEV-45779 150 mg, XOLAIR 300 mg and XOLAIR 150 mg.
Secondary objectives	
To compare further efficacy parameters between TEV-45779 and XOLAIR. The comparisons will be performed between the different doses (150 mg vs. EU approved300 mg) as well as between TEV 45779 and XOLAIR	Secondary efficacy endpoints are: • Change from baseline in ISS7 at Week 12 • Change from baseline in ISS7 at Week 4, • Change from baseline in the weekly urticaria activity score (UAS7; sum of the daily number of wheals score and itch severity score over 7 days) at Week 12 • Percentage of patients with a UAS7 ≤6 at Week 12 • Percentage of complete responders (UAS7=0) at Week 12 • Change from baseline in the physician's (in-clinic)

Objectives	Endpoints
	assessment of UAS at Week 12 • Change from baseline in the weekly number of wheals score at Week 12 • Change from baseline in the weekly size of the largest wheals score at Week 12 • Time to minimally important difference (MID; reduction from baseline in ISS7 of ≥5 points) response in ISS7 score up to Week 12 • Percentage of ISS7 MID responders at Week 12 (percentage of patients with reduction of ≥5 points from baseline in ISS7 at Week 12). • Percentage of angioedema-free days from Week 4 to Week 12 • Change from baseline in the overall dermatology life quality index (DLQI) score at Week 12
To compare efficacy parameters between TEV-45779 and XOLAIR after the switch from XOLAIR to TEV-45779. The comparisons will be performed between the different doses (150 mg vs. 300 mg) as well as between TEV 45779 and XOLAIR	Secondary efficacy endpoints are: • Change from Week 12 in ISS7 at Week 24 • Change from Week 12 in ISS7 at Week 40 • Change from Week 12 in UAS7 at Week 24 • Change from Week 12 in the physician's (in-clinic) assessment of urticaria activity score (UAS) at Week 24 • Change from Week 12 in the weekly number of wheals score at Week 24 • Change from Week 12 in the weekly number of wheals score at Week 40 • Change from Week 12 in the weekly size of the largest wheals score at Week 24 • Change from Week 12 in the weekly size of the largest wheals score at Week 40 • Percentage of angioedema-free days from Week 12 to Week 24 • Change from Week 12 in the overall DLQI score at

Objectives	Endpoints
	Week 24 • Change from Week 12 in the overall DLQI score at Week 40
To compare the safety and tolerability between TEV-45779 and XOLAIR • throughout the study • after the switch from XOLAIR to TEV-45779	The safety/tolerability parameters include: • Adverse events (and the number of patients who withdraw from the study due to adverse events) • Change from baseline in clinical laboratory measurements (serum chemistry, hematology, and urinalysis) and vital signs • Physical examination findings • Electrocardiogram findings • Local tolerability at the injection site after each investigational medicinal product (IMP) administration • Use of concomitant medication (including use of rescue medication)
To compare pharmacokinetics between TEV-45779 and XOLAIR after multiple doses	The pharmacokinetic parameters are: • Omalizumab serum concentration before next dose (C_{trough}) • Omalizumab serum concentration following last dose at Week 24, 28, 32, 36 and 40
To compare pharmacodynamics between TEV-45779 and XOLAIR after multiple doses	The pharmacodynamic parameters are: • Free immunoglobulin E (IgE) serum concentration • Total IgE serum concentration
To assess the immunogenicity of TEV-45779 in comparison with XOLAIR • throughout the study • after the switch from XOLAIR to TEV-45779	The immunogenicity parameters are: • Incidence of patients with a confirmed anti-drug antibody (ADA) positive sample • For confirmed positive samples, the ADA titer and the neutralizing potential will be tested

2.2 Primary Estimand

The primary estimand for the primary efficacy endpoint for the FDA submission is:

- The difference in mean change from baseline in ISS7 at Week 12 between TEV-45779 300 mg and XOLAIR 300 mg in patients with CIU/CSU who remain symptomatic despite antihistamine (H1) treatment, regardless of treatment-related adverse events. The treatment policy will be applied to account for the intercurrent event of patients discontinuing the treatment early, and patients receiving any disallowed concomitant medication between randomization and Week 12 ISS7 assessment. In order to account for the missing itch severity scores, the following strategy will be applied:
  - Daily itch severity score – If either the morning or evening score is missing, the available (morning or evening) itch severity score for that day will be used as the daily itch severity score, and if both the morning and evening itch severity scores are missing, the daily itch severity score will be considered missing.
  - Weekly itch severity score – If 4-7 daily itch severity scores are available for the calculation of the weekly score, the ISS7 will be defined as the sum of the available daily itch severity scores in that week, divided by the number of days for which a daily itch severity score is available, multiplied by 7. If no more than 3 daily itch severity scores are available (ie, 4-7 daily scores are missing), the ISS7 will be considered missing for that week.
  - Week 12 itch severity score – multiple imputation using the predictive mean matching multiple imputation method, under the MAR assumption for each treatment arm separately.

The primary estimand for the co-primary efficacy endpoint (for the FDA submission) of relative potency is:

- The relative potency of TEV-45779 and XOLAIR as measured by change in ISS7 at Week 12 using a 4-point assay, ie, TEV-45779 300 mg, TEV-45779 150 mg, XOLAIR 300 mg and XOLAIR 150 mg, in patients with CIU/CSU who remain symptomatic despite antihistamine (H1) treatment, regardless of treatment-related adverse events. The treatment policy will be applied to account for the intercurrent event of patients discontinuing the treatment early, and patients receiving any disallowed concomitant medication between randomization and Week 12 ISS7 assessment. The same rules for the missing daily and weekly itch severity score will be applied, as described for the primary endpoint of difference in mean change from baseline in weekly ISS7 at Week 12 between TEV-45779 300mg and XOLAIR 300 mg. Missing Week 12 itch severity scores will not be imputed for the relative potency analysis.

The primary estimand for the primary efficacy endpoint for the EMA submission is:

- The difference in mean change from baseline in weekly itch severity score (ISS7) at Week 12 between TEV-45779 300mg and XOLAIR 300 mg in patients with CIU/CSU

who remain symptomatic despite antihistamine (H1) treatment and have a baseline ISS7 assessment, regardless of treatment-related adverse events. The hypothetical strategy will be applied to account for the intercurrent event of patients discontinuing the treatment early, and patients receiving any disallowed concomitant medication between randomization and Week 12 ISS7 assessment. Thus, any available assessments after the intercurrent event should be excluded and imputed. In order to account for the missing or excluded itch severity scores the same imputation rules will be applied as described for the primary endpoint for the FDA submission.

2.3 Study Design

This is a multicenter, randomized, double-blind study to demonstrate similar efficacy and safety of TEV-45779 compared to XOLAIR administered sc at doses of 300 mg or 150 mg every 4 weeks for 24 weeks (6 treatments) in patients with CIU/CSU who remain symptomatic despite antihistamine (H1) treatment. This study will consist of a screening period (up to 3 weeks), a 24-week treatment period consisting of a 12-week double-blind main treatment period and a 12-week double-blind transition period, which is followed by a 16-week follow-up period.

The total duration of the study is up to 42 weeks.

Standard Treatment

Throughout the entire study, patients should remain on a single H1 antihistamine at stable and fixed doses not exceeding label recommendations as the standard treatment regimen. For the duration of the study, all patients will be provided with diphenhydramine (25 mg, maximum 3 times/day) as rescue medication for itch relief.

Disallowed concomitant treatment include the use of systemic and topical steroids, H1 antihistamines at greater than approved doses, H2 antihistamines, leukotriene receptor antagonists (LTRAs), hydroxychloroquine, methotrexate, cyclosporine, cyclophosphamide, and intravenously-given immunoglobulin.

Study Treatment

Patients will receive a total of 6 treatments, each consisting of 2 sc injections resulting in 150 mg or 300 mg of investigational medicinal product (IMP) (TEV-45779 or XOLAIR) as add on therapy every 4 weeks; patients will receive 3 treatments in the main treatment period and 3 treatments in the transition period.

Main Treatment Period: Following screening, eligible patients will be randomly assigned to treatment with TEV-45779 300 mg, XOLAIR 300 mg, TEV-45779 150 mg or XOLAIR 150 mg in a 2:2:1:1 ratio on day 1 of the main treatment period, stratified by baseline ISS7 (<13 vs. ≥13), and baseline body weight (<80 kg vs. ≥80 kg).

Transition Treatment Period: At the beginning of the transition period (Week 12), patients in the XOLAIR 300 mg and XOLAIR 150 mg groups will be re-randomized 1:1 to either continue with XOLAIR treatment (at the same dose level as prior to re-randomization) or transition to TEV-45779 (at the same dose level as prior to re-randomization) to primarily assess the immunogenicity and safety after the transition from XOLAIR to TEV-45779. All patients in the TEV-45779 group will continue treatment with TEV-45779 at the same dose level as prior to re-randomization.

After the End of Treatment Visit (Week 24), all patients will be followed for 16 weeks.

Patients who complete all scheduled visits will have final procedures and assessments performed at the End of Study Visit at the end of the follow-up (Week 40). Patients who withdraw from the study before completing the follow-up will have early termination procedures and assessments performed at their final visit.

An Independent Data Monitoring Committee (IDMC) will be established to ensure the continuing safety of the study patients during the study

The end of study (EoS) is defined as the last visit of the last patient.

2.3.1 Independent Data Monitoring Committee

During the conduct of this study, an IDMC will review accumulating unblinded safety data on a regular basis and ad hoc if needed, as detailed in the IDMC charter, to ensure the continuing safety of the study patients. The IDMC may request additional data (e.g., efficacy data) if deemed necessary. The IDMC will perform a safety review if any of the pausing criteria listed in the protocol section “Stopping Rules for the Study” is met.

The specific details regarding the IDMC sessions will be outlined in the IDMC charter.

The IDMC will provide recommendations about modifying, stopping, or continuing the study. The conduct and specific details regarding the IDMC sessions will be outlined in the IDMC charter.

2.4 Determination of Sample Size:

A sample size of 600 evaluable patients, randomized 2:2:1:1 to TEV-45779 300 mg, XOLAIR 300 mg, TEV-45779 150 mg or XOLAIR 150 mg, will provide:

- [redacted] power (marginal, eg, regardless of other endpoints) to demonstrate biosimilarity of efficacy based on the difference in change from baseline in ISS7 at Week 12 using 90% CI [redacted] between the TEV-45779 and XOLAIR 300 mg arms (200 patients per arm), [redacted]
- [redacted] power (marginal) to demonstrate biosimilarity of efficacy based on the difference in change from baseline in ISS7 at Week 12 using 95% CI [redacted] between the TEV-45779 and XOLAIR 300 mg arms (200 patients per arm), [redacted]

[redacted]

- [redacted] power to demonstrate biosimilarity of efficacy based on the difference in change from baseline in ISS7 score at Week 12 using 90% CI [redacted] between the TEV-45779 and XOLAIR 300 mg arms (200 patients per arm), [redacted]
- [redacted] power ([redacted]) for the co-primary endpoint of relative potency of TEV-45779 and XOLAIR as measured by change in ISS7 at Week 12 using a 4-point assay, [redacted] (TEV-45779 and XOLAIR at 300 mg and 150 mg).
- [redacted]

The justification for the equivalence margins chosen for the primary efficacy analysis (±2.0 for EMA submission; -2.5, +2.0 for FDA submission; Section 4.6.4) is based on the following reasoning:

- The equivalence margin of ±2.0 for this endpoint preserves 50% of the treatment effect of XOLAIR based on the lower bound of the 95% CI for the pooled XOLAIR treatment effect in placebo controlled studies (Saini et al 2015, Maurer et al 2013, Kaplan et al 2013).
- Mathias et al (2015) estimated a minimal important difference of 4.5 to 5.0 for the ISS7 from clinical data of the above mentioned originator studies. Therefore, demonstration of similarity within a margin of -2.5, +2.0 (ISS7 score points) for the comparison of TEV-45779 and XOLAIR ensures that no clinically important difference may occur between test and reference product. Furthermore, the more negative margin of -2.5 covers a more negative (better) treatment effect difference. Thus, the test product may be better in 2.5 score points and worse in only 2.0 score points than the reference product if similarity could be demonstrated.

Power assessment for the co-primary endpoint of relative potency of TEV-45779 and XOLAIR, as measured by change in ISS7 at Week 12 using a 4-point assay, was performed using the analysis method and the SAS code described in Vezzoli 2011 and simulations based on innovator studies data. The method is detailed in Section 4.6.4.2.

For the simulations, the response of change in ISS7 at Week 12 was assumed to be [redacted] for XOLAIR 150 mg and [redacted] for XOLAIR 300 mg. [redacted]

$\alpha_T + \beta \cdot x_T$ and $Y_R = \alpha_R + \beta \cdot x_R$, respectively. A theoretical relative potency value of 1 was [redacted]

2.5 Randomization and Blinding

This is a randomized double-blind study. At baseline, patients will be randomized in a 2:2:1:1 ratio to receive the first 3 doses of TEV-45779 300 mg, XOLAIR 300 mg, TEV-45779 150 mg or XOLAIR 150 mg (main treatment period). At Week 12, prior to receiving their fourth dose of study medication, patients in the XOLAIR 300 mg and the XOLAIR 150 mg treatment groups will be randomized 1:1 to receive 3 additional doses of XOLAIR (at the same dose level as prior to randomization) or switch to 3 doses of TEV-45779 of the same strength (150 mg or 300 mg) in the transition period. All patients in the TEV-45779 groups will continue to receive TEV-45779 of the same strength. To maintain blinding of the sponsor, patients, investigators (and other site staff involved in study assessments) to the treatment assignment of all patients during the entire study, , the re-randomization process will be performed for all patients, including the patients in the TEV-45779 groups (although only patients in the XOLAIR arm will actually be re-randomized while patients in the TEV-45779 groups will continue to receive TEV-45779 in the transition period). The randomization will be implemented using the Randomization and Trial Supply Management (RTSM) system.

During the main and transition treatment period, the persons who are involved in receipt, storage, distribution, administration, return, and accountability of IMP will be unblinded: these persons will not be involved in the conduct of any study procedures or assessments.

Before database lock (DBL), staff responsible for pharmacokinetic and immunogenicity bioanalysis will not have access to the patient treatment randomization.

Only after completion of the study (after Week 40) and DBL will the study be fully unblinded and analyzed.

3 DATA ANALYSIS CONSIDERATION

3.1 General Principles

The statistical analyses will be performed by [redacted], with approval of the Sponsor, using SAS Version 9.4 (or higher). All tables, figures and listings will be produced in landscape format.

In general, all data will be listed by subject and visit/time point where appropriate. The summary tables will be stratified by, or have columns corresponding to, treatment groups (see section 3.4).

The total number of subjects in the treatment group (N) under the specified analysis set will be displayed in the header of summary tables.

Data will be summarized using descriptive statistics for continuous variables. Unless otherwise specified, descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum. Number of subjects with missing values will also be displayed, but only if non-zero. The minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean and median will be presented to one more decimal place than the original data. The standard deviation will be presented to two more decimal places than the original data.

In summary tables of categorical variables, counts and percentages will be displayed. The count [n] indicates the actual number of subjects in a particular category, which should always be less than or equal to the total number of subjects in the respective study group [M]. Percentage will be obtained by: % = n/M*100. Unless otherwise specified, all percentages will be expressed to one decimal place.

All statistical tests will be two-sided at a significance level of $\alpha = 0.05$, unless otherwise indicated.

Baseline will be defined as the last assessment, scheduled or not, prior to the first dose of the study drug, unless otherwise specified.

Unscheduled and early termination (ET) visits will be mapped to the closest scheduled visit according to the allowed time window specified in Table 1 of the study protocol.

In by-visit summaries, only data collected on scheduled visits/timepoints will be summarized (including unscheduled visits remapped to scheduled ones per the previous paragraph). Data from unscheduled assessments that were not remapped to scheduled visits will be included in listings and may be used in determination of baseline if applicable.

Relative days will be calculated relative to date of first dose of the study drug. Relative days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing relative days).

For assessment on or after the day of first dose of the study drug:

Relative Day = Date of Assessment – Date of First Dose of Study Drug+1.

For assessment before the day of first dose of the study drug:

Relative Day = Date of Assessment – Date of First Dose of Study Drug.

Additionally transition period days will be calculated for data collected in the transition period as

Transition Period Day = Date of Assessments – Date of First Transition Period Dose + 1

Transition period days will be presented in listings of transition period data.

All dates will be displayed in DDMMMYYYY format.

3.2 Coding Dictionaries Used

Medical history and adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0.

Prior & concomitant medication will be coded using World Health Organisation-Drug Reference List (WHO-DRL) version March 2021 and by Anatomical Therapeutic Chemical (ATC) (the highest level available).

3.3 Analysis Sets

3.3.1 Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all randomized patients.

In the ITT analysis set, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

3.3.2 Modified Intent-to-Treat Analysis Set

The modified intent-to-treat (mITT) analysis set will include all randomized patients who received at least 1 dose of IMP and have a non-missing baseline ISS7.

In the mITT analysis set, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

3.3.3 Modified Intent-to-Treat 1 Analysis Set

The modified intent-to-treat1 (mITT1) analysis set will include all randomized patients who received at least 1 dose of IMP and have a non-missing ISS7 at baseline and week 12.

In the mITT1 analysis set, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

3.3.4 Transition Intent-to-treat Analysis Set

The transition intent-to-treat (TITT) analysis set will include all patients re-randomized in the transition period.

In the TITT analysis set, treatment will be assigned based on the treatment to which patients were randomized in the main and transition treatment periods, regardless of which treatment they actually received.

3.3.5 Transition Period Modified Intent to Treat Analysis Set

The transition period modified intent to treat (TmITT) analysis set will include all patients from the mITT analysis set who received IMP at Week 12, and have a non missing ISS7 at Week 12.

In the TmITT analysis set, treatment will be assigned based on the treatment to which patients were randomized in the main treatment period and in the transition period, regardless of which treatment they actually received.

3.3.6 Transition Period Modified Intent to Treat 1 Analysis Set

The transition period modified intent to treat 1 (TmITT1) analysis set will include all patients from the mITT1 analysis set who received IMP at Week 12, and have a non missing ISS7 at Week 24.

In the TmITT1 analysis set, treatment will be assigned based on the treatment to which patients were randomized in the main treatment period and in the transition period, regardless of which treatment they actually received.

3.3.7 Safety Analysis Set

The safety analysis set will include all randomized patients who received at least 1 dose of IMP.

In the safety analysis set, treatment will be assigned based on the treatment patients actually received, regardless of the treatment to which they were randomized, unless otherwise specified.

3.3.8 Transition Period Safety Analysis Set

The transition period safety analysis set will include all patients who received the IMP at Week 12.

In the transition period safety analysis set, treatment will be assigned based upon the treatment patients actually received during and transition period, regardless of the treatment to which they were randomized.

3.3.9 Per-Protocol Analysis Set

The per protocol (PP) analysis set is a subset of the mITT analysis set that includes only patients who remained on treatment up to and including Week 8 (i.e. received all 3 doses in the main treatment period), did not receive any disallowed concomitant medication after randomization up to and including Week 12, had a non-missing ISS7 at Week 12 and completed the main treatment period without any major protocol deviations that may impact the itch severity score biosimilarity assessments, in particular, received the correct randomized treatment.

The exclusion of patients from the PP analysis set will be discussed on a case-by-case basis and documented prior to DBL and unblinding for analysis.

3.3.10 Pharmacokinetic Analysis Set

The pharmacokinetic (PK) analysis set will include those patients from the safety analysis set who have omalizumab serum concentration data for at least 1 time point.

3.4 Treatment Groups

Summaries of the baseline characteristics and assessments in the main treatment period will be presented by the following treatment groups:

- TEV-45779 300 mg
- TEV-45779 150 mg
- XOLAIR 300 mg
- XOLAIR 150 mg

Where appropriate, only a subset of groups will be presented, e.g. only 300 mg groups will be presented for the analysis of the primary endpoint of change from baseline in ISS7 (section 4.6.4).

Summaries of the transition period will be presented by the following treatment groups, based on the subject's treatment in the main treatment period and transition period:

- TEV-45779/TEV-45779 300 mg
- TEV-45779/TEV-45779 150 mg
- XOLAIR/XOLAIR 300 mg
- XOLAIR/XOLAIR 150 mg
- XOLAIR/TEV-45779 300 mg
- XOLAIR/TEV-45779 150 mg

Summaries of assessments in the overall treatment period are planned for the safety analyses only and will include only subjects that stayed on the same treatment throughout the study. They will therefore include the following treatment groups:

- TEV-45779/TEV-45779 300 mg
- TEV-45779/TEV-45779 150 mg
- XOLAIR/XOLAIR 300 mg
- XOLAIR/XOLAIR 150 mg

Total treatment group can be included where appropriate.

3.5 Handling Withdrawals and Missing Data

For all diary-based endpoints, to account for missing itch severity, wheal or urticarial activity scores, the following strategy will be applied:

- Daily score – If either the morning or evening score is missing, the available (morning or evening) score for that day will be used as the daily score, and if both the morning and evening scores are missing, the daily score will be considered missing.
- Weekly score (ISS7, UAS7, weekly number of wheals score, weekly size of the largest wheal sore) – If 4-7 daily scores are available for the calculation of the weekly

score, the weekly score will be defined as the sum of the available daily scores in that week, divided by the number of days for which a daily score is available, multiplied by 7. If no more than 3 daily scores are available (i.e., 4-7 daily scores are missing), the weekly score will be considered missing for that week.

Data imputation is planned for the primary endpoint analysis, see section 4.6 for details. The missing assessments (either due to withdrawal from the study or for other reasons) are assumed to be missing at random (MAR) in this study. The ITT analysis set will be used for the primary analysis.

Underlying assumptions are that the drop-out rate prior to Week 12 will be similar in both treatment groups, and that drop-outs are not related to efficacy. As both treatment groups are active, improvement in the underlying disease should be similar between groups and so, these assumptions are considered reasonable. The assumption that drop-out rates are comparable between the treatment groups will be assessed using descriptive statistics (see section 4.1).

In the primary analysis, missing ISS7 at Week 12 will be imputed based on available assessments using multiple imputation under the MAR assumption (see Section 0); this is a conservative approach for similarity testing, as missing data will be imputed within each treatment group separately.

The imputation methodology is reliable as long as the missing ISS7 rate (i.e. percentage of patients with missing ISS7) at Week 12 is low. Sensitivity and supplementary analyses for missing data in the primary analysis are presented in section 4.6.5 and section 4.6.6.

For all the other variables, only the observed data from the patients will be used in the statistical analyses, ie, there is no plan to estimate missing data, unless otherwise specified.

3.6 Multiple Comparisons and Multiplicity

For the FDA submission, the change from baseline in ISS7 at week 12 for TEV-45779 mg compared to XOLAIR 300mg and the relative-potency endpoint of 2 dose levels (300 mg and 150 mg) of TEV-45779 and XOLAIR, as measured by change in ISS7 at Week 12, are considered co-primary The hierarchical approach for the 2 co primary endpoints will be applied, meaning that the relative potency endpoint will be tested for biosimilarity only if the similarity is shown for the primary endpoint of change from baseline in ISS7 at Week 12 for TEV 45779 300 mg compared to EU approved XOLAIR 300 mg.

The secondary efficacy analyses will be descriptive in nature, with no predefined control for multiplicity.

4 ANALYSIS METHODS

4.1 Disposition

The number of patients screened, patients screened but not randomized, and patients randomized in the main treatment period, in the transition period and in the follow-up period will be presented by treatment group.

For the main treatment period, the summary will include number and percentage of patients who were randomized (ITT analysis set), included in the mITT, mITT1, safety, PK, PP and PK analysis sets, patients that withdrew up to week 12, and patients that completed the main treatment period. Patients that withdrew will also be summarized by reason for withdrawal as recorded in the disposition eCRF. The percentages will be based on the number of randomized patients.

For the transition period, the summary will include number and percentage of patients randomized (TITT analysis set), patients in the TmITT, TmITT1 and transition period safety analysis sets, patients that withdraw during the transition period, and patients that completed the transition period. Patients that withdrew will also be summarized by reason for withdrawal as recorded in the disposition eCRF. The percentages will be based on the number of patients who were re-randomized for the transition period.

For the follow-up period, the summary will include number and percentage of patients who completed the follow-up period (i.e. completed the study) and discontinued in the follow-up period (i.e. completed the transition period, but did not complete the study) by reason for discontinuation. This summary will be based on the subjects who completed the transition period.

Number of subjects who discontinued due to reasons related to COVID-19 pandemic will be provided separately, as applicable.

If more than 10% of the patients withdraw from the study before the end of the main treatment period, Kaplan-Meier curves for the number of days until study discontinuation will be plotted by treatment group for the main and transition period, as applicable.

All disposition information will be listed. Also a separate listing will present the date of informed consent and inclusion/exclusion criteria violated, if any.

4.2 Demography and Baseline Characteristics

Patient demographic and baseline characteristics will include age, sex, race, ethnicity, baseline height, weight, as continuous and a categorical variable (<80 kg vs. ≥80 kg), and BMI, baseline ISS7, as a continuous and a categorical (<13 vs. ≥13), randomization strata, time since diagnosis of chronic idiopathic urticaria, total IgE at baseline, in-clinic UAS, UAS7, Weekly score for nnumber of hives, presence of angioedema, weekly no. of diphenhydramine tablets (25 mg) as rescue

medication. Demographic and baseline characteristics will be summarized using descriptive statistics based on the ITT, mITT and mITT1 analysis sets.

For continuous variables, descriptive statistics will be provided. For categorical variables, patient counts and percentages will be provided.

All demographic and baseline characteristics will be listed.

4.3 Medical History

Medical history will be summarized by the number and percentage of subjects by MedDRA system organ class, preferred term and treatment group for the safety analysis set.

Subjects will be counted only once for each applicable preferred term, and each applicable system organ class. System organ classes and preferred terms will be presented in alphabetical order.

All medical history information will be listed.

4.4 Protocol Deviations

Data from patients with any important protocol deviations as defined in Appendix H of the study protocol, and as recorded in protocol deviation CRF during the study will be summarized overall and for each category using descriptive statistics.

Each protocol deviation will be classified as minor or major/important. Major/important protocol deviations will exclude the subject from the PP analysis set. Specific deviation and their severities are defined in the separate Protocol Deviations Specification document.

All major protocol deviations will be summarized by deviation category and treatment group. This analysis will be performed for the ITT analysis set. All classification of protocol deviations will be performed prior to database lock.

Deviations related to the COVID-19 pandemic will be identified.

All protocol deviations will be listed.

4.5 Study Drug Exposure, Treatment and Compliance

Number and percentage of subjects receiving 1, 2 and 3 doses in the main treatment period will be presented by treatment group for the safety analysis set. Similarly, number and percentage of subjects receiving 1, 2 and 3 doses in the transition period will be presented by treatment group for the transition period safety analysis set.

Total dose of TEV-45779 and XOLAIR will also be summarized descriptively by period and overall.

All details of study drug administration captured on the eCRF will be listed.

4.5.1 Diary Compliance

Diary compliance will be assessed separately for the main treatment period, transition period and follow-up period. In each period the compliance will be calculated as [Number of completed itch entries in the diary in the period] / [Number of expected itch entries in the diary in the period] * 100%.

The last diary entry is expected on the day prior to Week 40 visit for subjects who completed the study and on the date of discontinuation for the subjects who discontinued from the study. For the calculation of diary compliance the study periods will be defined as follows:

- Main treatment period: from the date of Visit 3 to the date prior to Visit 6/Week 12 or the date of discontinuation if the subject discontinued prior to Visit 6/Week 12
- Transition period: from the date of Visit 6/Week 12 to the date prior to Visit 9/Week 24 or the date of discontinuation if the subject discontinued prior to Visit 9/Week 24
- Follow-up period: from the date of Visit 9/Week 24 to the date prior to Visit 13/Week 40 or the date of discontinuation if the subject discontinued prior to Visit 13/Week 40.

The number of expected itch entries is twice the number of days in the period.

The compliance will be summarized descriptively as a continuous variable and also categorically classified as 0-10%, >10-20%, etc. up to >90-100% and >100%.

4.6 Efficacy Analysis

The ITT analysis set will be used as the primary analysis set for efficacy in the main treatment period.

Supplementary analysis will be carried out using the mITT, mITT1 and PP analysis sets.

The TITT analysis set will be used as the primary analysis set for efficacy in the transition period. Supplementary analysis will be carried out using the TmITT and TmITT1 analysis sets.

4.6.1 Primary Endpoint

The primary endpoint is the change from baseline in the ISS7 at Week 12 in the TEV-45779 300 mg and XOLAIR 300 mg arms.

The co-primary efficacy endpoint (for the FDA submission only) is the relative potency of TEV-45779 and XOLAIR as measured by change in ISS7 at Week 12 using a 4-point assay, i.e., TEV-45779 300 mg, TEV-45779 150 mg, XOLAIR 300 mg and XOLAIR 150 mg.

4.6.2 Secondary Endpoints

4.6.2.1 Secondary Efficacy Endpoints in the Main Treatment Period

The secondary efficacy endpoints are:

- Change from baseline in ISS7 at Week 12 for TEV-45779 150 mg versus XOLAIR 150 mg; TEV-45779 300 mg versus TEV-45779 150 mg; XOLAIR 300 mg versus XOLAIR 150 mg.
- Change from baseline in the ISS7 at Week 4, TEV-45779 300 mg vs. XOLAIR 300 mg.
- Change from baseline in the UAS7 (sum of the daily number of wheals score and itch severity score over 7 days) at Weeks 12.
- Percentage of patients with a UAS7 ≤6 at Week 12.
- Percentage of complete responders (UAS7=0) at Week 12.
- Change from baseline in the physician's (in-clinic) assessment of UAS at Week 12.
- Change from baseline in the weekly number of wheals score at Week 12.
- Change from baseline in the weekly size of the largest wheals score at Week 12.
- Time to MID (reduction from baseline in ISS7 of ≥5 points) response by Week 12.
- Percentage of ISS7 MID responders at Week 12 (percentage of patients with reduction of ≥5 points from baseline in ISS7 at Week 12).
- Percentage of angioedema-free days from Week 4 to Week 12.
- Change from baseline in the overall dermatology life quality index (DLQI) score at Week 12.

The comparisons will be made between the different doses used in the study (150 mg vs. 300 mg) as well as between TEV-45779 and XOLAIR.

4.6.2.2 Secondary Efficacy Endpoints in the Transition Period

The secondary efficacy endpoints in the transition period are:

- change from Week 12 in ISS7 at Week 24
- change from Week 12 in ISS7 at Week 40
- change from Week 12 in UAS7 at Week 24
- change from Week 12 in the physician's (in-clinic) assessment of UAS at Week 24
- change from Week 12 in the weekly number of wheals score at Week 24

- change from Week 12 in the weekly number of wheals score at Week 40
- change from Week 12 in the weekly size of the largest wheals score at Week 24
- change from Week 12 in the weekly size of the largest wheals score at Week 40
- percentage of angioedema-free days from Week 12 to Week 24
- Change from Week 12 in the overall DLQI score at Week 24
- Change from Week 12 in the overall DLQI score at Week 40

The comparisons will be made between the different doses used in the study (150 mg vs. 300 mg) as well as between TEV-45779 and XOLAIR.

4.6.3 Calculation of the Primary Endpoint

Itch severity is recorded twice daily (morning and evening) in the patient's symptom diary, on a scale of 0 (none) to 3 (severe). A daily itch severity score is calculated as the average of the morning and evening scores. A weekly itch severity (ISS7) score is calculated as the sum of the daily itch severity scores over the study days that make up a given study week. If at least 1 itch severity score is missing or if a given study week is shorter than 7 days (ie, if a treatment visit occurs earlier or later, the study week before or after the treatment visit, respectively, would be shorter), the approach for handling the missing scores will be as described in section 3.5. Multiple imputation will be used for the missing ISS7 change from baseline (see section 0 for details).

ISS7 will be calculated at each study week using the subject diary. Study Week 1 is defined to comprise Study Days 1-7, Study Week 2 – Days 8-14, etc, i.e. Study Week N lasts from Day 7*N-6 to Day 7*N. Special handling is applied to Study Weeks 4, 8, 12, 16 and 20 (i.e. the weeks preceding study drug administration), as well as Study Weeks 5, 9, 13, 17 and 21 (i.e. the weeks following study drug administration), if the treatment visit does not occur exactly on the scheduled day.

- If a treatment visit occurs earlier than planned, the week preceding the visit will end on the day prior to the day of the visit and start 7 days prior to the day of the visit. Consequently the next prior week will end 8 days prior to the day of the visit, however, its start day will remain as scheduled (which may result in this week being shortened). The week following the treatment visit will not be affected and will start and end as scheduled.
    - For example, if Visit 6 (Week 12) occurs on Day 84 (instead of the scheduled Day 85), Study Week 12 will last from Day 77 to Day 83 (instead of Day 78 to Day 84 as would be normally scheduled). Consequently, Study Week 11 will last from Day 71 to Day 76 (i.e. will be shortened to 6 days). Week 13 will last from Day 85 to Day 91 as normally scheduled.

- If a treatment visit occurs later than planned, the weeks prior to the visit will not be affected and will start and end as scheduled. The week following the visit will start on the day of visit and end as scheduled (which may result in this week being shortened).
    - For example, if Visit 6 (Week 12) occurs on Day 86 (instead of the scheduled Day 85), Study Week 13 will last from Day 86 to Day 91 (i.e. will be shortened to 6 days). Study Weeks 12 and 11 will not be affected.

ISS7 at Baseline is the sum of the daily itch severity scores over the 7 days prior to the first treatment, e.g. days -7 to -1 (relative to the day of the first study drug administration). If a subject does not attend a treatment visit, but has data in the diary, then the Study Week will be calculated as if the visit occurred on the scheduled day.

4.6.4 Primary Efficacy Analysis

For the FDA submission, the following analyses will be considered co-primary:

- The analysis of change from baseline in the ISS7 at Week 12 will be an ANCOVA with treatment group (2 levels: TEV-45779 300 mg and XOLAIR 300 mg), as explanatory variable, baseline itch severity score, baseline weight and region (3 levels planned: Americas, Europe and Asia-Pacific) as covariates. Biosimilarity will be demonstrated if the 90% CI for the mean difference between TEV-45779 300 mg and XOLAIR 300 mg falls entirely within the asymmetric equivalence margin of (-2.5, +2.0).
- The analysis of relative potency of TEV-45779 and XOLAIR as measured by change from baseline in ISS7 at Week 12 using a 4-point assay, ie, TEV-45779 300 mg, TEV-45779 150 mg, XOLAIR 300 mg and XOLAIR 150 mg using a multi-step process. Relative potency will be demonstrated if the 90% CI for relative potency estimated as outlined below falls entirely within the equivalence margins of (0.5, 2).

For the EMA submission, the following analysis will be considered primary:

- The analysis of change from baseline in the ISS7 at Week 12 will be an ANCOVA with treatment group (2 levels: TEV-45779 300 mg and XOLAIR 300 mg as explanatory variable, baseline itch severity score, baseline weight and region (3 levels planned: Americas, Europe and Asia-Pacific) as covariates. Biosimilarity will be demonstrated if the 95% CI for the mean difference between TEV-45779 300 mg and XOLAIR 300 mg falls entirely within the equivalence margin of (-2.0, +2.0).

The primary analyses will be based on the ITT analysis set.

4.6.4.1 Missing ISS7 Multiple Imputation

The imputation rules below will be applied according to the region specific estimand. The change from baseline in ISS7 will be imputed at Weeks 4, 8 and 12:

- per the defined estimand for the FDA submission, for patients having a missing ISS7;
- per the defined estimand for the EMA submission, additionally for patients discontinuing the treatment early, i.e. not receiving all planned doses prior to the given week, or using any disallowed concomitant medication between randomization and given week assessment.

The imputation will proceed in two steps. In the first step intermittent missing values among Week 4 and 8 visits will be imputed 50 times using Markov Chain Monte Carlo (MCMC) method for each treatment arm separately: TEV-45779 300 mg, TEV-45779 150 mg, XOLAIR 300 mg or XOLAIR 150 mg. The imputation model will include baseline ISS7 value, baseline weight, and the available non-missing ISS7 changes from baseline at Weeks 4 and 8. The resulting dataset with monotone missing pattern will be used in next step in which trailing missing values will be imputed using the monotone regression predictive mean matching multiple imputation method (Heitjan and Little 1991, Schenker and Taylor 1996), also for each treatment arm separately. The imputation model will include baseline ISS7 value, baseline weight, region and the available non-missing ISS7 changes from baseline at Weeks 4, 8 as covariates. Note that the imputed values at Weeks 4 and 8 will not participate in the primary analysis, but will be used in the sensitivity MMRM analysis (see section 4.6.5).

The resulting complete, imputed datasets will each be analyzed using the model specified in the section 4.6.4, and the resulting statistics combined using methodology provided by Rubin (1987) and Little and Rubin (2002). See section 6.2.1 for sample SAS code.

4.6.4.2 Relative Potency

The relative potency of the test product to the reference product is defined as the dose of the test product that produces the same biological response as 1 unit of the dose of the reference product. The analysis of relative potency of TEV-45779 and XOLAIR will be performed using a 4-point assay, based on the 300 mg and 150 mg dose levels of each product. The methodology will be applied as presented in Vezzoli (2011) using the SAS code from the same source. If we define X_T and X_R as the doses of TEV-45779 and XOLAIR producing the same response, then the relative potency is given by $\rho = \frac{X_T}{X_R}$. Based on this definition, if relative potency is:

- <1, then a dose of the test produces the same result as does a higher dose of the reference (test is more potent).
- =1, then the 2 products produce the same result at the same dose (test and reference are equipotent).
- >1, then a dose of the test produces the same result as does a lower dose of the reference (test is less potent).

Relative potency will be estimated on the data without multiple imputations.

The estimation of relative potency in a parallel line assay requires the following assumptions to hold:

- Linearity, i.e. linear dependence of response on log dose: required but cannot be tested in a 4-point design.
- Parallelism: absence of significant deviations from parallelism of dose-response curves between test and reference drugs on the log-dose scale. In case of non-parallel curves a unique value for relative potency cannot be assumed.
- Dose-response relationship: if the slope of the dose-response curves β is not significantly different from zero, the data are consistent with a zero value for β and hence an undefined value for the relative potency.
- No difference between products: the difference between treatments should be non-significant. If this assumption does not hold, but relative potency is estimated anyway, the estimate obtained is expected to be far from unity.

Define $x_T = \log(X_T)$ and $x_R = \log(X_R)$ (assume without loss of generality natural logarithm). Assume that on the log-dose scale, the horizontal distance between the linear and parallel dose-response curves is constant. This condition ensures a unique value for relative potency, irrespective of the response level considered. The regression lines for the dose-response curves of the treatment (T) and reference (R) products can be expressed respectively as $Y_T = \alpha_T + \beta \cdot x_T$ and $Y_R = \alpha_R + \beta \cdot x_R$, where Y_i is the response, α_i is the intercept $(i = T, R)$ and β is a common slope. It can be shown algebraically that $\log(\rho) = x_T - x_R = \frac{\alpha_R - \alpha_T}{\beta}$, and can be estimated by plugging the corresponding estimates $\frac{a_R - a_T}{b}$.

The confidence interval (CI) of the $\log(\rho)$ is based on Fieller's theorem. The upper and the lower CI limits are:

$$\frac{R - \frac{g v_{12}}{v_{22}} \pm \frac{t}{b}\left[v_{11} - 2Rv_{12} + R^2 v_{22} - g\left(v_{11} - \frac{v_{12}^2}{v_{22}}\right)\right]^{\frac{1}{2}}}{1-g}.$$

where:

- $\mathrm{R} = \log(\rho) = \frac{a_R - a_T}{b}$;
- $g = \frac{t^2 v_{22}}{b^2}$;
- v_{11} is the variance of $a_R - a_T$;
- v_{12} is the covariance between $a_R - a_T$ and b;
- v_{22} is the variance of β;
- t is the appropriate percentile of the t-distribution with f degrees of freedom;

- f are the degrees of freedom on which the residual variance is based.

Estimates of relative potency and its CI are finally obtained by exponentiating R and the confidence limits calculated using Fieller's theorem.

The 2-Step Analysis

The method proposed in Vezzoli (2011) for the analysis of relative potency is based on a 2-step approach.

Step 1

In the first step an analysis of covariance (ANCOVA) model is estimated in order to verify the required assumptions. The treatment effect is decomposed into the fixed effects of product (TEV-45779 or XOLAIR), dose on the log-scale (log(150) or log(300), as continuous variable) and their interaction.

Baseline itch severity score, baseline weight and region will be used in the model as covariates.

Based on the estimated model, the assumptions are checked.

a. Absence of significant deviations from parallelism: the p-value of the interaction product * log(dose) should be ≥0.1.
b. Significant dose-response relationship: the p-value of the slope for log(dose) should be <0.05.
c. Absence of a significant difference between products: the p-value of the product effect should be ≥0.05.

Regarding assumption C, it should be noted that, since the model includes the interaction term, the estimate of the product effect and its significance depend on the dose level considered. The product effect corresponds to the vertical distance between the dose-response curves on the log-dose scale and, since non-parallelism is allowed by the model, this distance is not generally constant. For this reason the product effect well be tested at the two log(dose) levels corresponding to the 150 mg 300 mg doses actually administered in the study and at the mean log(dose) level.

In absence of evidence against the assumptions, we can proceed to the second step.

Step 2

The same model used in Step 1 is estimated excluding the non-significant term for interaction. Assumptions B and C may be checked for confirmation. The absence of a significant difference between products can now be verified without taking into account particular dose levels, since the vertical distance between the dose-response curves is constant due to the exclusion of the interaction term from the model. Then log relative potency can be estimated as the ratio between the estimated product effect (of note, the difference R-T should be considered instead of the usual T-R) and the

estimated slope for log(dose): $(a_R - a_T) / b$. Its confidence limits can be obtained based on the other results from the model. See section 6.2.2 for sample SAS code.

4.6.5 Sensitivity Analysis for the Primary Analysis

To assess the robustness of the primary efficacy analysis using the same estimand (separately for each regulatory agency, US and EMA), the analyses will include the following sensitivity analyses for the statistical model. The analysis of change from baseline in the ISS7 at Week 12 difference between TEV-45779 300 mg and XOLAIR 300 mg will use the same predefined confidence level and equivalence margins as in the primary analysis, according to region, US or EU:

- Change from baseline in the ISS7 at Week 12 difference between TEV-45779 300 mg and XOLAIR 300 mg:
  - primary model, but with a single factor for of treatment group
  - Primary analysis using mixed-model-for-repeated-measures (MMRM), with additional fixed effects of week (as a categorical variable with 3 levels: Weeks 4, 8, and 12) and treatment group by week interaction as well as patient as a random effect. The rules for imputation of the missing/excluded ISS7 at each week will be applied as defined for Week 12 in the primary analysis, as described in section 0. The model will employ an unstructured within subject covariance matrix and a restricted maximum likelihood (ReML) estimation method. The degree-of-freedom of the denominator will be estimated using the Kenward-Roger method. See section 6.2.3 for SAS code samples

    If the model fails to converge with the unstructured covariance matrix, a simpler covariance matrix will be employed in the order of 1) heterogeneous Toeplitz [SAS PROC MIXED type =TOEPH], 2) heterogeneous autoregressive of order 1 [type = ARH(1)], 3) heterogeneous compound symmetry [type = CSH], 4) Toeplitz [type = TOEP], 5) autoregressive of order 1 [type = AR(1)], 6) compound symmetry [type = CS]. The first covariance structure that does not have a convergence problem will be the one used for the primary analysis.
- 4-points relative potency between TEV-45779 and XOLAIR
  - The ANCOVA model in both steps of the procedure described in section 4.6.4.2 will be run without baseline covariates.

4.6.6 Supplementary Analysis for the Primary Analysis

Analyses for assumptions on missing data:

- tipping point (missing-not-at-random, MNAR)

In order to assess the sensitivity of the primary analysis to the MAR assumption on missing data, supplementary analysis for the primary analysis will be conducted using multiple imputation under different MNAR assumptions. In this sensitivity analysis, missing change from baseline in the ISS7 at Week 12 will be imputed similarly to the primary analysis, except in step 2 the monotone imputation model will be adjusted to different MNAR assumptions:

- the change from baseline in the ISS7 at Week 12 in patients randomized to TEV-45779 300 mg with missing ISS7 at Week 12 will be imputed assuming the treatment effect is worsened by δ_1 compared to the patients who have no missing value, where δ_1 varies in steps of 1 from 0 to 4 or estimated treatment effect of TEV-45779 300 mg group, whichever is higher. The estimated treatment effect of TEV-45779 300 mg group is this group's LS mean from the primary analysis model;
- the change from baseline in the ISS7 at Week 12 in patients randomized to XOLAIR 300 mg with missing ISS7 at Week 12 will be similarly imputed assuming the treatment effect is worsened by δ_2 compared to the patients who have no missing value, where δ_2 varies in steps of 1 from 0 to 4 or estimated treatment effect of XOLAIR 300 mg group, whichever is higher.

The resulting complete, imputed datasets will each be analyzed using the same model as the primary analysis model, and the resulting statistics combined using methodology provided by Rubin (1987) and Little and Rubin (2002). Analysis results will be presented for each combination of the worsening factors δ_1 and δ_2. Combinations of the worsening factors that lead to loss of biosimilarity will be considered tipping points.

- To further alleviate the concern on the uncertainty introduced by missing data, the following 2 separate 1-sided tests of alpha=0.05 with missing data imputed under the corresponding null using a multiple imputation method will be conducted (see section 6.2.5 for SAS code samples):
  - in the first test missing values for the TEV-45779 300 mg group will be imputed assuming the treatment effect is worsened (i.e. ISS7 value increased) by the upper margin value of 2 compared to the patients who have no missing value, while the missing values for the XOLAIR 300 mg group are imputed without penalization. Non-inferiority for the FDA submission will then be tested by checking that the upper one-sided 95% confidence limit (equivalently, 2-sided 90% limit) for the mean difference TEV-45779 - XOLAIR is less than the margin value of 2. For the EMA submission the upper-one sided 97.5% confidence limit (equivalently, 2-sided 95% limit) will be used.
  - in the second test, missing values for the TEV-45779 300 mg group will be imputed assuming the treatment effect is improved (i.e. ISS7 value decreased) by the lower

margin value of -2.5 for the FDA submission and -2.0 for the EMA submission compared to the patients who have no missing value, while the missing values for the XOLAIR 300 mg group are imputed without penalization. Non-superiority will then be tested by checking that the lower one-sided 95% confidence limit (equivalently, 2-sided 90% limit) for the mean difference TEV-45779 - XOLAIR is greater than the margin value of -2.5 for the FDA submission and the lower one-sided 97.5% confidence limit (equivalently, 2-sided 95% limit) is greater than -2.0 for the EMA submission.

- primary analysis repeated on the mITT analysis set

Other analyses:

- primary model repeated for the mITT1 analysis set on observed data without multiple imputations.
- primary model repeated for the PP analysis set on observed data without multiple imputations
- primary model repeated for the ITT analysis set, excluding patients who were mistreated by IMP at baseline and/or at later visits till Week 12.
- primary analysis using mixed-model-for-repeated-measures (MMRM), with additional fixed effects of week (as a categorical variable with 3 levels: Weeks 4, 8, and 12) and treatment group by week interaction as well as patient as a random effect on observed data without multiple imputations.
- Primary analysis repeated excluding subjects with detectable omalizumab concentrations in serum at baseline, if applicable.
- Primary analysis for EMA repeated including only subjects treated with EU-manufactured XOLAIR as control (while keeping all subjects in the TEV-45779 treatment group).
- Primary analysis for EMA with the additional data completeness factor: subjects for whom ≥8 assessments were available to calculate ISS7 at Week 12, and the subjects for whom <8 assessments were available. Subjects for whom the primary endpoint was imputed will be grouped with the subjects for whom <8 assessments were available.In this analysis the completeness factor and completeness factor by treatment interaction will be added to the primary analysis model. LS means will be estimated for the completeness factor by treatment interaction term and analysis similar to the primary analysis will be presented for each completeness factor subgroup.

Relative potency supplementary analysis:

- 90% CI for relative potency will be provided for each multiply imputed data set used in the primary efficacy endpoint per the defined estimand for the FDA submission for patients having a missing ISS7, and will be presented as a forest plot.

4.6.7 Secondary Efficacy Analysis

No formal hypothesis testing is planned for the secondary efficacy endpoints. Analysis will be descriptive in nature.

4.6.7.1 Continuous endpoints

For continuous endpoints such as change from baseline in ISS7, UAS7, in-clinic assessment of UAS, number of wheals score, weekly size of the largest wheals score, percentage of angioedema-free days from Week 4 to Week 12 and DLQI total score descriptive statistics will be presented by treatment group and visit. These endpoints will also be analyzed with an ANCOVA model similar to the primary analysis, but on all 4 treatment groups, i.e. with the endpoint as the outcome, treatment group and region as fixed effects, baseline weight and baseline value of the endpoint (if applicable) as covariates. For descriptive purposes, 95% CIs for the differences in LS means from this model between treatment groups will be presented: TEV-45779 300 mg vs XOLAIR 300 mg, TEV-45779 150 mg vs XOLAIR 150 mg, TEV-45779 300 mg vs TEV-45779 150 mg and XOLAIR 300 mg vs XOLAIR 150 mg.

UAS7, weekly number of wheals score, weekly size of the largest wheals score will be calculated from the diary data using the same approach as ISS7. In case of missing individual scores in the diary, the rules from section 3.5 will be followed, however, multiple imputation will not be used.

Percentage of angioedema-free days from Week 4 to Week 12 will also be calculated based on the diary data as the number of days in the diary between the dates of Week 4 and Week 12 visits with no angioedema episodes, divided by the total number of days with diary entries in this time span, times 100%. If the subject missed Week 4 or Week 12 visit, the scheduled date of this visit will be used instead. If the subject discontinues after Week 4, but prior to Week 12, then date of discontinuation will be used in place of Week 12 visit.

DLQI total score will be calculated by adding the score of each question (scored as follows: Very much = 3; Yes (in question 7.a) = 3; A lot = 2; A little = 1; Not at all = 0; Not relevant = 0; No (in question 7.a) = 0; Question unanswered = 0), resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

4.6.7.2 Binary endpoints

For binary endpoints such as patients with a UAS7 ≤6 at Week 12, complete responders (UAS7=0) at Week 12, ISS7 MID responders at Week 12, number and percentage of subjects achieving the endpoint will be presented by treatment group and visit. For descriptive purposes, 95% CIs for the

differences in percentages between treatment groups will be presented: TEV-45779 300 mg vs XOLAIR 300 mg, TEV-45779 150 mg vs XOLAIR 150 mg, TEV-45779 300 mg vs TEV-45779 150 mg and XOLAIR 300 mg vs XOLAIR 150 mg.

4.6.7.3 Time to event endpoint

Time to MID (reduction from baseline in ISS7 of ≥5 points) response by Week 12 will be defined as follows. For the purpose of this endpoint ISS7 will calculated for each week, i.e. for Days 1-7, 8-14, 15-21, etc, up to Week 12, i.e. Days 78 to 84 (or the day prior to the 1st transition period dose, whichever is earlier). Time to MID (in weeks) will be defined as the first week in which reduction in ISS7 by at least 5 points from baseline is observed. For subjects who do not achieve such reduction by Week 12, the time will be censored at the last available week in the diary no later than Week 12.

Median as well as the 1st and 3rd quartiles of time to MID with their 95% CI will be presented by treatment group. Cox proportional hazards model will be applied with treatment group, baseline ISS7,baseline weight and region as covariates, using the exact method for ties. If the model with exact method for ties does not converge, Efron method will be used instead. Hazard Ratio (HR) and their 2-sided 95% Confidence Interval will be presented for the following pairs of treatment:

- TEV-45779 300 mg to XOLAIR 300 mg
- TEV-45779 150 mg to XOLAIR 150 mg
- TEV-45779 300 mg to TEV-45779 150 mg
- XOLAIR 300 mg to XOLAIR 150 mg

4.6.8 Efficacy Analysis in the Transition Period

Descriptive statistics will be presented by the treatment groups to which the patients were assigned in the main treatment and transition periods (TEV-45779/TEV-45779, XOLAIR/XOLAIR and XOLAIR/TEV-45779, further subdivided by dose 300 mg or 150 mg). In addition, these endpoints will also be analyzed with an ANCOVA model similar to the analysis in the main treatment period, but on the 6 treatment groups applicable to the transition period, i.e. with the endpoint as the outcome, treatment group and region as fixed effects, baseline weight and Week 12 value of the endpoint as covariates. The difference and 95% CI for the difference between the XOLAIR/XOLAIR and XOLAIR/TEV-45779 groups at both doses will be presented.

The efficacy analyses in the transition period will be based on the TITT, TmITT and TmITT1 analysis sets.

All efficacy analyses in the transition period are considered descriptive and no formal hypothesis testing is planned.

Endpoints will be calculated and summarized similar to the secondary endpoints in the main treatment period with the exception that the treatment arms will be consistent with the treatment in both the main period and in the transition period.

Percentage of angioedema-free days from Week 12 to Week 24 will be calculated based on the diary data during the 84 days (12 weeks) starting with the day of the first transition period treatment. The number of days in the diary with no angioedema episodes will be divided by the total number of days with diary entries in this time span and multiplied by 100%

4.7 Safety Analysis

Safety analyses will be performed on the safety and transition period safety analyses sets.

The safety of TEV-45779 and XOLAIR will be assessed throughout the study by evaluating adverse events, clinical laboratory test results, vital signs measurements, ECG, physical examination results, local tolerability, and concomitant medication usage.

4.7.1 Safety Analysis in the Main Treatment Period

Safety analyses in the main treatment period will be performed on the safety analysis set. Summaries will be presented by treatment group (TEV-45779, XOLAIR, further subdivided by dose 150 mg or 300 mg) and for all patients.

All safety variables at the Week 12 Visit that are assessed prior to IMP administration will be considered as occurring during the main treatment period.

4.7.2 Safety Analysis in the Transition Period

Safety analyses in the transition period will be performed on the transition period safety analysis set. Summaries will be presented by the treatment groups to which the patients were assigned in the main treatment and transition periods (TEV-45779/TEV-45779, XOLAIR/XOLAIR and XOLAIR/TEV-45779, further subdivided by dose 150 mg or 300 mg) and for all patients.

4.7.3 Safety Analysis in the Overall Treatment Period

Safety analyses in the overall treatment period will be performed on the safety analysis set. The analyses will include only patients in the TEV-45779/TEV-45779, XOLAIR/XOLAIR treatment groups, further subdivided by dose 150 mg or 300 mg and for all patients.

The analyses will be similar to the analyses of the main treatment period. Summaries will be presented by treatment group and for all patients included in the analysis.

4.7.4 Adverse Events

Adverse Events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA) AE coding system for purposes of summarization.

Only Treatment Emergent Adverse Events (TEAE) will be used for the summary analysis. An AE will be considered as treatment-emergent if the date of onset is on or after the first study drug administration date. AEs with unknown start dates will be counted as treatment-emergent unless the AE resolution date is prior to the first study drug administration date. If the AE start date is partially missing, the AE will be considered treatment-emergent, unless the month and year (when available) rule out the possibility that the event occurred post start of the study drug.

All TEAEs will be assigned to either main treatment period or transition period based on the date of onset. In case a TEAE has a partial start date so that is ambiguous whether the AE started in the main treatment period or transition period, it will be assigned to the main treatment period.

In summaries of TEAEs a subject experiencing the same AE (with the same preferred term) multiple times within the same study period will only be counted once for that preferred term and study period. Similarly, if a subject experiences multiple AEs within the same system organ class in the same study period, that subject will be counted only once in that system organ class for that study period. When summarizing AEs by severity, only the most severe occurrence within the preferred term or system organ class and study period will be used. Similarly, when summarizing AEs by relationship to study drug, only the most related occurrence within the preferred term or system organ class and study period will be selected for displays in summary tables.

AEs will be summarized for the main treatment period, transition period and also the overall treatment period.

An overall summary will include, by study period and by treatment group and overall, the number and percentage of subjects reporting at least 1 TEAE in the following categories:

- Any TEAE
- Treatment-related TEAE
- Serious TEAE
- TEAE leading to discontinuation of the study drug
- TEAE leading to death.

The following TEAE frequency tables will be prepared summarizing the overall number of TEAEs, the number and percentage of subjects reporting at least one TEAE by MedDRA System Organ Class (SOC) and preferred term (PT), by treatment group and by study period:

- All TEAEs
- Serious TEAEs

- Treatment-related TEAEs
- TEAEs leading to discontinuation of the IMP
- TEAEs in subjects with COVID-19, as applicable
- TEAEs by severity
- Treatment-related TEAEs by severity

The summaries by SOC and PT will be ordered alphabetically by SOC and PT.

All information pertaining to adverse events noted during the study will be listed by subject, detailing verbatim, preferred term, system organ class, start date, stop date, severity, outcome, action taken and causal relationship to the study drug. Separate listings will be prepared for serious AEs and AEs leading to discontinuation of the IMP.

4.7.5 Laboratory Evaluations

Serum chemistry, hematology and urinalysis tests will be performed at visits 1, 3, 6, 9 and 13.

Urine β-HCG tests will be performed for all women of childbearing potential at screening (visit 2), visit 6 and visit 9. If the urine pregnancy test result is positive a serum pregnancy test should be performed by the central laboratory.

COVID-19 testing will be performed at screening and at any other time point during the study if the patient exhibits clinical symptoms that may indicate COVID-19 infection.

Actual values and changes from baseline in numeric hematology, chemistry and urinalysis results will be summarized descriptively by visit and treatment group for the main treatment period and overall treatment period for the safety analysis set. Similarly changes from Week 12 will be presented for the transition period using the transition period safety analysis set.

Additionally, numeric hematology, chemistry and urinalysis results will be classified as Low (below the reference range), Normal (within the reference range) or High (above the reference range). Categorical Urinalysis results will be classified as Normal or Abnormal. Shifts among these categories between baseline and last available post-baseline assessment will be provided for the main treatment period and overall treatment period for the safety population. Similarly shifts from Week 12 to the last available assessment in the transition period will be provided for the transition period safety population.

Potentially clinically significant values will be summarized and listed separately.

Number and percentage of subjects with potentially clinically significant abnormal values will be summarized for the main treatment period, transition period and overall treatment period using the criteria specified in Table 1.

Table 1: Criteria for Potentially Clinically Significant Laboratory Values

Test		Criterion / value
Serum chemistry		
Alanine aminotransferase (ALT)		≥3 x ULN
Aspartate aminotransferase (AST)		≥3 x ULN
Alkaline phosphatase		≥3x ULN
Gamma-glutamyl transpeptidase (GGT)		≥3x ULN
Lactate dehydrogenase (LDH)		≥3x ULN
Creatinine		≥177 µmol/L
Uric acid	Men	≥625 µmol/L
	Women	≥506 µmol/L
Bilirubin (total)		≥34.2 µmol/L
Hematology		
Hematocrit	Men	<0.37 L/L
	Women	<0.32 L/L
Hemoglobin	Men	≤115 g/L
	Women	≤95 g/L
White blood cell (WBC) counts		≤3 x 10^9/L ≥20 x 10^9/L
Eosinophils		≥10%
Platelet counts		≤75 x 10^9/L ≥700 x 10^9/L

ULN=upper limit of normal range

All results will be listed. A separate listing of subjects who tested positive for COVID-19, if any, will be provided.

4.7.6 Vital Signs

Vital signs will be collected at all visits except Visit 2. Pulse rate, blood pressure (systolic/diastolic), and respiratory rate will be recorded. Weight will be measured at visits 1, 6 and 13.

Vital signs (including weight) and their changes from baseline will be summarized descriptively by visit and treatment group for the main treatment period and overall treatment period for the safety population. Similarly changes from Week 12 will be presented for the transition period for the transition period safety population.

Number and percentage of subjects with potentially clinically significant abnormal values will be summarized using the criteria specified in Table 2 for the main treatment period, transition period and overall treatment period. These summaries will include all post-baseline values (including scheduled, unscheduled, and early termination time points/visits). Note that in order to qualify as potentially clinically significant abnormal, a value needs to meet both criteria below: i.e., have a value beyond the criterion value and a change of at least the magnitude specified in the change relative to baseline column. For the transition period summaries Week 12 will serve as baseline.

Table 2: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign	Criterion value	Change relative to baseline
Pulse	≥120 bpm	Increase of ≥15
	≤50 bpm	Decrease of ≥15
Systolic blood pressure	≥180 mm Hg	Increase of ≥20
	≤90 mm Hg	Decrease of ≥20
Diastolic blood pressure	≥105 mm Hg	Increase of ≥15
	≤50 mm Hg	Decrease of ≥15
Body temperature	≥38.3°C	Change of ≥1.1°C

All vital signs will be listed.

4.7.7 Electrocardiogram

ECG will be performed at visits 1, 6, 9 and 13. Standard ECGs parameters will be recorded and the ECG will be interpreted locally by the principal investigator (or qualified physician). Only ECG

interpretation (Normal, Abnormal Not Clinically Significant or Abnormal Clinically Significant) will be entered into the study database and used in analysis.

Overall interpretation will be summarized categorically by visit and treatment group.

Shifts in overall interpretation from baseline to the last available post-baseline assessment will be tabulated.

All results will be listed.

4.7.8 Physical Examination

Physical examination will be performed at all visits except Visit 2. At Visit 1 physical examination should be comprehensive while subsequent examinations may be abbreviated to detect changes in symptoms of CIU/CSU as well as directed by patient complaints regarding adverse events.

A comprehensive physical examination will include, at a minimum, head, eyes, ears, nose, and throat (HEENT), chest, cardiovascular, abdominal, and skin examination. An abbreviated physical examination will include, at a minimum, chest, cardiovascular, abdomen, and skin examinations.

Each system will be classified as Normal, Abnormal Not Clinically Significant (NCS) or Abnormal Clinically Significant (CS).

Number and percentage of subjects with each assessment result will be tabulated by body system, visit and treatment group.

All results will be listed.

4.7.9 Assessment of Local Tolerability and Pain

Local tolerability at the injection site (erythema, ecchymosis, induration, tenderness, warmth, swelling) will be assessed using standardized scales: None, Mild, Moderate or Severe.
Patient-reported pain at the injection site will be reported using a standardized 11-point pain intensity numerical response scale (NRS-11) where 0 is “No pain” and 10 is “Worst possible pain”; patients will be asked to respond to the following question: “How much pain do you feel at the drug injection site, where 0 is ‘No pain’ and 10 is ‘Worst possible pain’?”.

The assessments will be performed at 20, 60 and 120 minutes after dosing.

Number and percentage of subjects with each severity level of injection site tolerability signs will be presented by visit/timepoint and treatment group. Patient-reported pain NRS will be summarized descriptively by visit/timepoint and treatment group.

4.7.10 Prior and Concomitant Medications

Prior medications are defined as medications that were taken prior to subject's first dose of the IMP. Concomitant medications are defined as medications taken after the first dose of the IMP, i.e. either stopped after the first dose of the IMP or ongoing.

A concomitant medication will be associated with the main treatment period, if it is taken during that period, i.e. prior to the first transition period treatment. A concomitant medication will be associated with the transition period if it is taken after the first transition period treatment. Concomitant medications taken both prior to and after the first transition period treatment will be associated with both periods.

Prior medications will be summarized for the ITT analysis set. Concomitant medications will be summarized separately for the main treatment period for the safety analysis set and for the transition period for the transition period safety analysis set.

In all cases prior and concomitant medications will be summarized by ATC class (highest level available), WHO Drug Dictionary preferred name and treatment group. One subject will be counted once for each applicable preferred name and ATC class. ATC classes and preferred names will be presented alphabetically.

Change in number of tablets/week of sedating H1 antihistamine (diphenhydramine) for itch relief from baseline to Week 12 will be presented by treatment group. If a subject did not attend Week 12 visit, but has diary data to derive the number of antihistamine tablets, the planned date of Week 12 visit will be used for derivation. Subjects who do not have appropriate diary information will be excluded from this analysis.

All prior and concomitant medications will be presented in separate listings.

4.8 Pharmacokinetic Analysis

Omalizumab serum concentration before next dose (C_{trough}) and Omalizumab serum concentrations every 4 weeks after the last dose will be summarized by treatment group and time point using descriptive statistics for all patients who have omalizumab serum concentration data for ≥1 time point.

Individual data will be listed.

4.9 Pharmacodynamic Analysis

Free and total IgE will be summarized descriptively by treatment group and time point using descriptive statistics in the main treatment period and the transition period. Individual data will be listed.

4.10 Immunogenicity Analysis

Results of the immunogenicity analysis will be provided by immunogenicity incidence (number and percent of ADA positive patients by treatment group), antibody titer and neutralization potential by treatment group.

The safety analysis set will be used for immunogenicity analysis.

The immunogenicity analysis will be performed after completion of the main treatment period at Week 12 for the TEV-45779 and XOLAIR treatment groups, and for TEV-45779 and XOLAIR/TEV-45779 treatment groups after the completion of the transition period at Week 24 and after the follow-up period (EOS) at Week 40.

Results of immunogenicity assessment will be listed.

The incidence of ADA positive will be summarized by treatment group, and ADA positive/negative, titer level, and neutralizing ADA positive/negative will be summarized at each visit using descriptive statistics.

4.11 Changes to Analyses Specified in Protocol

There are no changes to the analyses specified in the protocol.

5 REFERENCES

1. Study Protocol: "A Multinational, Multicenter, Randomized, Double Blind Study to Evaluate the Efficacy, Pharmacokinetics, Pharmacodynamics, Safety, Tolerability, and Immunogenicity of TEV 45779 Compared to Omalizumab (XOLAIR) in Patients With Chronic Idiopathic Urticaria/Chronic Spontaneous Urticaria who Remain Symptomatic Despite Antihistamine (H1) Treatment"
2. Heitjan, F., and Little, R. J. A. (1991). "Multiple Imputation for the Fatal Accident Reporting System." *Journal of the Royal Statistical Society, Series C* 40:13–29.
3. Kaplan A, Ledford D, Ashby M, Canvin J, Zazzali JL, Conner E, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. J Allergy Clin Immunol 2013;132(1):101-9
4. Little RJA, Rubin DB. Statistical Analysis with Missing Data, Second Edition. 2002, New York: John Wiley & Sons.
5. Mathias SD, Crosby RD, Rosẹn KE, Zazzali JL. The minimal important difference for measures of urticaria disease activity: Updated findings. Allergy Asthma Proc 2015;36(5):394-8

6. Maurer M, Rosén K, Hsieh H-J, Saini S, Grattan C, Gimenéz-Arnau A, et al. Omalizumab forthe treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med 2013;368(10):924-35.
7. Rubin DB. Multiple Imputation for Nonresponse in Surveys. 1987, New York: John Wiley & Sons.
8. Saini SS, Bindslev-Jensen C, Maurer M, Grob JJ, Baskan EB, Bradley MS, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. J Invest Dermatol. 2015;135(1):67-75
9. Schenker, N., and Taylor, J. M. G. (1996). "Partially Parametric Techniques for Multiple Imputation." *Computational Statistics and Data Analysis* 22:425–446.
10. Vezzoli S. Estimation of relative potency in a 4-point, parallel line assay. Paper SP01. PhUSE 2011.

6 APPENDICES

6.1 Study Schedule

Table 3: Study Procedures and Assessments

Study period	Screening		Main treatment period				Transition period			Follow-up period			
			BL			EoMTP/ BL TP[a]			EoT				EoS/ET
Visit	V1[b]	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13
Week	-2	-1	0	4	8	12	16	20	24	28	32	36	40
Day	-14	-7	1	29	57	85	113	141	169	197	225	253	281
Allowed time window (days)	-7/+2	-2	-	±3	±3	+3	±3	±3	±3	±3	±3	±3	±3
Procedures and assessments													
Informed consent	X												
Demographics	X												
Medical and surgical history	X												
Prior medication and treatment history	X	X											
Inclusion and exclusion criteria	X	X	X										
Randomization/Re-randomization			X			X[c]							
IMP administration [d, e, f, g]			X	X	X	X	X	X					
Local tolerability at injection site [h]			X	X	X	X	X	X					
Adverse events inquiry	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication inquiry, including the use of			X	X	X	X	X	X	X	X	X	X	X

Study period	**Screening**		**Main treatment period**				**Transition period**			**Follow-up period**			
			BL			**EoMTP/ BL TP[a]**			**EoT**				**EoS/ET**
Visit	**V1[b]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**
Week	**-2**	**-1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**
Day	**-14**	**-7**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**
Allowed time window (days)	**-7/+2**	**-2**	**-**	**±3**	**±3**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Procedures and assessments													
rescue medication													
COVID-19 inquiry	X	X	X	X	X	X	X	X	X	X	X	X	X
Procedures and assessments													
Patient Symptom Diary (eDiary)[i] including UAS	X	X	X	X	X	X	X	X	X	X	X	X	X
Physician's (in-clinic) assessment of UAS[j]	X	X	X	X	X	X	X	X	X	X	X	X	X
Dermatology Life Quality Index (DLQI)			X			X			X				X
Physical examination[k]	X		X	X	X	X	X	X	X	X	X	X	X
Body weight	X		X			X							X
Height	X												
12-lead ECG	X					X			X				X

Study period	**Screening**		**Main treatment period**				**Transition period**			**Follow-up period**			
			BL			**EoMTP/ BL TP[a]**			**EoT**				**EoS/ET**
Visit	**V1[b]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**
Week	**-2**	**-1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**
Day	**-14**	**-7**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**
Allowed time window (days)	**-7/+2**	**-2**	**-**	**±3**	**±3**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Procedures and assessments													
Vital signs measurement	X		X	X	X	X	X	X	X	X	X	X	X
Stool ova and parasite evaluation		X[l]											
Blood sample for:													
Free IgE	X		X	X	X	X	X	X	X	X	X	X	X
Total IgE	X		X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics			X	X	X	X	X	X	X	X	X	X	X
Procedures and assessments													
Clinical laboratory tests (serum chemistry, hematology, urinalysis, COVID-19[m])	X		X			X			X				X
Pregnancy test[n]		X				X			X				

Study period	Screening		Main treatment period				Transition period			Follow-up period			
			BL			EoMTP/ BL TP[a]			EoT				EoS/ET
Visit	V1[b]	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13
Week	-2	-1	0	4	8	12	16	20	24	28	32	36	40
Day	-14	-7	1	29	57	85	113	141	169	197	225	253	281
Allowed time window (days)	-7/+2	-2	-	±3	±3	+3	±3	±3	±3	±3	±3	±3	±3
Procedures and assessments													
ADA evaluation[o]			X	X		X			X				X

[a] The assessments made at visit 6 (Week 12) before the administration of IMP constitute the end of the main treatment period and the baseline for the transition period.

[b] The interval between V1 and V2 should be at least 5 days; patients that require a 3-day adjustment period to reach an approved dose of their H1 antihistamine treatment will need an interval of at least 8 days.

[c] Patients in the XOLAIR treatment group will be re-randomized 1:1 to XOLAIR or switch to TEV-45779. Patients who were initially randomized to TEV-45779 will continue to receive TEV-45779, however, to maintain blinding, the re-randomization process will be performed for all patients (although only patients in the XOLAIR treatment group will actually be re-randomized).

[d] Assessments scheduled on the day of IMP administration should be completed before IMP administration, except for the assessment of local tolerability at the injection site.

[e] IMP will be preferably administered in the front and middle of the thigh area (both injections at least 1 inch (2.5 cm) apart). Alternatively, if injection in the thigh is not possible, the injection may be given in the abdomen, avoiding the 2-inch (5 cm) area directly around the navel. The used injection site will be documented.

[e, f] All device-related adverse events, malfunctions etc will be recorded; their impact relative to the safety and tolerability of the IMP will be evaluated.

[g] If during IMP administration or during the 2-hour post-IMP administration observation the patient develops clinical symptoms or signs, vital signs should be collected and a physical examination (brief or full, at the discretion of the investigator) performed. The patient should be assessed for anaphylaxis/hypersensitivity reactions as detailed in Section 7.1.6 of the protocol

[h] Assessments will be performed at 20, 60 and 120 minutes after IMP administration and include the assessment of erythema, ecchymosis, induration, tenderness, warmth, swelling, and pain at the injection site.

[i] Patients receive the electronic Patient Symptom Diary (eDiary) during the V1 (on day −14) visit. It includes the twice daily (morning and evening) assessment of the number of wheals (hives) and of the itch severity. Patients must have diary entries during at least 4 of the 7 days prior to randomization on day 1.

[j] The physician's (in-clinic) assessment is a non−diary based, in-clinic assessment of UAS (itch score + number of wheals [hives] score) based on the patient's condition over 12 hours prior to the visit. It should be completed prior to reviewing the diary entries of the patients and must be completed prior to administration of IMP on visits 3 to 8.

[k] The V1 (day -14) visit physical examination should be comprehensive while subsequent examinations may be abbreviated to detect changes in symptoms of CIU/CSU as well as directed by patient complaints regarding adverse events.

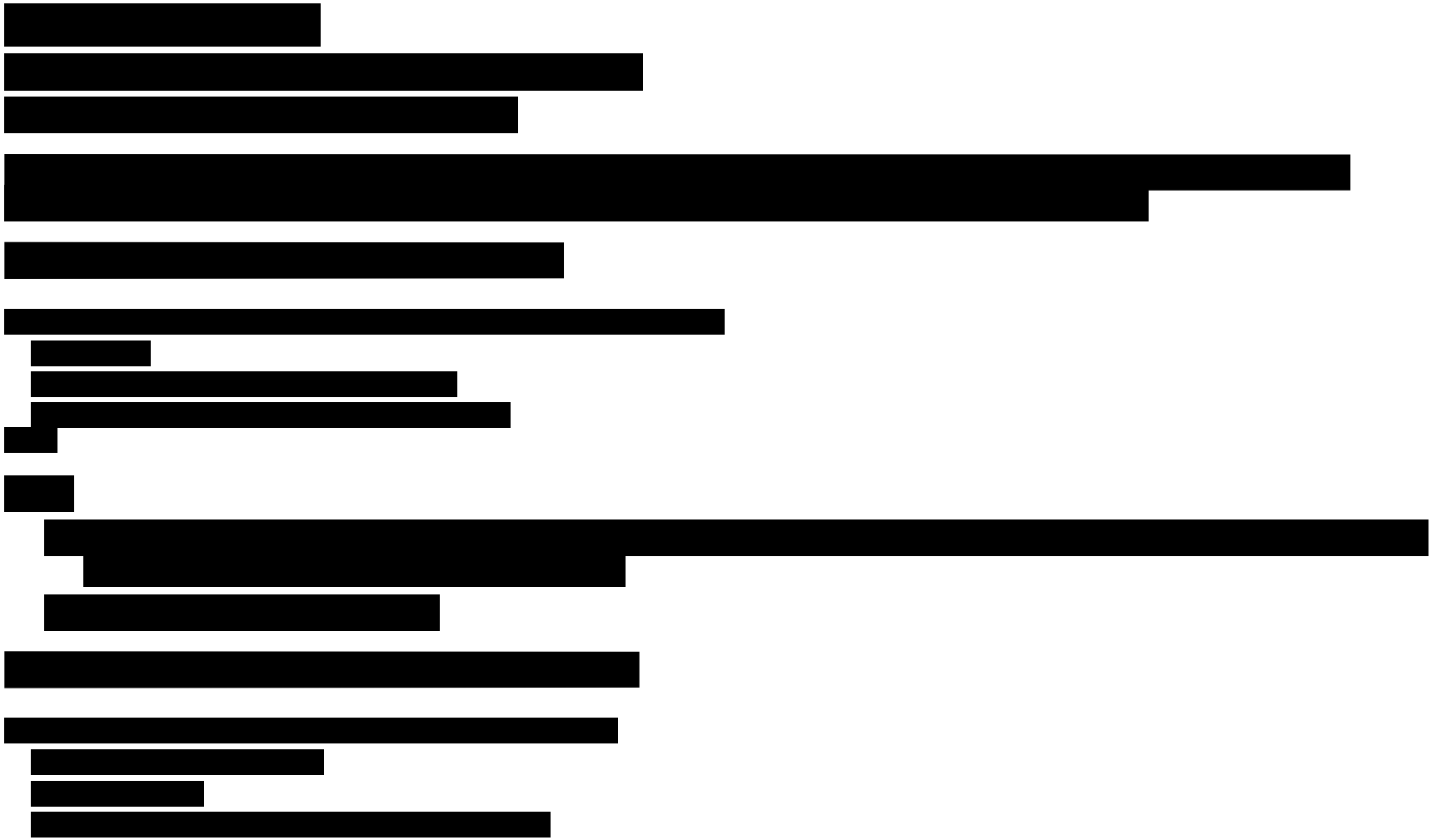
[l] The stool ova and parasite evaluation should be performed at the V2 (day -7) visit in patients with an eosinophil count >2 times the ULN on day -14 and risk factors for parasitic disease. Stool ova and parasite evaluation will be performed by a local laboratory. In case the stool ova and parasite evaluation needs to be done by the central laboratory (for some countries), the test can be done at the V1 visit or at an unscheduled visit shortly after the V1 visit and the preceding eosinophil count can be done locally.

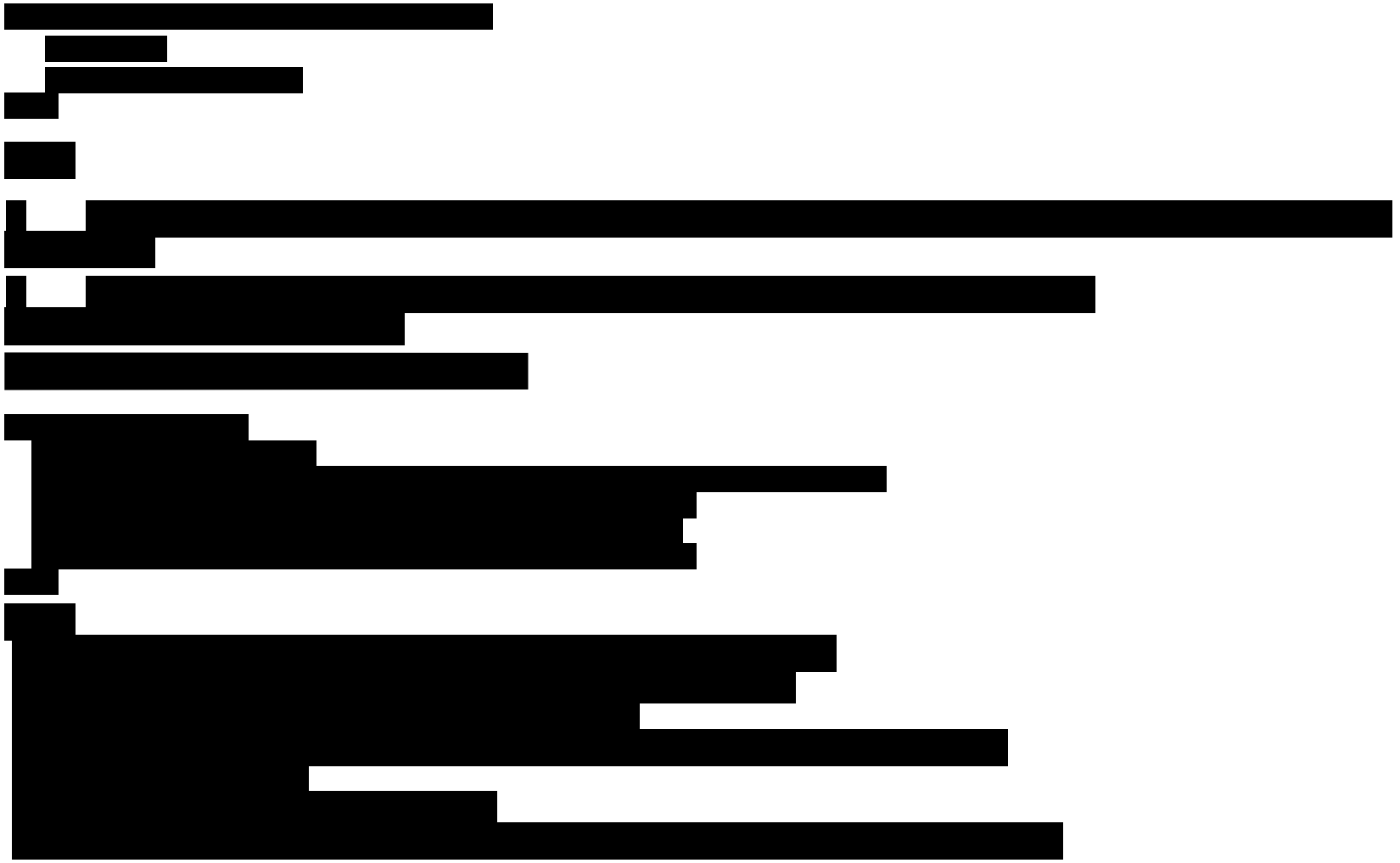
[m] Additional laboratory parameters, such as FSH and β-HCG (see footnote j) or as applicable (see inclusion criterion c in the protocol), may be assessed at screening and baseline. COVID-19 testing to be performed at screening and at any other time point during the study if the patient exhibits clinical symptoms that may indicate COVID 19 infection. COVID-19 testing will be performed locally (if available) or centrally (if not available locally).

[n] Only for women of childbearing potential. Women will have a urine pregnancy test at screening (visit 2), at the start of the transition period (visit 6) and at EoT (visit 9). If the urine pregnancy test result is positive a serum pregnancy test should be performed by the central laboratory. Urine pregnancy tests will be performed at the site.

[o] If any severe hypersensitivity reaction (eg, anaphylaxis) or immunogenicity-related adverse event (serious or non-serious) is observed, additional sample(s) will be collected for immunogenicity assessment as close to the onset of the event as possible, at resolution of the event, and 30 days following the event onset, if possible. ADA samples should also be collected for analysis of neutralizing antibodies if treatment-related ADA-positive samples are detected. When a number of assessments are to be conducted at the same time point, the immunogenicity blood sample should be taken after other assessments and before drug administration.

ADA=anti-drug antibody; BL=baseline; BL TP=baseline transition period; β-HCG=human chorionic gonadotropin; CIU/CSU=chronic idiopathic urticaria/chronic spontaneous urticaria; COVID-19=Coronavirus disease 2019; ECG=electrocardiography; eDiary=electronic Patient Symptom Diary; EoMTP=end of main treatment period; EoS=end of study; EoT=end of treatment; ET=early termination; FSH=follicle stimulating hormone; IgE=immunoglobulin E; UAS=urticaria activity score; ULN=upper limit of normal; V=visit.





[redacted]

[redacted]