Clinical Study Protocol

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

Protocol with Amendment 04 Approval Date: 15 February 2023

Clinical Study Protocol with Amendment 04

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

Short title: **A Randomized, Double-Blind Study of Efficacy, Pharmacokinetics, Pharmacodynamics, and Safety of TEV-45779 in Adults with Chronic Idiopathic Urticaria/Chronic Spontaneous Urticaria**

Title of the protocol for lay people: **A Study to Find Out if TEV-45779 Helps to Treat Chronic Idiopathic Urticaria/Chronic Spontaneous Urticaria That is Not Helped by Antihistamines**

Efficacy and Safety Study (Phase 3)

IND number: 145915; EudraCT number: 2021-001796-17

EMA Decision number of Pediatric Investigation Plan: Not applicable

Article 45 or 46 of 1901/2006 does not apply

Clinical Study Protocol with Amendment 04 Version Date: 15 February 2023

Sponsor

Teva Pharmaceuticals, Inc.
400 Interpace Parkway, Building A,
Parsippany, NJ 07054, United States of America

Information regarding clinical laboratories and other departments and institutions is found in Appendix A

This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Council for Harmonisation (ICH); United States (US) Code of Federal Regulations (CFR), and European Union (EU) Directives and Regulations (as applicable in the region of the study); national country legislation; and the sponsor's Standard Operating Procedures (SOPs).

Confidentiality Statement

AMENDMENT HISTORY

The protocol for study TV45779-IMB-30086 (original protocol dated 18 April 2021) has been revised and reissued as follows:

Amendment 04	15 February 2023 372 patients enrolled as of 6 February 2023
Administrative Letter 07 (For India)	19 December 2022
Administrative Letter 06 (For India)	20 October 2022
Administrative Letter 05	01 August 2022
Amendment 03	10 May 2022 36 patients enrolled as of 27 April 2022
Administrative Letter 04 (For S. Korea)	23 February 2022 14 patients enrolled to date
Administrative Letter 03	28 January 2022 8 patients enrolled to date
Amendment 02	23 November 2021 0 patients enrolled to date
Administrative Letter 02	10 November 2021 0 patients enrolled to date
Administrative Letter 01	26 October 2021 0 patients enrolled to date
Amendment 01	11 June 2021 0 patients enrolled to date

The Summary of Changes to the Protocol includes the corresponding reason/justification for each change and is provided in Section 16.

INVESTIGATOR AGREEMENT

Clinical Study Protocol with Amendment 04 Version Date: 15 February 2023

Study 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.

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

I have read the protocol with Amendment 04 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes agreement with this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national or local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the investigational medicinal product (IMP) that were furnished to me by the sponsor to all physicians and other study personnel reporting to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the IMP and the conduct of the study. I agree to keep records on all patient information, IMP shipment and return forms, and all other information collected during the study, in accordance with national and local Good Clinical Practice (GCP) regulations as well as all other national and international laws and regulations.

Principal Investigator	**Signature**	**Date**

Executed signature pages are maintained separately within the Trial Master File

SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative	Signature	Date
[redacted]		

Executed signature pages are maintained separately within the Trial Master File

COORDINATING INVESTIGATOR AGREEMENT

Clinical Study Protocol with Amendment 04 Version Date: 15 February 2023

Study 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.

Coordinating Investigator: [redacted]

Title: [redacted]

Address of Investigational Center: [redacted]

[redacted]

[redacted]

Tel: [redacted]

I have read the protocol with Amendment 04 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes agreement with this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national or local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the investigational medicinal product (IMP) that were furnished to me by the sponsor to all physicians and other study personnel reporting to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the IMP and the conduct of the study. I agree to keep records on all patient information, IMP shipment and return forms, and all other information collected during the study, in accordance with national and local Good Clinical Practice (GCP) regulations as well as all other national and international laws and regulations.

Coordinating Investigator	Signature	Date

Executed signature pages are maintained separately within the Trial Master File

CLINICAL STUDY PROTOCOL SYNOPSIS

With Amendment 04

Study TV45779-IMB-30086

Title of Study: 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.

Sponsor: Teva Pharmaceuticals, Inc.

Investigational New Drug (IND) Number: 145915 **EudraCT Number: 2021-001796-17**

European Medicines Agency (EMA) Decision number of Pediatric Investigation Plan: Article 45 or 46 of 1901/2006 does not apply

Name of Test Investigational Medicinal Product (IMP) or Device: TEV-45779

Active Substance: Omalizumab solution for injection

EudraVigilance (EV) code for the IMP, if applicable: Not applicable

Type of the Study: Phase 3 - Efficacy and Safety

Indication: Chronic Idiopathic Urticaria (CIU)/Chronic Spontaneous Urticaria (CSU)

Is this study conducted to investigate the New Use of an approved, marketed product? No

Number of Investigational Centers Planned: The study is planned to be conducted in approximately 140 investigational sites.

Countries Planned: The study is planned to be conducted in approximately 18 countries in North America, Latin America, Europe, and Asia-Pacific.

Planned Study Period and Duration: Approximately 2 years from quarter (Q)3 2021 to Q2 2024

Number of Patients Planned (total): Approximately 600 patients (200:200:100:100 to TEV-45779 300 mg, XOLAIR 300 mg, TEV-45779 150 mg and XOLAIR 150 mg) will be randomized.

Study Population: Patients with CIU/CSU who remain symptomatic despite antihistamine (H1) treatment.

Primary and Secondary Objectives and Endpoints: To demonstrate that there are no clinically meaningful differences in efficacy, pharmacokinetics, pharmacodynamics, and safety between TEV-45779 and XOLAIR administered subcutaneously (sc) in patients with CIU/CSU. The primary and secondary study objectives and endpoints are presented below.

Primary and Secondary Study Objectives and Endpoints

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 CIU/CSU	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

Objectives	Endpoints
in patients who remain symptomatic despite antihistamine (H1) treatment.	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 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 change from baseline 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. 300 mg) as well as between TEV-45779 and XOLAIR	Secondary efficacy endpoints are as follows. • Change from baseline in ISS7 at Week 12 • Change from baseline in the 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 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 UAS7 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 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

Objectives	Endpoints
	• 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
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) • Device-related adverse events and malfunctions
To compare pharmacokinetics between TEV-45779 and XOLAIR after multiple doses	The pharmacokinetic parameter is: • Omalizumab serum concentration before next dose (Ctrough) • 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

Primary Estimand:

The primary estimand for the primary efficacy endpoint for the Food and Drug Administration (FDA) submission is:

- The difference in mean change from baseline in weekly itch severity score (ISS7; sum of the daily itch severity score for 7 days) 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 (as defined in "Statistical Considerations" below), 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 (Heitjan and Little 1991, Schenker and Taylor 1996), 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 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, 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 300 mg 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 300 mg 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.

General 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 43 weeks.

During the conduct of this study, an Independent Data Monitoring Committee (IDMC) will review accumulating unblinded safety data on a regular basis and also ad hoc if needed, as detailed in the IDMC charter, to ensure the continuing safety of the study patients. The specific details regarding the IDMC sessions will be outlined in the IDMC charter.

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 hydrochloride (25 mg, maximum 3 times/day) as rescue medication for itch relief.

Disallowed concomitant treatment includes the use of systemic and topical steroids, H1 antihistamines at greater than approved doses, H2 antihistamines, leukotriene receptor antagonists (LTRAs), hydroxychloroquine, methotrexate, cyclosporine, cyclophosphamide, intravenously-given immunoglobulin, and disallowed medications according to the contraindications for diphenhydramine hydrochloride.

Study Treatment

Patients will receive a total of 6 treatments, each consisting of 2 sc injections resulting in 150 mg or 300 mg of 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 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.

Method of 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 treatments 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 (transition period) at the same dose level as prior to randomization. All patients in the TEV-45779 groups will continue to receive TEV-45779 at the same dose levels as prior to randomization.

During the main treatment period, the sponsor, investigators (including other site staff involved in study assessments) and patients will be blinded to the treatment assignment of all patients. To maintain blinding to the treatment assignment, the re-randomization process will be performed for all patients, including the patients in the TEV-45779 group (although only patients in the XOLAIR arm will actually be re-randomized while patients in the TEV-45779 group will continue to receive TEV-45779 in the transition period). Randomization will be implemented using the Randomization and Trial Supply Management (RTSM) system. After last patient last visit and database lock (DBL) of the main treatment period, the sponsor will unblind the treatments for the analysis of the main treatment period. After last patient last visit and DBL of the main treatment period, staff responsible for population pharmacokinetics, and/or the pharmacokinetics/pharmacodynamics model will receive access to the patient treatment randomization. The investigators, patients, and staff responsible for the pharmacokinetic, pharmacodynamics, and immunogenicity bioanalysis will remain blinded to the main treatment period treatment assignments.

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 as the IMPs differ in appearance: these persons will not be involved in the conduct of any study procedures or assessments.

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

Investigational Medicinal Products: Dose, Pharmaceutical Form, Route of Administration, and Administration Rate

IMP		Test	Reference	Placebo
IMP name		**TEV-45779 (omalizumab)**	**XOLAIR® (omalizumab) Injection**	**Placebo (no active) to complement TEV-45779 (omalizumab) or XOLAIR® (omalizumab)**
Trade name or company-assigned number		TEV-45779	XOLAIR	Placebo
Formulation	Active	150 mg/mL	150 mg/mL	NA
	Histidine	20 mM	20 mM	20 mM
	Arginine hydrochloride	200 mM	200 mM	200 mM
	Polysorbate 20	0.04%	0.04%	0.04%
Unit dose strength(s)/Dosage level(s)		150 mg/mL 150 mg/dose (single sc injection) or 300 mg/dose (2 sc injections)	150 mg/mL 150 mg/dose (single sc injection) or 300 mg/dose (2 sc injections)	NA
Route of administration		sc injection	sc injection	sc injection
Device		Automatically activated needle safety guard	Automatically activated needle safety guard	Automatically activated needle safety guard
Storage conditions		2°C to 8°C (36°F to 46°F), protected from direct light and heat. Avoid vigorous shaking. Do not freeze	2°C to 8°C (36°F to 46°F), protected from direct light and heat. Avoid vigorous shaking. Do not freeze	2°C to 8°C (36°F to 46°F), protected from direct light and heat. Avoid vigorous shaking. Do not freeze
Manufacturer		[redacted]	[redacted]	[redacted]

IMP=investigational medicinal product; NA=not applicable; sc=subcutaneous; USA=United States of America.

The IMP will be prepared in a separate room by the non-blinded person (eg, pharmacist or designee) as the IMPs differ in appearance. The blinding will be maintained during the transportation from and to the dosing room. Dosing will be performed by a non-blinded staff member in the dosing room. The original IMP packaging and syringes should not be visible when the patient or any other blinded study team member enters the room. In order to ensure additional patient blinding, a blindfold with an additional pillow at chest level (or similar device) will be used during the IMP injection as a shield to hide the IMP from the patient. 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.

Duration of Patient Participation and Maximal Exposure to IMP: The total duration of patient participation in the study is planned to be approximately 42 weeks including up to an approximately 3-week screening period, approximately 12-week double-blind main treatment period, an approximately 12-week transition period, and an approximately 16-week follow-up.

End of Study: End of study is defined as the last visit of the last patient.

Plans for Treatment or Care after the Patient Has Ended Participation in the Study: After study end, no IMP will be provided as XOLAIR is commercially available.

Inclusion Criteria: Patients may be randomized/enrolled in this study only if they meet all of the following criteria:

a. Male or female patients aged ≥18 years and ≤75 years.

b. Diagnosis of CIU/CSU refractory to H1 antihistamines at the time of randomization, as defined by all of the following:

   – The presence of itch and wheals for ≥8 consecutive weeks at any time prior to enrollment despite current use of H1 antihistamine treatment during this time period.

   – Weekly urticaria activity score (UAS7; sum of the daily number of wheals score and itch severity score over 7 days) ≥16 (range 0-42) and itch component of UAS7 ≥8 (range 0-21) during 7 days prior to randomization.[1]

   – Urticaria activity score (UAS) ≥4 assessed by a clinician on ≥1 of the screening visit days.

   – Patients must have been on an approved dose of an H1 antihistamine for CIU/CSU for ≥3 consecutive days immediately prior to the start of screening and must document current use on the day of the initial screening visit, OR, have their H1 antihistamine for CIU/CSU adjusted to an approved dose during the first 3 days of screening and have their adjusted use documented at the end of the dose adjustment.

   – CIU/CSU diagnosis for ≥3 months.[2]

c. Women may be included if they fulfill one of the following criteria:

   – Women of non-childbearing potential who are either surgically (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile as assessed by a physician, or 1-year postmenopausal (no menses for 12 months without an alternative medical cause plus an increased concentration of

[1] Refer to Section 9.3.1 for handling of missing data for daily and weekly scores.
[2] Diagnosis or symptoms leading to this diagnosis have to be present for ≥3◦months.

follicle stimulating hormone [FSH] of more than 35 U/L) in women not using hormonal contraception or hormonal replacement therapy.

- Women of childbearing potential whose male partners are potentially fertile (ie, no vasectomy) must:
  - have a negative beta-human chorionic gonadotropin (β-HCG) test result at screening (visit 2); and
  - use highly effective birth control methods for the duration of the study (ie, starting at screening) and for 5 half-lives (20 weeks) after last dose of IMP.

Highly effective birth control methods are methods that can achieve a failure rate of less than 1% per year when used consistently and correctly (see such methods in Appendix J).

d. Male patients (including vasectomized men) with partners who are of childbearing potential (whether pregnant or not) must use condoms prior to IMP administration and until 20 weeks after last IMP dose.

e. Must be able to understand the requirements of the study and to provide their written informed consent to participate in the study.

f. Must be willing and able to comply with study requirements and procedures as specified in this protocol. In particular, the patient must be willing and able to complete a symptom diary twice daily (morning and evening) for the duration of the study. The patients must have diary entries during at least 4 of the 7 days prior to randomization.

Exclusion Criteria: Patients will not be randomized/enrolled in this study if they meet any of the following criteria:

a. Body weight <40 kg.

b. Clearly defined underlying etiology for chronic urticarias other than CIU/CSU.

c. Evidence of parasitic infection defined as meeting the following 3 criteria:
   - Risk factors for parasitic disease (living in an endemic area, chronic gastrointestinal symptoms, travel within the last 6 months to an endemic area and/or chronic immunosuppression), and
   - An absolute eosinophil count more >2× the upper limit of normal (ULN), and
   - Evidence of parasitic colonization or infection on stool evaluation for ova and parasites. Note that stool ova and parasite evaluation will only be conducted in patients with risk factor(s) and an eosinophil count >2× the ULN.

d. Atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile pruritus, or other skin disease associated with itch.

e. Treatment with an investigational agent within 30 days or longer depending on half-life (>5 half-lives) prior to the start of screening.

f. Previous treatment with omalizumab or other Anti-IgE therapy within a year prior to the start of screening.

g. Routine (daily or every other day during 5 or more consecutive days) doses of the following medications within 30 days prior to screening: Systemic or cutaneous (topical) corticosteroids (prescription or over-the-counter), hydroxychloroquine, methotrexate, cyclosporine, or cyclophosphamide.

h. Intravenous immunoglobulin G, or plasmapheresis within 30 days prior to the start of screening.

i. Regular (daily/every other day) doxepin (oral) use within 2 weeks prior to the start of screening.

j. Any H2 antihistamine use within 7 days prior to the start of screening.

k. Any LTRA (montelukast or zafirlukast) use within 7 days prior to the start of screening.

l. Any H1 antihistamines at greater than approved doses use from 3 days after the start of screening.

m. Current malignancy, history of malignancy within the last 5 years, or currently under work-up for suspected malignancy except non-melanoma skin cancer that has been treated or excised and is considered resolved.

n. Hypersensitivity to omalizumab or any component of the formulation.

o. History of anaphylactic shock.

p. Contraindications to diphenhydramine hydrochloride.

q. Pregnant or lactating woman, or plans to become pregnant during the study.

r. Presence of clinically significant cardiovascular, neurological, psychiatric, metabolic, or other pathological conditions that could interfere with the interpretation of the study results and or compromise the safety of the patients.

s. Evidence of current drug or alcohol abuse.

t. Patients taking either LTRAs or H2 blockers for diseases other than CIU (eg, asthma or gastroesophageal reflux disease, respectively) will be permitted to continue their use during the study. These diseases must be recorded as part of the medical history collected during the screening period. Inhaled asthma controllers, including corticosteroids, are also permitted during the study.

Statistical Considerations

The statistical analysis of the study is planned to assess the biosimilarity (efficacy and safety) between TEV-45779 and XOLAIR, and to support the safety and immunogenicity assessment of a single switch from XOLAIR to TEV-45779.

Sample Size Rationale: 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% confidence interval (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] power 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), an [redacted]
- [redacted] power ([redacted]) for the co-primary endpoint of relative potency of TEV-45779 and XOLAIR as measured by change from baseline in ISS7 at Week 12 using a 4-point assay, [redacted] (TEV-45779 and XOLAIR at 300 mg and 150 mg).
- [redacted]

Power assessment for the co-primary endpoint of relative potency of TEV-45779 and XOLAIR, as measured by change from baseline in ISS7 at Week 12 using a 4-point assay, was performed using simulations based on innovator studies data.

Primary Efficacy Analysis: 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 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.

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 daily 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 data will be similar to the one used by the originator. Multiple imputation will be used for the missing ISS7 at Week 12 for the analysis of change from baseline to Week 12 in ISS7.

<u>For the EMA Submission:</u>

The primary analysis of change from baseline in the ISS7 at Week 12 will be an analysis of covariance (ANCOVA) with treatment group (2 levels: TEV-45779 300 mg and XOLAIR 300 mg), 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.

The primary analysis will be based on the intent to treat (ITT) analysis set.

For the FDA Submission:

The following analyses will be considered co-primary:

1. The primary analysis of change from baseline in the ISS7 at Week 12 will be an analysis of covariance (ANCOVA) with treatment group (2 levels: TEV-45779 300 mg and XOLAIR 300 mg), 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).
2. 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 falls entirely within the equivalence margins of (0.5, 2).

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

Efficacy Analysis in the Transition Period:

Descriptive statistics will be presented by the treatment groups and dose level to which the patients were assigned in the main treatment and transition periods (TEV-45779/TEV-45779, XOLAIR/XOLAIR and XOLAIR/TEV-45779). In addition, 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 transition period modified intent-to-treat (TmITT) analysis set.

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

Sensitivity/Supplementary Analysis: The main sensitivity/supplementary analyses to assess the robustness of the primary efficacy analysis will include:

- 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 of treatment group
  - primary analysis using mixed-model-for-repeated-measures, 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.
- 4-points relative potency between TEV-45779 300 mg and XOLAIR 300 mg
  - the ANCOVA model in the %RELPOT macro run without baseline covariates

- Supplementary analyses for missing data for change from baseline in the ISS7 at Week 12 difference between TEV-45779 300 mg and XOLAIR 300 mg
  - tipping point (missing-not-at-random)
  - 2 separate 1-sided tests of alpha=0.05 with missing data imputed under the corresponding null using a multiple imputation method

Secondary Efficacy Analysis: No formal statistical analysis of secondary efficacy endpoints is planned; descriptive statistics will be presented.

Multiple Comparisons and Multiplicity: For the FDA submission, the above efficacy endpoint and the relative-potency endpoint of 2 dose levels (300 mg and 150 mg) of TEV-45779 and XOLAIR, as measured by change from baseline 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 efficacy similarity is demonstrated for the endpoint of change from baseline in ISS7 at Week 12 for TEV-45779 300 mg compared to XOLAIR 300 mg. The secondary efficacy analyses will be descriptive in nature.

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

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each patient will be counted only once in each preferred term or system organ class (SOC) category for the analyses of safety. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to test IMP (ie, reasonable possibility) (defined as related or with missing relationship) (overall and by severity), serious adverse events, and adverse events causing withdrawal from the study. Summaries for the main treatment period, transition period and overall treatment period will be presented as indicated below. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

Changes in laboratory and vital signs data will be summarized descriptively by treatment period. All values will be compared with predefined criteria to identify potentially clinically significant values or changes, and such values will be listed.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics by treatment period.

For continuous variables, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided. Descriptive summaries of serious adverse events, patient withdrawals due to adverse events, and potentially clinically significant abnormal values (clinical laboratory or vital signs) based on predefined criteria will be provided as well by treatment period.

If any patient dies during the study, a listing of deaths will be provided and all relevant information will be discussed in the patient narrative included in the clinical study report (CSR).

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.

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.

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.

The analyses will be similar to the analyses of the main treatment period. Summaries will be presented by treatment group (TEV-45779, XOLAIR, further subdivided by dose 150 mg or 300 mg) and for all patients included in the analysis.

Tolerability Analysis: If more than 10% of the patients withdraw from the study before the end of the main treatment period, the number of days until study discontinuation will be analyzed using Kaplan-Meier methodology using the ITT analysis set.

Pharmacokinetic Analysis: Omalizumab serum concentrations will be summarized by treatment and time point using descriptive statistics for all patients who have omalizumab serum concentration data for ≥1 time point.

Individual data will be listed.

Pharmacodynamic Analysis: Free and total IgE will be summarized by treatment and time point using descriptive statistics. Individual data will be listed.

Immunogenicity Analysis: Results of the immunogenicity analysis will be provided by immunogenicity incidence (number and percent of treatment-related ADA positive patients by treatment group), antibody titration and neutralization potential by treatment group.

The safety analysis set will be used for immunogenicity analysis.

Interim Analysis: No interim analysis is planned for this study.

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Abbreviation	Term
β-HCG	beta-human chorionic gonadotropin
εRI	epsilon RI
ADA	anti-drug antibody
ADE	adverse device effect
ADL	activities of daily living
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate aminotransferase (SGOT)
ATE	arterial thromboembolic events
AUC_{ext}	area under the concentration-time curve
BPD	Biological Product Development
BUN	blood urea nitrogen
CDMS	clinical data management system
CFR	Code of Federal Regulations (USA)
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CIU	chronic idiopathic urticaria
CL	total body clearance
COVID-19	Coronavirus disease 2019
CPK	creatine phosphokinase
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
CRSwNP	chronic rhinosinusitis with nasal polyp
CSR	clinical study report
CSU	chronic spontaneous urticaria
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	omalizumab serum concentration before next dose
DBL	database lock
DLQI	Dermatology Life Quality Index
ECG	electrocardiogram
eDiary	electronic Patient Symptom Diary
EMA	European Medicines Agency

Abbreviation	Term
EoS	end of study
EoT	end of treatment
ePRO	electronic patient-reported outcome
EU	European Union
EV	EudraVigilance
F	Bioavailability
Fc	crystallizable fragment
FcRn	neonatal Fc receptor
FcεRI	high-affinity IgE receptor
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FSH	follicle stimulating hormone
GCA	Global Quality Assurance
GCP	Good Clinical Practice
GGT	gamma glutamyl transpeptidase
GMP	Good Manufacturing Practice
GPSP	Global Patient Safety and Pharmacovigilance
HDL	high density lipoprotein
HEENT	head, eyes, ears, nose, and throat
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	The International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgE	immunoglobulin E
IgG	immunoglobulin G
IgG1	immunoglobulin G1
IMP	investigational medicinal product
INC	intranasal corticosteroids
IND	Investigational New Drug
INN	international nonproprietary name
INR	international normalized ratio
IRB	Institutional Review Board
ISO	International Organization for Standardization

Abbreviation	Term
ISS7	weekly itch severity score (sum of the daily itch severity score for 7 days)
ITT	intent-to-treat
LDH	lactic dehydrogenase
LDL	low density lipoprotein
LSO	local safety officer
LTRA	leukotriene receptor antagonist
MAA	Marketing Authorisation Application
mAb	monoclonal antibody
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry for Food and Drug Safety
MID	minimally important difference
mITT	modified intent to treat
MMRM	mixed-model-for-repeated-measures
MNAR	missing-not-at-random
n	number
NIAID/FAAN	National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network
NRS-11	11-point pain intensity numerical response scale
PDAESI	protocol-defined adverse event of special interest
PFS	prefilled syringe
PP	per-protocol
PT	prothrombin time
PTT	partial prothromboplastin time
Q	quarter
RBC	red blood cell count
RSI	reference safety information
RTSM	Randomization and Trial Supply Management
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
sc	subcutaneous/subcutaneously
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics

Abbreviation	Term
SOC	system organ class
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reaction
TITT	transition intent-to-treat
t_{max}	time to maximum observed drug concentration
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)
ULN	upper limit of normal
US	United States (of America)
USPI	US Prescribing Information
VC	videoconference
V_z	volume of distribution
W	week
WBC	white blood cell count
WHO	The World Health Organization
WHO Drug	World Health Organization Drug Dictionary
XML	Extensible Markup Language

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Introduction

1.1.1. TEV-45779

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 and 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). Both XOLAIR and TEV-45779 are presented in a prefilled syringe (PFS) with needle safety device for single-use subcutaneous (sc) administration.

Omalizumab is comprised of 2 identical light chains and 2 identical heavy chains. Each light chain consists of 218 amino acid residues while each heavy chain is predicted to contain 451 residues. The molecular weight of omalizumab is 149 kDa.

Omalizumab binds to IgE at an epitope that IgE requires for its binding to the crystallizable fragment (Fc) epsilon RI (εRI) (FcεRI; high-affinity IgE receptor) (Pelaia et al 2011). Thus, it inhibits the binding of IgE to the FcεRIs found on mast cells, basophils, and dendritic cells. In addition, as omalizumab depletes free IgE, the FcεRIs on basophils, mast cells, and dendritic cells are down-regulated. Consequently, the likelihood for mast cells and basophils to release the mediators necessary to elicit an inflammatory response is decreased by a reduction of both the ligand and the receptor necessary to initiate such a release.

TEV-45779 drug substance is produced using a Chinese hamster ovary K1SV cell line. The analysis for biosimilarity includes structural and functional assessments. The functional assays panel includes the assessment of activities associated with the mechanism of action, which is binding to IgE and therefore inhibiting IgE binding to FcεRI and human neonatal Fc receptor (FcRn), and effector functions. The data show overall similarity in these assays between TEV-45779 and XOLAIR.

1.1.2. TEV-45779 and Chronic Idiopathic Urticaria/Chronic Spontaneous Urticaria

CIU, also known as CSU, is defined as the occurrence of daily, or almost daily, wheals and frequently intractable pruritus (itching) for ≥6 weeks without an obvious cause. Itch is the most concerning symptom for patients and has the greatest impact on their quality of life. Angioedema or deep tissue swelling occurs in over 40% of patients with CIU; it is unpredictable and can involve swelling anywhere in the body or upper respiratory tract. Swelling of the face, lips, or airway is particularly uncomfortable and can be very serious (XOLAIR, European Public Assessment Report- Assessment Report EMEA/H/C/000606/II/0048, EMEA 2020).

The majority of CIU patients achieve symptomatic control with conventional H1 antihistamine therapy. Less commonly, a triple regimen of H1 and H2 antihistamines combined with a LTRA is used, although H2 antihistamines and LTRAs are not approved for the treatment of CIU (Viegas et al 2014). In some patients, CIU can be a debilitating condition and can have a profound negative influence on the patient's quality of life (Maurer et al 2011, Balp et al 2015).

Some patients may remain symptomatic despite ongoing H1 antihistamine treatment, and for this group of patients, therapies such as immunosuppressants (including cyclosporine, corticosteroids, intravenous IgG, and methotrexate) and plasmapheresis have been used (Kozel and Sabroe 2004). However, these agents have varying success and may be associated with severe adverse effects.

TEV-45779 is being developed as a biosimilar candidate to XOLAIR.

In the US, XOLAIR is currently approved for:

- Moderate to severe persistent asthma in patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids.
- Nasal polyps in adult patients 18 years of age and older with inadequate response to nasal corticosteroids, as add-on maintenance treatment.
- CSU in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment (XOLAIR Prescribing Information 7/2021).

In the EU, XOLAIR is currently approved for:

- Allergic asthma
  - Adults and adolescents (12 years of age and older): XOLAIR is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and who have reduced lung function (forced expiratory volume in 1 second [FEV_1] <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.
  - Children (6 to <12 years of age): XOLAIR is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.
- CSU: XOLAIR is indicated as add-on therapy for the treatment of CSU in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment.
- CRSwNP: XOLAIR is indicated as an add-on therapy with intranasal corticosteroids (INC) for the treatment of adults (18 years and above) with severe CRSwNP for whom therapy with INC does not provide adequate disease control (XOLAIR Summary of Product Characteristics 25/10/2021).

1.1.3. Purpose of the Study

TEV-45779 is a biosimilar candidate for XOLAIR. The purpose of the study is to compare the efficacy, pharmacokinetics, pharmacodynamics, safety, tolerability, and immunogenicity of TEV-45779 compared to XOLAIR in patients with CIU/CSU who remain symptomatic on H1 antihistamine treatment.

1.2. Findings from Nonclinical and Clinical Studies

1.2.1. Nonclinical Studies

Animal studies were not performed with TEV-45779, as agreed with the US FDA, because the available physicochemical and biological data from the current biosimilarity assessment did not indicate product quality differences that would require such studies to resolve remaining uncertainties.

Information on the nonclinical pharmacology, pharmacokinetics, and toxicology of omalizumab is available in the public domain, and is summarized below.

Omalizumab is a recombinant humanized IgG1 monoclonal anti-IgE antibody that binds to IgE at the same epitope as the FcεRI. Thus, omalizumab binding reduces the pool of IgE available to interact with mast cells and basophils via the FcεRI, and allergic responses are attenuated.

Omalizumab binds to Cynomolgus monkey and human IgE with similar affinity but does not bind non-primate IgE, therefore, the majority of the nonclinical studies with omalizumab were conducted in the Cynomolgus monkey.

Omalizumab pharmacokinetics in the Cynomolgus monkey were characteristic of a high-affinity mAb targeting cellularly expressed targets. Clearance of omalizumab involved IgG clearance processes, as well as clearance via specific binding and complex formation with its target ligand, IgE. Omalizumab:IgE complexes were eliminated by saturable interactions with Fc gamma receptors within the reticuloendothelial system at rates that were generally faster than IgG clearance rates. Clearance of omalizumab:IgE complexes was significantly slower than clearance of free IgE (XOLAIR Prescribing Information 7/2021).

No drug-related effects were observed for vital functions such as blood pressure, electrocardiograph measurements, heart rate, and respiration rate in Cynomolgus monkey toxicology studies.

Chronic intravenous or sc administration of omalizumab was well tolerated in Cynomolgus monkeys, except for a dose-related decrease in blood platelets, with a greater sensitivity in juvenile animals. The omalizumab serum concentration required to attain a 50% drop in platelets from baseline in adult Cynomolgus monkeys was roughly 4- to 20-fold higher than maximum clinical serum concentrations. Other adverse effects were acute hemorrhage and inflammation at injection sites.

There were no effects on fertility, reproductive performance, maternal toxicity, embryotoxicity, or teratogenicity in Cynomolgus monkeys that received XOLAIR at sc doses up to 75 mg/kg/week (approximately 10 times the maximum recommended human dose on a mg/kg basis). Omalizumab did not elicit adverse effects on fetal or neonatal growth when administered

throughout late gestation, delivery, and nursing (XOLAIR Prescribing Information 7/2021), although it crosses the placental barrier and is excreted into non-human primate breast milk.

Omalizumab was not mutagenic in the Ames test (XOLAIR Product Monograph 1/11/2022) and no carcinogenicity studies have been performed in animals with omalizumab (XOLAIR Prescribing Information 7/2021).

Special toxicity studies have demonstrated safety in a Cynomolgus monkey model challenged with ragweed allergen, no evidence of in vitro tissue cross-reactivity with Cynomolgus monkey and human tissues, no evidence of in vitro hemolysis of human and Cynomolgus monkey erythrocytes or incompatibility with human and Cynomolgus monkey serum and plasma, and no evidence of irritation in the rabbit (XOLAIR Product Monograph 1/11/2022).

1.2.2. Clinical Studies

Clinical data for TEV-45779 are available from the pivotal pharmacokinetic/pharmacodynamic study TV45779-BE-10160 (report approval date: 25 November 2021). This first-in-human study was a phase I, single dose, 3-arm, parallel-group study in subjects with serum IgE levels of <100 IU/mL to demonstrate pharmacokinetic biosimilarity between TEV-45779 150 mg and XOLAIR 150 mg sourced from the US (US-licensed XOLAIR) and XOLAIR 150 mg sourced from the EU (EU-approved XOLAIR), and to evaluate pharmacodynamics based on total and free IgE.

A total of 228 healthy subjects were enrolled into the study: 75 subjects were randomized to receive a single sc injection of TEV-45779, 76 subjects to XOLAIR EU, and 77 subjects to XOLAIR US.

Blood sampling for PK, PD and anti-drug antibody (ADA) assessment and routine safety visits occurred up to 126 days after study drug administration.

Overall, 218 (96%) subjects completed the study. From the 10 subjects who withdrew from the study: 7 subjects were in the TEV-45779 group, 1 subject in the XOLAIR EU group, and 2 subjects in the XOLAIR US group. The most frequent reason for withdrawal was lost to follow-up, which occurred in 4 subjects in the TEV-45779 group and 1 subject in the XOLAIR US group. A further 3 subjects were withdrawn due to pregnancy (2 in the TEV-45779 group and 1 subject in the XOLAIR EU group), and 2 subjects withdrew voluntarily (1 subject in each of the TEV-45779 and XOLAIR US groups).

1.2.2.1. Pharmacokinetics

Omalizumab serum concentrations were measured in serum samples for up to 126 days after administration of TEV-45779, XOLAIR US, or XOLAIR EU using a validated assay. All 3 groups had a similar mean omalizumab serum concentration-time profile.

Pharmacokinetic similarity was demonstrated between TEV-45779 and XOLAIR US, TEV-45779 and XOLAIR EU, and XOLAIR US and XOLAIR EU: for each of the 2 co-primary endpoints (C_{max} and $AUC_{0-\infty}$), the 90% CI for the GMRs were fully contained within the pre-defined limits of 0.8000 to 1.2500.

Evaluation of the secondary pharmacokinetic parameters (time to maximum observed drug concentration [t_{max}], percentage extrapolated area under the concentration-time curve [$\%AUC_{ext}$], apparent total body clearance [CL/F], apparent volume of distribution [V_z/F], terminal

elimination rate constant [λ_z] and terminal elimination half-life [$t_{½}$]) and partial AUCs support that the pharmacokinetics of the 3 treatments are similar.

1.2.2.2. Pharmacodynamics

Pharmacodynamic similarity was evaluated comparing the change of free and total IgE in serum following drug administration. TEV-45779, XOLAIR EU, and XOLAIR US had similar mean free IgE and total IgE concentration time profiles for both total and free IgE. For each pharmacodynamic parameter evaluated (negative AUEC of free IgE change from baseline, positive AUEC of total IgE change from baseline, $C_{min,IgE,free}$, and $C_{max,IgE,total}$), the results were descriptively similar for each treatment group.

1.2.2.3. Safety and Immunogenicity

The proportion of subjects reporting adverse events and treatment-related adverse events was low and similar between treatment groups. All adverse events were mild or moderate in severity. There were no deaths, other serious adverse events, or withdrawals due to adverse events, and no protocol defined adverse events of special interest (ie, anaphylaxis) during the study. There were 5 pregnancy cases reported in the TV45779-BE-10160 study, 3 in the TEV-45779 group, 1 in the XOLAIR EU group, and 1 in the XOLAIR US group. In 2 cases (1 each in the TEV-45779 and XOLAIR US groups), the pregnancy outcome was elective termination while in another case in the TEV-45779 group, the event of biochemical pregnancy was reported to have no viable pregnancy. One case in the TEV-45779 group was considered as lost to follow up. One serious adverse event of spontaneous abortion was reported after completion of the study for a subject who received XOLAIR EU. There were no findings of clinical importance in any treatment group for vital signs, ECGs, or clinical laboratory data. Local tolerability at the injection site was good following sc administration of each treatment, with no clinically meaningful differences between the groups.

Anti-drug antibody formation occurred during the study for 30% to 40% of subjects in each group, with no substantial difference between TEV-45779, XOLAIR EU, and XOLAIR US. ADA had returned to baseline levels at the last sampling point, 126 days post dose. Only a small percentage of ADA-positive subjects tested positive for neutralizing ADA during the study (1% to 9%), with no marked difference between groups.

The adverse events and other safety data observed after dosing of 228 healthy subjects are in line with the known safety profile of XOLAIR (XOLAIR Prescribing Information 7/2021; XOLAIR Summary of Product Characteristics 25/10/2021) and also with events expected in a healthy study population.

Clinical data on omalizumab, the reference product, have been published in the scientific literature (Rivière et al 2011) and in the XOLAIR US Prescribing Information (USPI) (XOLAIR Prescribing Information 7/2021), EU Summary of Product Characteristics (SmPC) (XOLAIR Summary of Product Characteristics 25/10/2021), and Canadian Consumer Information Leaflet (XOLAIR Consumer Information 04/2017). Since TEV-45779 is being developed as a biosimilar candidate to XOLAIR, the clinical findings for TEV-45779 are expected to be similar to those of XOLAIR, particularly the safety, pharmacokinetic, pharmacodynamic, immunogenicity response, and efficacy profiles.

Further information can be found in the current version of the TEV-45779 Investigator's Brochure (IB).

1.3. Known and Potential Benefits and Risks to Patients

1.3.1. Known and Potential Benefits and Risks of TEV-45779

No safety concerns have been observed in Study TV45779-BE-10160 (Section 1.2.2). Since TEV-45779 is being developed as a proposed biosimilar to XOLAIR, treatment risks with TEV-45779 are anticipated based on the safety information for the use of XOLAIR in the US and EU.

Additional information regarding risks to patients may be found in the IB.

1.3.2. Known and Potential Benefits and Risks of Reference Investigational Medicinal Product

Information regarding benefits and risks to patients may be found in the current SmPC for XOLAIR (XOLAIR Summary of Product Characteristics 25/10/2021), the XOLAIR USPI (XOLAIR Prescribing Information 7/2021), and the IB.

1.3.2.1. Important Identified Risks with Omalizumab (XOLAIR)

1.3.2.1.1. Anaphylaxis/Anaphylactoid Reactions

Anaphylaxis has been reported to occur after administration of XOLAIR in premarketing clinical trials and in post marketing spontaneous reports. Signs and symptoms in these reported cases have included bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue. Some of these events have been life threatening. In premarketing clinical trials in patients with asthma, anaphylaxis was reported in 3 of 3507 (0.1%) patients. Anaphylaxis occurred with the first dose of XOLAIR in 2 patients and with the fourth dose in 1 patient. The time to onset of anaphylaxis was 90 minutes after administration in 2 patients and 2 hours after administration in 1 patient.

A case control study showed that, among XOLAIR users, patients with a history of anaphylaxis to foods, medications, or other causes were at increased risk of anaphylaxis associated with XOLAIR, compared to those with no prior history of anaphylaxis.

1.3.2.1.2. Churg-Strauss Syndrome/Hypereosinophilic Syndrome

In rare cases, patients with asthma on therapy with XOLAIR may present with serious systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, paranasal sinus abnormalities, and/or neuropathy presenting in their patients. A causal association between XOLAIR and these underlying conditions has not been established.

1.3.2.2. Important Potential Risks with Omalizumab (XOLAIR)

1.3.2.2.1. Arterial Thromboembolic Events

In controlled clinical trials and during interim analyses of an observational study, a numerical imbalance of arterial thromboembolic events (ATE) was observed. The definition of the composite endpoint, ATE, included stroke, transient ischemic attack, myocardial infarction, unstable angina, and cardiovascular death (including death from unknown cause). In the final analysis of the observational study, the rate of ATE per 1,000 patient-years was 7.52 (115/15, 286 patient-years) for XOLAIR-treated patients and 5.12 (51/9,963 patient-years) for control patients. In a multivariate analysis controlling for available baseline cardiovascular risk factors, the hazard ratio was 1.32 (95% CI: 0.91-1.91). In a separate analysis of pooled clinical trials, which included all randomized double-blind, placebo-controlled clinical trials lasting 8 or more weeks, the rate of ATE per 1,000 patient-years was 2.69 (5/1,856 patient-years) for XOLAIR-treated patients and 2.38 (4/1,680 patient-years) for placebo patients (rate ratio: 1.13, 95% CI: 0.24-5.71).

1.3.2.2.2. Malignant Neoplasms in Adults and Adolescents ≥12 Years of Age

Malignant neoplasms were observed in 20 of 4127 (0.5%) XOLAIR-treated patients compared with 5 of 2236 (0.2%) control patients in clinical studies of adults and adolescents ≥12 years of age with asthma and other allergic disorders. The observed malignancies in XOLAIR-treated patients were a variety of types, with breast, non-melanoma skin, prostate, melanoma, and parotid occurring more than once, and 5 other types occurring once each. The majority of patients were observed for less than 1 year. The impact of longer exposure to XOLAIR or use in patients at higher risk for malignancy (eg, elderly, current smokers) is not known.

In a subsequent observational study of 5007 XOLAIR-treated and 2829 non-XOLAIR-treated adolescent and adult patients with moderate to severe persistent asthma and a positive skin test reaction or in vitro reactivity to a perennial aeroallergen, patients were followed for up to 5 years. In this study, the incidence rates of primary malignancies (per 1000 patient-years) were similar among XOLAIR-treated (12.3) and non-XOLAIR-treated patients (13.0). However, study limitations preclude definitively ruling out a malignancy risk with XOLAIR.

1.3.3. Overall Benefit and Risk Assessment for this Study

TEV-45779 is a proposed biosimilar to XOLAIR and physiochemical and functional characterization has shown similarity between both products.

All patients in the study will receive active urticaria treatment for 24 weeks, either XOLAIR or TEV-45779, which is expected to show no relevant clinical difference in efficacy and safety compared to XOLAIR.

The TEV-45779 and XOLAIR dosing schedule, ie, 300 mg or 150 mg administered as a sc injection every 4 weeks, reflects the US recommendation for XOLAIR to treat patients with CSU who remain symptomatic despite antihistamine (H1) treatment. In the EU, the 300 mg dose is recommended with the same schedule.

Data from the originator studies show differences between the 300 mg and 150 mg dose of about 2 score points for the sum of the daily itch severity score for 7 days (ISS7) (Maurer et al 2013). It

is expected that this difference will not be considered clinically meaningful, as Mathias et al (Mathias et al 2010) estimated a minimally important difference (MID) value of 4.5-5.0 for ISS7. Furthermore, patients will be provided with rescue medication for itch relief (diphenhydramine hydrochloride, 25 mg, maximum 3 times/day) that patients can take if required. Therefore, all patients are likely to derive significant benefit from the urticaria treatment in the clinical study.

Since TEV-45779 is being developed as a proposed biosimilar to XOLAIR, the risks of treatment with TEV-45779 are expected to be similar to the known risks of treatment with omalizumab. All study interventions are routine clinical practice for patients with CSU.

The purpose of the development of biosimilars, and TEV-45779 in particular, is to provide high quality biological products to patients, that in turn should result in increased patient access to treatment.

Information regarding risks to patients may be found in the EU SmPC (XOLAIR Summary of Product Characteristics 25/10/2021), the XOLAIR USPI (XOLAIR Prescribing Information 7/2021), and the IB.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary and Secondary 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 CIU/ 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 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.
Secondary objectives	
To compare further efficacy parameters between TEV-45779 and XOLAIR. 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 as follows: • 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) assessment of UAS7 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 in ISS7 score 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
To compare efficacy parameters between TEV-45779 and XOLAIR after the switch	Secondary efficacy endpoints are:

Objectives	Endpoints
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	• 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
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 IMP administration • Use of concomitant medication (including use of rescue medication) • Device-related adverse events and malfunctions
To compare pharmacokinetics between TEV-45779 and XOLAIR after multiple doses	The pharmacokinetic parameter is: • 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 IgE serum concentration • Total IgE serum concentration
To assess the immunogenicity of TEV-45779 in comparison with XOLAIR • throughout the study	The immunogenicity parameters are: • Incidence of patients with a confirmed treatment-related ADA positive sample

Objectives	Endpoints
• after the switch from XOLAIR to TEV-45779	• For confirmed positive samples, the ADA titer and the neutralizing potential will be tested

2.1.1. 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 (as defined in "Statistical Considerations" below), 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 (Heitjan and Little 1991, Schenker and Taylor 1996), 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 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, 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 300 mg 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 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 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.

2.1.2. Justification of Primary Endpoint and Equivalence Margins

The primary endpoint of the study is the change from baseline in the ISS7 at Week 12 after 3 treatments of 300 mg of TEV-45779 compared to XOLAIR. This primary endpoint was agreed with the FDA and the European Medicines Agency (EMA) as being sensitive enough to confirm that there is no relevant clinical difference in efficacy between TEV-45779 and XOLAIR. The ISS7 is a reliable, clinically well-established, and reproducible measure of urticaria itch symptoms and is considered appropriate to detect potential differences in clinical efficacy since the results of the originator studies (Asteria I [Saini et al 2015]); Asteria II [Maurer et al 2013]; GLACIAL [Kaplan et al 2013]) showed a clear and dose-dependent treatment response for doses of 75, 150, and 300 mg at Week 12 in comparison to placebo treatment, leading to FDA and EMA approval. Thus, the graduated response of ISS7 should reflect potential differences in potency and clinical efficacy between test and reference product.

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 9.5.1.1) 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 (Mathias et al 2015) estimated a minimal important difference of 4.5 to 5.0 for the ISS7 from clinical data of the mentioned above originator studies mentioned above. 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.

Co-primary endpoint

The co-primary endpoint for the FDA submission is the relative potency of TEV-45779 and XOLAIR (using a 4-point assay with a margin of [0.5, 2.0]), as recommended by the FDA in

their written response to the Biological Product Development (BPD) Type 2 meeting (BPD Type 2 Meeting Written Responses 2021).

The inclusion of the 150 mg and 300 mg doses of both products allows:

1. Comparisons of 150 versus 300 mg to support the assay sensitivity of the study.
2. Comparisons of TEV-45779 and XOLAIR at both approved doses for CIU.
3. An evaluation of relative potency between TEV-45779 and XOLAIR.

These additional evaluations are especially important given the range of doses that are approved for asthma and could be used as part of the justification to support extrapolation from CIU to asthma.

3. STUDY DESIGN

3.1. General Study Design and Study Schematic Diagram

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 43 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 India, Cetirizine is to be used as the single H1 antihistamine at stable and fixed doses, not exceeding label recommendations, as a uniform standard treatment regimen, throughout the entire study (Appendix T). For the duration of the study, all patients will be provided with diphenhydramine hydrochloride (25 mg, maximum 3 times/day) as rescue medication for itch relief.

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

Study Treatment

Patients will receive a total of 6 treatments, resulting in 150 mg or 300 mg sc of 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. Patients in the 300 mg groups will receive 2 sc injections of 150 mg IMP whereas patients in the 150 mg groups will receive 1 sc injection of 150 mg IMP and an additional placebo injection in order to administer 2 injections per dosing in all groups and, thereby, ensure maintaining of the blind to treatment.

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 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.

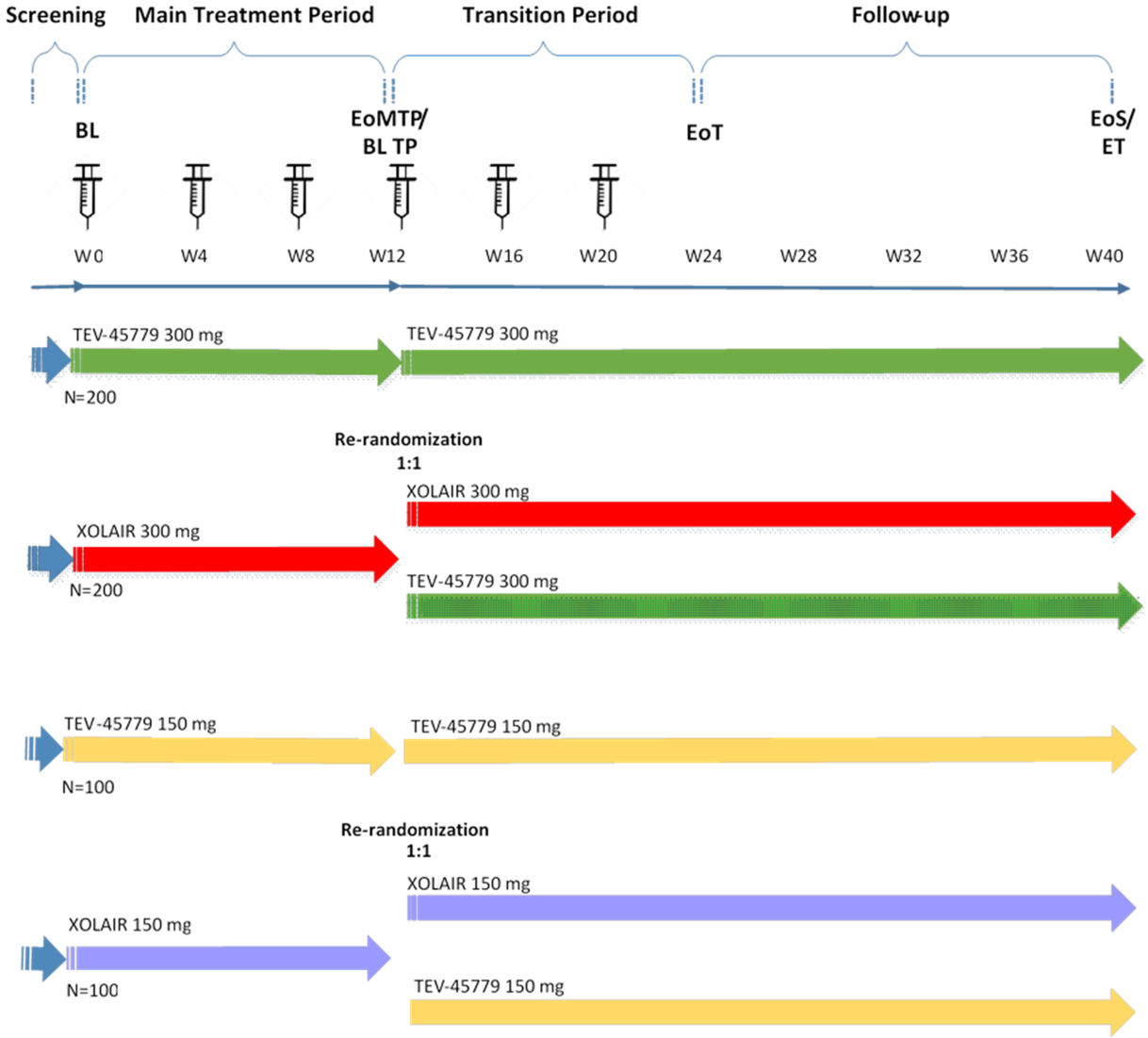
An Independent Data Monitoring Committee (IDMC) will be established to ensure the continuing safety of the study patients during the study (Section 5.9.2).

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

The assessments and procedures performed during each study visit are detailed in Table 1 and Appendix B.

The study schematic diagram is presented in Figure 1.

Figure 1: Overall Study Schematic Diagram



BL=baseline; BL TP=baseline transition period; EoMTP=end of main treatment period; EoS=end of study; EoT=end of treatment; ET=early termination, N=number; W=week.

3.2. Planned Number of Patients and Countries

Approximately 600 patients (200:200:100:100 to TEV-45779 300 mg, XOLAIR 300 mg, TEV-45779 150 mg and XOLAIR 150 mg) will be randomized (also see Appendix S).

Details on the definition of evaluable patients and sample size are given in Section 9.

The study is planned to be conducted at approximately 140 investigational sites in approximately 18 countries in North America, Latin America, Europe, and Asia-Pacific. The study is expected to start in quarter Q3 2021 and last until approximately Q2 2024.

3.3. Justification for Study Design and Selection of Population

The design of the current study in patients with CSU/CIU was agreed with the FDA and EMA and is regarded as appropriate to show that there is no clinically meaningful difference in efficacy, safety and immunogenicity between TEV-45779 and XOLAIR.

The study population, as defined by the inclusion and exclusion criteria, is a sensitive and homogenous population similar to the population of the clinical studies performed for the approval of XOLAIR. The EMA confirmed in the Scientific Advice, Question 9: "The selected CSU population is a relatively homogenous population, easier to diagnose, with shorter treatment periods, higher effect size and less concomitant medication as compared to asthma patients. Hence, it is acceptable to test comparability of TEV-45779 safety and efficacy to XOLAIR in the selected CSU population." (Scientific Advice. Procedure No.: EMEA/H/SA/4461/1/2020/II. 09/2020).

Patients in the XOLAIR arm will be re-randomized at their Week 12 visit to either continue with XOLAIR or transition to TEV-45779 to assess whether a single transition would result in an increased risk in terms of hypersensitivity, immunogenicity, or other reactions.

3.4. Stopping Rules for the Study

During the conduct of the study, serious adverse events will be reviewed (Section 7.1.5) as they are reported from the investigational centers to identify safety concerns.

The study may be terminated by the sponsor for any reason at any time. For example, the sponsor should terminate the study in the event of:

- New toxicological or pharmacological findings or safety issues invalidate the earlier positive benefit-risk assessment.
- Discontinuation of the development of the IMP.
- Additional criteria for pausing enrollment and review by the IDMC are:
  - A death for which the cause is judged to be related to the study drug by the treating investigator.
  - A life-threatening SAE judged to be related to the study drug by the treating investigator.

- Any combination of 4 occurrences of Grade 3 or higher (per Common Terminology Criteria for Adverse Events [CTCAE] grading) toxicities that are assessed to be related to the study drug by the investigator.
- For the same Preferred Term, 2 occurrences of Grade 3 or higher (per CTCAE grading) toxicities that are assessed to be related to the study drug by the investigator.
- Any combination of 4 occurrences of a clinically significant Grade 3 or higher (per CTCAE grading) laboratory abnormality for different laboratory parameters assessed to be related to the study drug by the investigator.
- Two occurrences of a clinically significant Grade 3 or higher (per CTCAE grading) laboratory abnormality for the same laboratory parameter that are assessed to be related to the study drug by investigator."

If the whole study or arms of the study will be stopped, the patients that are terminated early will be followed according to Withdrawal Criteria and Procedures for the Patient (Section 4.3).

3.5. Schedule of Study Procedures and Assessments

Study procedures and assessments with their time points are presented in Table 1. Detailed descriptions of each method of procedures and assessments are provided in Section 6 (efficacy assessments), Section 7 (safety assessments), and Section 8 (pharmacokinetics, pharmacodynamics, and immunogenicity). Study procedures and assessments by visit are listed in Appendix B.

Medical history: any medical event relevant to eligibility and further participation should be collected and reported in source documents and case report form (CRF) (eg, completely cured non-melanoma skin malignancy, hysterectomy, allergic diseases or any other significant medical event).

Table 1: 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)[c]	**-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[d]	X												
Prior medication and treatment history	X	X											
Inclusion and exclusion criteria	X	X	X										
Randomization/ Re-randomization			X			X[e]							
IMP administration[f, g, h, i]			X	X	X	X	X	X					
Local tolerability at injection site[j]			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 rescue medication			X	X	X	X	X	X	X	X	X	X	X
COVID-19 inquiry	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Symptom Diary (eDiary)[k] including UAS	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1: Study Procedures and Assessments (Continued)

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)[c]	**-7/+2**	**-2**	**-**	**±3**	**±3**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Procedures and assessments													
Physician's (in-clinic) assessment of UAS[l]	X	X	X	X	X	X	X	X	X	X	X	X	X
Dermatology Life Quality Index (DLQI)			X			X			X				X
Physical examination[m]	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
Vital signs measurement	X		X	X	X	X	X	X	X	X	X	X	X
Stool ova and parasite evaluation		X[n]											
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

Table 1: Study Procedures and Assessments (Continued)

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)[c]	**-7/+2**	**-2**	**-**	**±3**	**±3**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Procedures and assessments													
Clinical laboratory tests (serum chemistry, hematology, urinalysis, COVID-19)[o]	X		X			X			X				X
Pregnancy test[p]		X				X			X				
ADA evaluation[q]			X	X		X			X				X
Rescue medication dispensation[r]	X	X	X	X	X	X	X	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] In case of an out-of-window visit, the date of the next visit will be calculated based on the baseline date (V3) or will be scheduled at least 21 days apart.

[d] Any medical event relevant to eligibility and further participation should be collected and reported in source documents and CRF (eg, completely cured non-melanoma skin malignancy, hysterectomy, allergic diseases or any other significant medical event).

[e] 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)

[f] 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.

[g] 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.

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

[i] 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.

[j] 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.

[k] 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.

[l] 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.

[m] 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.

[n] 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.

[o] Additional laboratory parameters, such as FSH and β-HCG (see footnote n) or as applicable (see inclusion criterion c, Section 4.1), may be assessed at screening and baseline. COVID-19 testing to be performed at V1. In addition, the patient should be tested 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. At V1, serum chemistry sample in non-fasting state may be acceptable.

[p] 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.

[q] 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.

[r] Dispensation of rescue medication must be done at V1 in amount of maximum dose (3 tablets/day) until V2. At subsequent visits, patients have to return all unused rescue medication, the consumption from previous visit should be confirmed, and based on it further dispensation should ensure that subject has sufficient rescue medication to cover the period till the next subject visit with a maximum dose.

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.

4. SELECTION AND WITHDRAWAL OF PATIENTS

Prospective waivers (exceptions) from study inclusion and exclusion criteria to allow patients to be randomized/enrolled are not granted by Teva.

Changes to inclusion or exclusion criteria are indicated below and detailed in Section 16.

4.1. Patient Inclusion Criteria

Patients may be randomized/enrolled in this study only if they meet all of the following criteria:

a. Male or female patients aged ≥18 years and ≤75 years.

b. Diagnosis of CIU/CSU refractory to H1 antihistamines at the time of randomization, as defined by all of the following:

- The presence of itch and wheals for ≥8 consecutive weeks at any time prior to enrollment despite current use of H1 antihistamine treatment during this time period.
- Weekly urticaria activity score (UAS7; sum of the daily number of wheals score and itch severity score over 7 days) ≥16 (range 0-42) and itch component of UAS7 ≥8 (range 0-21) during 7 days prior to randomization.[3]
- UAS ≥4 assessed by a clinician on ≥1 of the screening visit days.
- Patients must have been on an approved dose of an H1 antihistamine for CIU/CSU for ≥3 consecutive days immediately prior to the start of screening and must document current use on the day of the initial screening visit, OR, have their H1 antihistamine for CIU/CSU adjusted to an approved dose during the first 3 days of screening and have their adjusted use documented at the end of the dose adjustment.
- CIU/CSU diagnosis for ≥3 months.[4]

c. Women may be included if they fulfill one of the following criteria:

- Women of non-childbearing potential who are either surgically (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile as assessed by a physician, or 1-year postmenopausal (no menses for 12 months without an alternative medical cause plus an increased concentration of FSH of more than 35 U/L) in women not using hormonal contraception or hormonal replacement therapy.
- Women of childbearing potential whose male partners are potentially fertile (ie, no vasectomy) must:
  - have a negative β-HCG test result at screening (visit 2); and

[3] Refer to Section 9.3.1 for handling of missing data for daily and weekly scores.
[4] Diagnosis or symptoms leading to this diagnosis have to be present for ≥3◦months.

- use highly effective birth control methods for the duration of the study (ie, starting at screening) and for 5 half-lives (20 weeks) after last dose of IMP.

Highly effective birth control methods are methods that can achieve a failure rate of less than 1% per year when used consistently and correctly (see such methods in Appendix J).

d. [Revision 1] Male patients (including vasectomized men) with partners who are of childbearing potential (whether pregnant or not) must use condoms prior to IMP administration and until 20 weeks after last IMP dose.

e. Must be able to understand the requirements of the study and to provide their written informed consent to participate in the study.

f. Must be willing and able to comply with study requirements and procedures as specified in this protocol. In particular, the patient must be willing and able to complete a symptom diary twice daily (morning and evening) for the duration of the study. The patients must have diary entries during at least 4 of the 7 days prior to randomization.

4.2. Patient Exclusion Criteria

Patients will not be randomized/enrolled in this study if they meet any of the following criteria:

a. Body weight <40 kg.

b. Clearly defined underlying etiology for chronic urticarias other than CIU/CSU.[5]

c. Evidence of parasitic infection defined as meeting the following 3 criteria:

- Risk factors for parasitic disease (living in an endemic area, chronic gastrointestinal symptoms, travel within the last 6 months to an endemic area and/or chronic immunosuppression), and
- An absolute eosinophil count >2× the ULN, and
- Evidence of parasitic colonization or infection on stool evaluation for ova and parasites. Note that stool ova and parasite evaluation will only be conducted in patients with risk factor(s) and an eosinophil count >2× the ULN.

d. Atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile pruritus, or other skin disease associated with itch.

e. Treatment with an investigational agent within 30 days or longer depending on half-life (>5 half-lives) prior to the start of screening.

f. Previous treatment with omalizumab or other Anti-IgE therapy within a year prior to the start of screening.

[5] Other chronic urticarias include: acute, solar, cholinergic, heat, cold, aquagenic, delayed pressure, or contact. The following diseases should be considered for exclusion as they may have symptoms of urticaria or angioedema: urticarial vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary or acquired angioedema, lymphoma, leukemia, or generalized cancer.

g. Routine (daily or every other day during 5 or more consecutive days) doses of the following medications within 30 days prior to start of screening: Systemic or cutaneous (topical) corticosteroids (prescription or over-the-counter), hydroxychloroquine, methotrexate, cyclosporine, or cyclophosphamide.

h. Intravenous IgG, or plasmapheresis within 30 days prior to the start of screening.

i. Regular (daily/every other day) doxepin (oral) use within 2 weeks prior to the start of screening.

j. Any H2 antihistamine use within 7 days prior to the start of screening.

k. Any LTRA (montelukast or zafirlukast) use within 7 days prior to the start of screening.

l. [Revision 1] Any H1 antihistamines at greater than approved doses use from 3 days after the start of screening.

m. [Revision 1] Current malignancy, history of malignancy within the last 5 years, or currently under work-up for suspected malignancy except non-melanoma skin cancer that has been treated or excised and is considered resolved.

n. Hypersensitivity to omalizumab or any component of the formulation.

o. History of anaphylactic shock.

p. Contraindications to diphenhydramine hydrochloride [6]

q. Pregnant or lactating woman, or plans to become pregnant during the study.

r. Presence of clinically significant cardiovascular, neurological, psychiatric, metabolic, or other pathological conditions that could interfere with the interpretation of the study results and or compromise the safety of the patients.[7]

s. Evidence of current drug or alcohol abuse.

t. Patients taking either LTRAs or H2 blockers for diseases other than CIU (eg, asthma or gastroesophageal reflux disease, respectively) will be permitted to continue their use during the study. These diseases must be recorded as part of the medical history collected during the screening period. Inhaled asthma controllers, including corticosteroids, are also permitted during the study.

[6] To include: over-reactivity against the agent diphenhydramine hydrochloride, other antihistaminic agents, or other components of this agent; acute bronchial asthma; acute angle-closure glaucoma; pheochromocytoma; hyperplasia of the prostate gland with formation of residual urine; epilepsy; hypokalemia; hypomagnesemia; bradycardia; congenital long QT syndrome or other clinically significant cardiac disorders (especially coronary heart disease, disturbances in conduction, arrhythmias); simultaneous application of drugs which prolong the QT interval (eg, antiarrhythmic drugs class IA or III, antibiotics, cisapride, malaria drugs, antihistaminic drugs, neuroleptic drugs) or lead to hypokalemia (eg, certain diuretic drugs); simultaneous application of monoamine inhibitors; simultaneous uptake of alcohol.

[7] To include medical examination or laboratory findings that suggest the possibility of decompensation of co-existing conditions for the duration of the study. Any findings must be reviewed with the medical monitor.

4.3. Withdrawal Criteria and Procedures for the Patient

Each patient is free to withdraw from the study or discontinue from IMP at any time, without prejudice to their continued care. Patients must be withdrawn from the study if any of the following events occur:

1. Patient withdraws consent or requests withdrawal from the study or discontinuation from IMP for any reason.
2. Patient develops an illness that would interfere with his/her continued participation.
3. Patient is noncompliant with the study procedures and assessments in the opinion of the investigator.
4. Patient takes prohibited concomitant medications as defined in this protocol (see Appendix L). Under certain circumstances, a patient may be eligible to remain in the study when taking prohibited concomitant medications - such cases should be discussed with, and approved by, the medical monitor.
5. The sponsor requests withdrawal of the patient.
6. Patients experiencing anaphylaxis (Section 7.1.6) have to be discontinued from IMP.
7. Patient experiences an adverse event or other medical condition which indicates to the investigator that continued participation is not in the best interest of the patient.
8. A female patient has a confirmation of pregnancy during the study from a positive serum pregnancy test.

Patients who discontinue from IMP while remaining in the study are invited to continue safety follow-up per study schedule and to complete the remaining study visits and assessments (with the exception of administration of IMP) including the EoS visit within the original time frames based on date of randomization. The investigator should determine the reason for and the date of discontinuation of study treatment and record this information in both the source documentation and the CRF. The patient should not be considered withdrawn from the study due to interruption or discontinuation of IMP.

Patients should be treated with standard of care after withdrawal from or termination of the study as appropriate.

Investigators should attempt to obtain information on patients in the case of withdrawal from the study. Results of any evaluations and observations, together with a narrative describing the reason(s) for withdrawal from the study, must be recorded in the source documents. The CRF must document the primary reason for withdrawal from the study.

If a patient exhibits clinical symptoms that may indicate Coronavirus disease 2019 (COVID-19) infection after entering the study, the patient should be tested for active COVID-19. If the patient tests positive for active COVID-19, he/she may continue for scheduled visits when recovered (ie, tests negative for active COVID-19), assuming he/she has no protocol violations including use of disallowed medications. See Appendix C for information regarding study conduct during COVID-19 outbreaks.

See Appendix K for information regarding how the study will define and address lost to follow-up patients to help limit the amount and impact of missing data.

If the reason for withdrawal from the study is an adverse event and/or clinically significant abnormal laboratory test result, monitoring will be continued as applicable (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the IMP/device or study procedure is made). The specific event or test result (including repeated test results, as applicable) must be recorded both on the source documentation and in the CRF; both the adverse events page and the relevant page of the CRF will be completed at that time.

The patient will be monitored as applicable (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the test IMP/device or study procedure is made). The investigator must inform the sponsor's medical expert as soon as possible of each patient who is being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

If a patient is withdrawn from the study for multiple reasons that include also adverse events, the relevant page of the CRF should indicate that the withdrawal was related to an adverse event. An exception to this requirement will be the occurrence of an adverse event that in the opinion of the investigator is not severe enough to warrant discontinuation but that requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason for discontinuation would be "need to take a prohibited medication", not the adverse event.

In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records and transcribed to the CRF.

4.4. Replacement of Patients

A patient who is randomized but does not complete all treatment periods will not be replaced.

4.5. Re-screening

A patient who is screened but not enrolled (eg, because inclusion and exclusion criteria were not met or enrollment did not occur within the specified time) may be considered for re-screening 1 time if there is a change in the patient's medical background or other relevant change. (Note: the medical monitor should approve re-screening after review of the enabling reasons.)

If the patient is re-screened, a new informed consent form (ICF) will need to be signed and all study assessments will need to be repeated.

4.6. Screening Failure

Screening failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study.

Selected information about patients who screen-fail will be collected to comply with reporting and publishing requirements. This information may include, but is not limited to, demography, screening failure details, eligibility criteria, and any serious adverse events.

5. TREATMENTS

Investigational medicinal products (IMPs) in this study include TEV-45779 (omalizumab) solution for injection 150 mg/mL PFS (test IMP) and XOLAIR (omalizumab) injection (reference IMP). Patients will receive a total of 6 treatments, each consisting of 2 sc injections resulting in 150 mg or 300 mg of 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.

Detailed information about the composition of the test IMP and reference IMP can be found in the following sections.

5.1. Investigational Medicinal Products Used in the Study

IMPs are defined as the test IMP (TEV-45779) and reference IMP (XOLAIR).

5.1.1. Test Investigational Medicinal Product

TEV-45779 (omalizumab) is provided as a sterile, preservative-free, clear to slightly opalescent and colorless to pale brownish-yellow solution intended for sc injection. It will be supplied in a combination product consisting of a PFS with an integrated needle safety guard for single-use administration to mirror the XOLAIR configuration.

Each PFS of TEV-45779 contains 150 mg TEV-45779 in 1 mL of solution.

Refer to Table 2 for specific details regarding TEV-45779. Additional details may be found in the Pharmacy Manual and the IB for TEV-45779.

5.1.2. Reference Investigational Medicinal Product

XOLAIR (omalizumab) injection is supplied as a single dose PFS. Each PFS of XOLAIR contains 150 mg of omalizumab in 1 mL of solution.

Refer to Table 2 for specific details regarding XOLAIR.

5.1.3. Placebo Investigational Medicinal Product

Placebo (no active) to complement TEV-45779 (omalizumab) or XOLAIR (omalizumab) is supplied as a single dose PFS. Each PFS of placebo contains 1 mL solution of the same composition as the TEV-45779 (omalizumab) and XOLAIR (omalizumab) syringes, but without active drug substance.

Refer to Table 2 for specific details regarding placebo.

Table 2: Investigational Medicinal Products Used in the Study

IMP		Test	Reference	Placebo
IMP name		**TEV-45779 (omalizumab)**	**XOLAIR® (omalizumab) Injection**	**Placebo (no active) to complement TEV-45779 (omalizumab) or XOLAIR® (omalizumab)**
Trade name or company-assigned number		TEV-45779	XOLAIR	Placebo
Formulation	Active	150 mg/mL	150 mg/mL	NA
	Histidine	20 mM	20 mM	20 mM
	Arginine hydrochloride	200 mM	200 mM	200 mM
	Polysorbate 20	0.04%	0.04%	0.04%
Unit dose strength(s)/Dosage level(s)		150 mg/mL 150 mg/dose (single sc injection) or 300 mg/dose (2 sc injections)	150 mg/mL 150 mg/dose (single sc injection) or 300 mg/dose (2 sc injections)	NA
Route of administration		sc injection	sc injection	sc injection
Device		Automatically activated needle safety guard	Automatically activated needle safety guard	Automatically activated needle safety guard
Storage conditions		2°C to 8°C (36°F to 46°F), protected from direct light and heat. Avoid vigorous shaking. Do not freeze	2°C to 8°C (36°F to 46°F), protected from direct light and heat. Avoid vigorous shaking. Do not freeze	2°C to 8°C (36°F to 46°F), protected from direct light and heat. Avoid vigorous shaking. Do not freeze
Manufacturer		[redacted]	[redacted]	[redacted]

EU=European Union; IMP=investigational medicinal product; INN=international nonproprietary name; PFS=prefilled syringe; sc=subcutaneous; USA=United States of America.

5.1.4. Medical Devices

The medical device for TEV-45779, manufactured by Teva and provided for use in this study is:

- a PFS with an automatically activated needle safety guard for single-use administration.

This automatically activated needle safety guard requires no additional actions by the user to shield the needle after use, and thus reduces the potential for accidental needle stick injuries.

The medical device for XOLAIR provided for use in this study is:

- a PFS with automatically activated needle safety guard for single-use administration.

This automatically activated needle safety guard requires no additional actions by the user to shield the needle after use, and thus reduces the potential for accidental needle stick injuries.

Instructions for use of both devices are provided in the Pharmacy Manual.

All device-related adverse events, malfunctions, etc. will be recorded; their impact relative to the safety and tolerability of the IMP will be evaluated (see Section 7.2 and Appendix O).

5.2. Preparation, Handling, Labeling, Storage, and Accountability for Investigational Medicinal Products

5.2.1. Storage and Security

The investigator or designee must confirm appropriate temperature conditions have been maintained for all IMP received and any discrepancies are reported and resolved before use of the IMP.

The IMP (TEV-45779, XOLAIR, and placebo) must be stored at a controlled temperature of 2°C to 8°C [36°F to 46°F]) in a secure area (eg, locked refrigerator). The site should have a process for monitoring the storage temperature of unused IMP.

5.2.2. Labeling

Supplies of IMP will be labeled according to the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) and will include any locally required statements. If necessary, labels will be translated into the local language.

5.2.3. Accountability

Each IMP shipment will include a packing slip listing the contents of the shipment, return instructions, and any applicable forms.

The investigator is responsible for ensuring that deliveries of IMP and other study materials from the sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with the Code of Federal Regulations (CFR) or national and local regulations, and used in accordance with this protocol.

Only patients enrolled in the study may receive IMP and only authorized staff at the investigational center may supply or administer IMP. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions or appropriate instructions with access limited to the unblinded authorized staff (eg, unblinded pharmacist, unblinded designee, IMP administrator) at the investigational center.

The unblinded pharmacist, unblinded designee, or IMP administrator is responsible for IMP accountability, reconciliation, and record maintenance (eg, receipt, reconciliation, and final disposition records).

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 as the IMPs differ in appearance: these persons will not be involved in the conduct of any study procedures or assessments.

A record of IMP accountability (ie, IMP and other study materials received, used, retained, returned, or destroyed) must be prepared and signed by the pharmacist, designee, or IMP administrator, with an account given for any discrepancies. Empty and partially-used IMP will be disposed of on site, and unused IMP can be disposed of on site or returned to Teva or its designee.

Further guidance and information are provided in the Pharmacy Manual.

5.3. Justification for Investigational Medicinal Products

5.3.1. Justification for Dose of Test Investigational Medicinal Product

The dose of IMP to be evaluated for the primary endpoint in this double-blind study (ie, 300 mg) was selected to match the approved dose of XOLAIR for CSU in the EU and CIU in the US, respectively. The 150 mg dose required for the evaluation of the relative potency as co-primary endpoint (for FDA submission) is approved for CIU in the US as well.

5.3.2. Justification for Use of Reference Investigational Medicinal Product

As TEV-45779 is being developed as a potential biosimilar to XOLAIR, XOLAIR was selected as the reference IMP.

5.3.3. Justification for Use of Placebo Investigational Medicinal Product

Placebo syringes are only required as a complementary injection to the 150 mg doses of TEV-45779 or XOLAIR in order to administer 2 injections per dosing in all groups and, thereby, maintain the blinding of patients and investigators regarding the strength of the dose.

5.4. Treatment After the End of the Study

After study end, no IMP will be provided as XOLAIR is commercially available. Patients should be further treated with omalizumab as appropriate.

5.5. Restrictions

Patients will be required to comply with the restrictions detailed below.

5.5.1. Activity

Patients must remain seated, semi-recumbent, or supine as needed for assessments or other procedures, including dosing.

Patients will fast overnight prior to the morning of blood sampling for lipid profiling (at V1 non-fasting state before blood sampling may be acceptable).

Blood donation is forbidden for the duration of the study.

There are no additional restrictions in this study.

5.6. Prior and Concomitant Medication or Therapy

See Section 4.1 and Section 4.2 for patient inclusion and exclusion criteria.

Any prior or concomitant medication (including prior CIU/CSU medication), or procedure a patient has had from 4 weeks before screening through the end of the study will be recorded in the source documentation and in the CRF. Also, any prior intake of IMP and omalizumab (and any anti-IgE medications) before screening or treatment with an investigational agent within 30 days or longer depending on half-life (>5 half-lives) before screening needs to be recorded in the source documentation and in the CRF. Trade name and international nonproprietary name (INN) (if available), indication, dose, and start and end dates of the administered medication or treatment will be recorded. The sponsor will encode all medication and treatment according to the World Health Organization (WHO) drug dictionary (WHO Drug).

The list of prohibited medications and guidance rules are located in Appendix L.

At each visit at the investigational center after the screening visit (visits 1 and 2), the investigator will ask patients whether they have taken any medications, including over-the-counter medications, vitamins, or herbal or nutritional supplements, since the previous visit.

Concomitant medication and treatment will be recorded until the EoS visit (visit 13 [Week 40±3 days]).

5.7. Procedures for Monitoring Patient Compliance

The investigator will be responsible for monitoring patient compliance with this protocol from the start of the screening period through the transition period. If the investigator or the sponsor determines that the patient is not in compliance with the study protocol, the investigator and the sponsor should determine whether the patient should be withdrawn from the study. The Independent Ethics Committee (IEC)/Institutional Review Board (IRB) should be notified if required by local regulation.

5.8. Randomization and Blinding

This is a randomized, double-blind study. Patients and investigators will remain blinded to IMP assignment during the 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). Patients in the 150 mg groups will receive an additional placebo injection in order to administer 2 injections per dosing in all groups and, thereby, ensure maintaining of the blind to treatment. At Week 12, prior to receiving their fourth dose of study medication, patients in the XOLAIR treatment group will be re-randomized 1:1 to receive 3 additional doses of XOLAIR (at the same dose level as prior to re-randomization) or switch to 3 doses of TEV-45779 (at the same dose level as prior to re-randomization) for the transition period. All patients in the TEV-45779 group will continue to receive TEV-45779 during the transition period at the same dose level as prior to re-randomization.

During the main treatment period, the sponsor, investigators (including other site staff involved in study assessments) and patients will be blinded to the treatment assignment of all patients. To assure continued blinding to the treatment assignments after the main treatment period,

re-randomization will be performed for all patients, including patients in the TEV-45779 group (although only patients in the XOLAIR arm will actually be re-randomized while patients in the TEV-45779 group will continue to receive TEV-45779 in the transition period). The randomization will be implemented using a Randomization and Trial Supply Management (RTSM) system. Further details on unblinding during the transition and follow-up periods are provided in Section 5.9.1.

5.9. Maintenance of Randomization and Blinding

5.9.1. Blinding and Unblinding

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 as the IMPs differ in appearance: these persons will not be involved in the conduct of any study procedures or assessments. The IMP will be prepared in a separate room by the non-blinded person (eg, pharmacist or designee). The blinding will be maintained during the transportation from and to the dosing room. Dosing will be performed by a non-blinded staff member in the dosing room. The original IMP packaging and syringes should not be visible when the patient or any other blinded study team member enters the room. In order to ensure additional patient blinding, a blindfold with an additional pillow at chest level (or similar device) will be used during the IMP injection as a shield to hide the IMP from the patient. 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.

During the main treatment period, the staff responsible for population pharmacokinetics, and/or the pharmacokinetics/pharmacodynamics model will be blinded. The staff responsible for the pharmacokinetic, pharmacodynamics, and immunogenicity bioanalysis, will remain blinded to the subject treatment randomization during the main and transition treatment period.

During the transition period, investigators (and other site staff involved in study assessments) and patients will remain blinded to the randomized treatment of patients who received XOLAIR in the main treatment period and are re-randomized for the transition period.

After last patient last visit and DBL of the main treatment period, the sponsor will unblind the treatments for the analysis. Staff responsible for population pharmacokinetics, and/or the pharmacokinetics/pharmacodynamics model will receive access to the patient treatment randomization of the main treatment period (up to and including week 12; not including fourth IMP dose and assessments following the fourth dose). A full CSR may be prepared with all data up to week 12 (end of main treatment phase procedures).

Only after completion of the study (after Week 40), final DBL and formal request to unblind from the sponsor statistician, will the study be fully unblinded and analyzed. The results will be reported separately in a CSR addendum, including any updates to the safety analysis of the main treatment period. If a full CSR is not prepared after the main treatment period, then the full study results will be analyzed in a single CSR after end of study.

In case of an emergency, serious adverse event (see Section 7.1.5), or in cases when knowledge of the IMP assignment is needed to make treatment decisions, the investigator may unblind the

patient's IMP assignment as deemed necessary, mainly in emergency situations. Individual randomization codes, indicating the IMP assignment for each randomized patient, will be available to the investigator(s) or pharmacist(s) at the investigational center via the RTSM, both via telephone and internet. Breaking of the treatment code can always be performed by the investigator without prior approval by the sponsor; however, the sponsor should be notified following the breaking of the treatment code. The patient's assignment should not be revealed to the sponsor.

When a blind is broken for safety reasons, the patient will be withdrawn from the study treatment and the event will be recorded on the CRF. The patient will be invited to continue safety follow-up per study schedule. The circumstances leading to the breaking of the code should be fully documented in the investigator's study files and in the patient's source documentation. Assignment of IMP should not be recorded in any study documents or source document.

In blinded studies, for an adverse event defined as a suspected unexpected serious adverse reaction (SUSAR) (ie, reasonable possibility; see Section 7.1.4), Global Patient Safety and Pharmacovigilance (GPSP) may independently request that the blind code be broken (on a case-by-case basis) to comply with regulatory requirements. The report will be provided in an unblinded manner for regulatory submission. If this occurs, blinding will be maintained for the investigator and for other personnel involved in the conduct of the study, and analysis and reporting of the data.

5.9.2. 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 (eg, efficacy data) if deemed necessary. The IDMC will perform a safety review if any of the pausing criteria listed in Section 3.4 is met.

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

The IDMC will be composed of 2 independent physicians with expertise in the relevant therapeutic field and an independent statistician.

The IDMC chairperson will communicate with the sponsor in regard to issues resulting from the conduct and clinical aspects of the study. The sponsor will work closely with the committee to provide the necessary data for review.

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.

5.10. Total Blood Volume

The total blood volume to be collected for each patient in this study is approximately 250 mL.

Details on blood volumes to be collected during the study are provided in the ICF and the laboratory manual.

6. ASSESSMENT OF EFFICACY

6.1. Patient Symptom Diary

The electronic Patient Symptom Diary (eDiary) including UAS will be performed continuously during the study according to the time points detailed in Table 1.

The eDiary questions will consist of UAS (composite of itch severity score and number of wheals score), largest wheal size, rescue medication (diphenhydramine hydrochloride) use, angioedema episodes, and calls to doctor or nurse practitioner (see Appendix D).

The eDiary is to be completed twice a day (morning and evening) by the patient for the duration of the study. The eDiary will be given to the patient at the day -14 visit (V1).

The UAS is a composite eDiary-recorded score with numeric severity intensity ratings on a scale of 0-3 (0=none to 3=intense/severe) for (1) the number of wheals (hives); and (2) the intensity of the itch (see Appendix E), measured twice daily (morning and evening). The daily UAS is the average of the morning and evening scores and the UAS7 is the sum of the daily UAS scores over 7 days.

The primary endpoint, ISS7, is obtained from the eDairy based on the itch severity component. A daily itch severity score is calculated as the average of the morning and evening scores. The ISS7 score is calculated as the sum of the daily itch severity scores over the study days that make up a given study week.

6.2. Physician's Assessment of Urticaria Activity Score

Physician's (in-clinic) assessment of UAS score will be performed at the time points detailed in Table 1 using the in-clinic UAS (the maximum achievable score is 6; see Appendix F). 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.

The physician, or the person he or she designates, will provide the sum of the score of the patient’s urticaria lesions (number of wheals [hives]) and pruritus (itch) reflective of the patient's condition over the 12 hours prior to the visit using the rating scale detailed in Appendix F.

6.3. Dermatology Life Quality Index

The DLQI will be performed at the time points detailed in Table 1. The DLQI consists of 10 questions concerning patients' perception of the impact of skin diseases on different aspects of their health-related quality of life over the last week (Finlay and Khan 1994; further information is available at: https://www.cardiff.ac.uk/medicine/resources/quality-of-life-questionnaires/dermatology-life-quality-index). The DLQI is calculated by adding the score of each question, resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. A score higher than 10 indicates that the patient's life is being severely affected by their skin disease.

6.4. Timing and Description of Assessments and Procedures

Refer to Table 1 for the timing of assessments and procedures. See Appendix B for a detailed description of assessments and procedures.

7. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study personnel by evaluating reported adverse events (including adverse device effects), local tolerability at the injection site, clinical laboratory test results, vital signs measurements, ECG findings, physical examination findings, and use of concomitant medication. Refer to Table 1 for the timing of assessments and procedures.

Adverse events are categorized by ICH guidelines and adverse device effects are categorized and classified according to International Organization for Standardization (ISO) standard 14155:2011(E). Device deficiencies that are not associated with an adverse event as well as those that have the potential to cause a serious adverse event are covered in Appendix O.

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

In this study, any adverse event occurring after the patient has signed the ICF through the end of the study should be recorded and reported as an adverse event.

An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study, or of any concurrent disease, whether or not considered related to IMP. A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered adverse events.

Accordingly, an adverse event can include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of pre-existing conditions
  (Note: A condition recorded as pre-existing that is intermittently symptomatic [eg, headache] and that occurs during this study should be recorded as an adverse event)
- drug interactions
- events occurring during diagnostic procedures or during any washout phase of this study
- laboratory or diagnostic test abnormalities that result in the withdrawal of the patient from the study, are associated with clinical signs and symptoms or a serious adverse event, require medical treatment or further diagnostic work-up, or are considered by the investigator to be clinically significant.

(Note: Abnormal laboratory or diagnostic test results at the screening visit that preclude a patient from entering the study or receiving study treatment are not considered adverse events.)

7.1.2. Recording and Reporting of Adverse Events

For recording of adverse events, the study period is defined for each patient as the time period from signature of the ICF to the end of the study. The period for reporting treatment-emergent adverse events is defined as the period after the first dose of IMP is administered and until the end of the study.

All adverse events that occur during the defined study period must be recorded both on the source documentation and the CRF, regardless of the severity of the event or judged relationship to the IMP. For serious adverse events, the serious adverse event form must be completed and the serious adverse event should be reported within 24 hours of when the investigator becomes aware of it (Section 7.1.5.3.1). The investigator does not need to actively monitor patients for adverse events after the defined study period.

At each contact with the patient, the investigator or designee must question the patient about adverse events by asking an open-ended question such as “Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe.” A precise diagnosis should be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the CRF and, if it is a serious adverse event, on the serious adverse event form. Reported or observed signs and symptoms that are not manifestations of a known diagnosis should be reported individually.

The clinical course of each adverse event will be monitored at suitable intervals until resolved, stabilized, or returned to baseline; or until the patient is referred for continued care to a health care professional; or until a determination of a cause unrelated to the IMP or study procedure is made.

The onset and end dates, duration (in case of adverse event duration of less than 24 hours), action taken regarding IMP, treatment administered, and outcome for each adverse event must be recorded both on the source documentation and the CRF.

The relationship of each adverse event to IMP and study procedures, and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.

Further details are given in the Safety Monitoring Plan.

7.1.3. Severity of an Adverse Event

The severity of each adverse event, including clinical laboratory adverse events, will be graded according to the CTCAE grading scale (Appendix R).

The severity of each adverse event must be recorded as 1 of the following:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). (Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to adverse event.

7.1.4. Relationship of an Adverse Event to the Investigational Medicinal Product

The relationship of an adverse event to the IMP will be captured separately. Determination of this relationship will be made according to the criteria in Table 3.

Table 3: The Relationship of an Adverse Event to the Investigational Medicinal Products

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the IMP.	The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if ≥2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the IMP. • It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the IMP. • It does not reappear or worsen when the IMP is re-administered.
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the administration of IMP cannot be ruled out with certainty.	The relationship of an adverse event may be considered "reasonable possibility" if ≥2 of the following apply: • It follows a reasonable temporal sequence from administration of the IMP. • It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear after discontinuation of the IMP, yet an IMP relationship clearly exists. • It follows a known pattern of response to the IMP.

7.1.5. Serious Adverse Events

For recording of serious adverse event, the study period is defined for each patient as that time period from signature of the ICF to the end of the study. Serious adverse events occurring in a patient after the end of the study should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

7.1.5.1. Definition of a Serious Adverse Event

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- Results in death.
- Is life-threatening adverse event (ie, the patient was at risk of death at the time of the event); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event.
- Hospitalizations scheduled before the patient signed the ICF will not be considered serious adverse events, unless there was worsening of the pre-existing condition during the patient's participation in this study.
- Results in persistent or significant disability/incapacity (refers to a substantial disruption of one's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- An important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition.
  Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.
- All occurrences of possible drug-induced liver injury that meet Hy's law criteria, defined as **all** of the below, must be reported by the investigator to the sponsor as a serious adverse event:
  - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increase of >3x the ULN
  - total bilirubin increase of >2x ULN
  - absence of initial findings of cholestasis (ie, no substantial increase of alkaline phosphatase [ALP])

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a non-serious adverse event.

7.1.5.2. Expectedness

In this study, the reference safety information (RSI) for determination of suspected serious adverse reaction is included in the IB. A serious adverse reaction that is not included in the relevant RSI by its specificity, severity, outcome, or frequency is considered an unexpected adverse reaction.

The sponsor's GPSP will determine the expectedness for all serious adverse events.

For the purpose of SUSAR reporting, the version of the IB at the time of occurrence of the SUSAR applies.

7.1.5.3. Reporting a Serious Adverse Event

7.1.5.3.1. Investigator Responsibility

To satisfy regulatory requirements, all serious adverse events that occur during the study, regardless of judged relationship to administration of the IMP, must be reported to the sponsor by the investigator. The event must be reported within 24 hours of when the investigator learns about it. Completing the serious adverse event form and reporting the event must not be delayed, even if not all the information is available. The investigator does not need to actively monitor patients for adverse events once this study has ended.

Serious adverse events occurring to a patient after the last administration of IMP of that patient has ended, should be reported to the sponsor if the investigator becomes aware of them.

The serious adverse event form should be sent to the local safety officer (LSO) or designee, ie, a contract research organization (CRO) in a country without a sponsor LSO (the email address will be provided on the serious adverse event report form).

The following information should be provided to record the event accurately and completely:

- study number
- investigator and investigational center identification
- patient number
- onset date and detailed description of adverse event
- investigator's assessment of the relationship of the adverse event to the IMP (no reasonable possibility, reasonable possibility, as described in Table 3)

Additional information includes:

- age and sex of patient
- date of first dose of IMP
- date and amount of last administered dose of IMP
- action taken

- outcome, if known
- severity
- explanation of assessment of relatedness
- concomitant medication (including doses, routes of administration, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical history
- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death
  - cause of death (whether or not the death was related to IMP)
  - autopsy findings (if available)

Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to the IMP, study procedures, and to underlying disease.

Additional information (follow-up) about any serious adverse event unavailable at the initial reporting should be forwarded by the investigator within 24 hours of when it becomes known to the same address as the initial report.

For all countries, the sponsor's GPSP will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/Extensible Markup Language (XML) file or MedWatch of serious adverse events to the LSO/CRO for submission to the competent authorities, IEC/IRBs, and investigators, according to local regulations. The investigator must ensure that the IEC/IRB is also informed of the event, in accordance with national and local regulations.

The sponsor's GPSP will submit the XML of SUSARs to the EMA in an unblinded manner, when applicable and according to local regulations. Submission of SUSARs to the FDA using MedWatch forms is done by the Regulatory Affairs department upon receipt from the LSO.

In the case of a SUSAR, only the LSO/unblinded personnel from the CRO, site, and sponsor will receive the unblinded report for regulatory submission; the others will receive a blinded report.

7.1.5.3.2. Sponsor Responsibility

If a serious unexpected adverse event is believed to be related to the IMP or study procedures, the sponsor will take appropriate steps to notify all investigators participating in sponsored clinical studies of TEV-45779 and the appropriate competent authorities (and IEC/IRB, as appropriate).

In addition to notifying the investigators and competent authorities (and IEC/IRB, as appropriate), other action may be required, including the following:

- altering existing research by modifying the protocol
- discontinuing or suspending the study

- modifying the existing consent form and informing all study participants of new findings
- modifying listings of expected toxicities to include adverse events newly identified as related to TEV-45779

7.1.6. Protocol-Defined Adverse Events of Special Interest

Anaphylaxis will be considered a protocol-defined adverse event of special interest (PDAESI). Anaphylaxis is described as highly likely when any 1 of the following 3 criteria based on the 2006 Joint National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN) Second Symposium on Anaphylaxis are fulfilled (Sampson et al 2006):

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, or swollen lips-tongue-uvula) and at least 1 of the following:
   - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory function, or hypoxemia).
   - Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, or incontinence).
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   - Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, or swollen lips-tongue-uvula).
   - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory function, or hypoxemia).
   - Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, or incontinence).
   - Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).
3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):
   - Adults: systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that person's baseline.

The process for reporting this PDAESI is the same as that for reporting a serious adverse event (see Section 7.1.5.3).

In the event of suspected anaphylaxis while the patient is at the site during the 2-hour observation period following drug administration, vital signs should be collected and a physical examination (brief or full, at the discretion of the investigator) performed. Blood samples to test omalizumab serum concentration and ADA formation should be collected if possible. Collection of blood samples to test tryptase and/or histamine levels is encouraged if available locally at the time of the suspected hypersensitivity event. Other assessments may be performed at the discretion of the investigator. As a precaution, each site should have a resuscitation

medication/equipment (at a minimum according to local regulations) nearby. Information about all suspected anaphylaxis and hypersensitivity events will be recorded on the Suspected Anaphylaxis CRF, which is based on the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis (Sampson et al 2006).

Patients should be instructed to contact the investigator or seek appropriate medical support (eg, in an emergency room) should they experience any signs or symptoms indicative of anaphylaxis after leaving the site.

7.1.7. Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, deviations from the protocol may be allowed on a case-by-case basis. To ensure patient safety, after the event has stabilized or treatment has been administered (or both), the investigator or other physician in attendance must contact the CRO medical monitor as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the patient should continue to participate in the study.

7.2. Adverse Device Effects

An adverse device effect is an adverse event related to the use of an investigational medical device or a combination product. This includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the investigational medical device, including any event resulting from user error or from intentional misuse of the investigational medical device.

Device deficiencies that are not associated with an adverse event as well as those that have the potential to cause a serious adverse event are covered in Appendix O.

7.2.1. Adverse Device Effect Reporting

Adverse device effects (Figure 2) must be recorded both on the source documentation and the CRF.

All adverse device effects shall be reviewed by the investigator, the medical monitor, and the sponsor. The investigator and sponsor will record all relevant information regarding every adverse device effect/serious adverse device effect and will categorize each as guided in Section 7.2.2.1.

The investigator should make an initial determination if the adverse event may be related to a device deficiency.

Adverse device effects and device deficiencies will be listed in the CSR.

7.2.2. Serious Adverse Device Effects

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (Section 7.1.5.1).

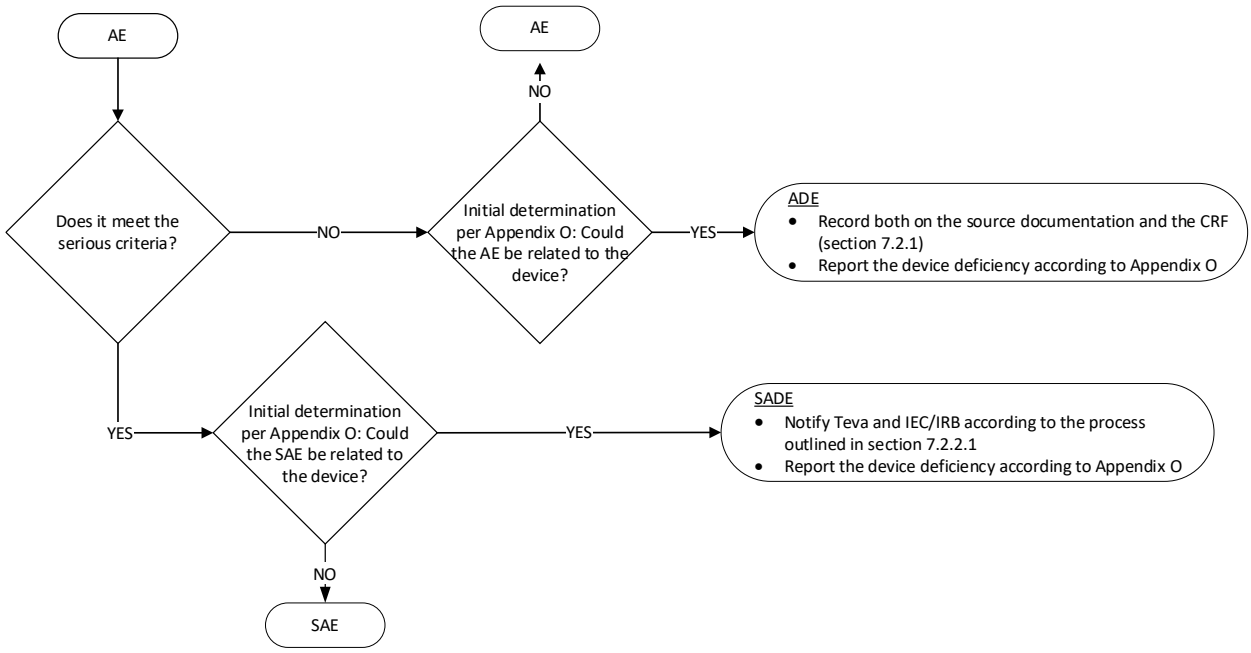
7.2.2.1. Serious Adverse Device Effect Reporting

The investigator will report to the sponsor, without unjustified delay, all serious adverse device effects (within 24 hours); this information shall be promptly followed by detailed written reports as described below.

The process and contact details for serious adverse device effect reporting are the same as for serious adverse event reporting provided in Section 7.1.5.3.

Events shall be reported to the IEC/IRB by the investigator and to the regulatory authorities by the sponsor using the appropriate form according to the national and local regulations.

Figure 2: Decision Tree for Adverse Events and Adverse Device Effects Classification



AE=adverse event; ADE=adverse device effect; CRF=case report form; IEC=Institutional ethics committee; IRB=Institutional Review Board; SADE=serious adverse device effect; SAE=serious adverse event.

7.3. Pregnancy

Any female patient becoming pregnant during the study will discontinue IMP and will be discontinued from the study.

All pregnancies of women participating in the study and female partners of men participating in the study, if applicable, that occur during the study, or within 5 half-lives after the last dose or 30 days after EoS, are to be reported within 24 hours to the physician identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the sponsor (LSO/CRO) with the completed pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form (Section 7.1.5.3).

The investigator is not required to report patients who are found to be pregnant between screening (visit 1) and baseline (visit 3), provided no study drug (IMP) administrations were applied. These patients will be considered as screen failures.

All female patients (or female partners of men participating in the study) who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous, elective, or voluntary abortion). Female partners of men participating in the study who become pregnant will be asked to sign an ICF. If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the investigator becomes aware of after withdrawal from the study, will be reported as an adverse event or serious adverse event, as appropriate.

If the pregnancy in a woman participating in the study and/or the female partner of a man participating in the study does not continue to term, one of the following actions will be taken:

- For a spontaneous abortion, report as a serious adverse event.
- For an elective abortion due to developmental anomalies, report as a serious adverse event.
- For an elective abortion **not** due to developmental anomalies, report on the pregnancy form; do not report as an adverse event.

7.4. Medication Error and Special Situations Related to the Investigational Medicinal Products

Any administration of IMP that is not in accordance with the study protocol should be reported in the patient's source documents, regardless of whether or not an adverse event occurs as a result. When meeting important protocol deviation criteria, all instances of incorrect IMP administration should be categorized as “Non-Compliance to IMP.”

The following are types of medication errors and special situations:

- Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer.
- Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied. Any dose of IMP (whether the test IMP, reference IMP, or placebo IMP), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor.
- Misuse: Situations where the IMP is intentionally and inappropriately used not in accordance with the authorized product information.
- Abuse: Persistent or sporadic, intentional excessive use of IMP which is accompanied by harmful physical or psychological effects.
- Occupational exposure: Exposure to an IMP, as a result of one’s professional or non-professional occupation.

7.5. Clinical Laboratory Tests

All clinical laboratory test results outside of the reference range will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

A laboratory test result that is judged by the investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event (except at the initial screening visit, which will be captured as medical history), and monitored as described in Section 7.1.2. A laboratory or diagnostic test abnormality (once confirmed by repeated testing) that results in the withdrawal of the patient from the study, the temporary or permanent withdrawal of IMP or medical treatment, or further diagnostic work-up may be considered adverse events. If further diagnostic work-up of abnormal laboratory results leads to the investigator concluding that the initial abnormality was not clinically significant, it is at the investigator's discretion whether or not the result triggering the work-up is an adverse event. (Note: Abnormal laboratory or diagnostic test results at the screening visit that preclude a patient from entering the study or receiving IMP are not considered adverse events.)

Details of clinical laboratory tests will be included in the study reference manual.

7.5.1. Serum Chemistry, Hematology, and Urinalysis

Clinical laboratory tests (serum chemistry, hematology, and urinalysis) will be performed at the time points detailed in Table 1. Clinical laboratory tests will be performed using the central laboratory (see Appendix A). Specific laboratory tests to be performed are listed in Table 4.

Table 4: Clinical Laboratory Tests

Serum chemistry	Hematology	Urinalysis
• calcium • phosphate • sodium • potassium • chloride • bicarbonate or carbon dioxide • glucose • blood urea nitrogen (BUN) • creatinine • total cholesterol (low density lipoprotein [LDL] and high density lipoprotein [HDL]) • triglycerides (after overnight fasting) • uric acid • alanine aminotransferase (ALT) • aspartate aminotransferase (AST) • lactic dehydrogenase (LDH) • gamma glutamyl transpeptidase (GGT) • alkaline phosphatase (ALP) • creatine phosphokinase (CPK) • total protein • albumin • total bilirubin	• hemoglobin • hematocrit • red blood cell (RBC) count • RBC indices • platelet count • absolute neutrophil count (ANC) • white blood cell (WBC) count and differential count – neutrophils – lymphocytes – eosinophils – monocytes – basophils – atypical lymphocytes • coagulation tests – international normalized ratio (INR) – prothrombin time (PT) – partial thromboplastin time (PTT)	• protein • glucose • ketones • blood (hemoglobin) • pH • nitrates • specific gravity • microscopic – bacteria – RBCs – WBCs – casts – crystals

7.5.2. Other Clinical Laboratory Tests

7.5.2.1. Human Chorionic Gonadotropin Tests

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.

7.5.2.2. Follicle Stimulating Hormone

At screening, women will have a serum FSH assessment, as applicable, to confirm postmenopausal status.

7.5.2.3. Coronavirus Disease 2019 Testing

COVID-19 testing will be performed at screening (V1). In addition, the patient should be tested 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 and reported in the CRF.

7.6. Physical Examinations

Physical examinations will be performed at the time points detailed in Table 1.

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.

Any physical examination finding that is judged by the investigator as clinically significant (except at the initial screening visit, which will be captured as medical history) may be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.

7.7. Height and Weight

Height (in centimeters) and weight (in kilograms) will be measured at the time points detailed in Table 1.

7.8. Vital Signs

Vital signs (pulse rate, blood pressure [systolic/diastolic], and respiratory rate) will be measured at the time points detailed in Table 1. All vital sign results outside of the reference ranges will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

Before blood pressure and pulse are measured, the patient must rest in a supine or seated position for at least 5 minutes. The same position and arm should be used each time vital signs are measured for a given patient. For any abnormal vital sign value, the measurement should be repeated as soon as possible. Any vital sign value that is judged by the investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event, and monitored as described in Section 7.1.2.

7.9. Electrocardiography

A 12-lead ECG will be recorded at the time points detailed in Table 1.

Standard ECGs parameters will be recorded and the ECG will be interpreted locally by the principal investigator (or qualified physician). All ECG results outside of the reference ranges will be judged by the investigator (or qualified physician) as belonging to one of the following categories:

- abnormal and not clinically significant

- abnormal and clinically significant

Any ECG finding that is judged by the investigator (or qualified physician) as clinically significant (except at the screening visit) will be considered an adverse event, recorded on the source documentation and in the CRF, and monitored as described in Section 7.1.2.

7.10. Assessment of Local Tolerability and Pain

Local tolerability at the injection site (erythema, ecchymosis, induration, tenderness, warmth, swelling, and pain) will be assessed using standardized scales. 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 (Table 1).

Severity of local tolerability symptoms should be assessed as described in Table 5. Erythema, ecchymosis, and induration will be considered only if they reach a diameter of at least 5 mm. The surface diameter in millimeters should be recorded. Induration must be assessed by careful superficial palpation avoiding pressuring or squeezing the injection site.

In the case that symptoms do not resolve, assessments will proceed at each ambulatory visit. Appropriate treatment may be provided if necessary, in which case it must be recorded as concomitant medication. In case the site(s) of injection need visual representation, in addition to comments in the source documents, the injection site(s) may also be photographed along with a metric ruler and patient identification number for later review. Any features that could be used to identify the patient will not be captured on the photograph.

Table 5: Severity Assessment of Local Tolerability

Test	Response
Erythema	Absent Erythema surface diameter 5 mm to ≤50 mm (mild) Erythema surface diameter >50 to ≤100 mm (moderate) Erythema surface diameter >100 mm (severe)
Ecchymosis	Absent Ecchymosis surface diameter 5 mm to ≤50 mm (mild) Ecchymosis surface diameter >50 to ≤100 mm (moderate) Ecchymosis surface diameter >100 mm (severe)
Induration	Absent Induration surface diameter 5 mm to ≤50 mm (mild) Induration surface diameter >50 to ≤100 mm (moderate) Indurations surface diameter >100 mm (severe)
Tenderness Warmth Swelling	None Mild Moderate Severe

Injection site findings will not be captured as adverse events unless they fulfill characteristics that are beyond those in the specified forms/scales (eg, necrosis, abscess, etc) or fulfill seriousness criteria and then they must be recorded and reported as specified in Section 7.1.

8. ASSESSMENT OF PHARMACOKINETICS, PHARMACODYNAMICS, AND IMMUNOGENICITY

8.1. Pharmacokinetic Assessment

Blood samples (4 mL) will be collected via venipuncture before drug administration at the time points detailed in Table 1 for measurements of serum concentration of omalizumab. The dates and times of IMP administration and the date and time point (24 hour clock time) of each pharmacokinetic sample, will be recorded both on the source documentation and the CRF.

Samples will be analyzed for concentration of TEV-45779 and XOLAIR using validated methods.

Details on sample handling, storage, shipment, and analysis are given in Appendix M.

8.2. Pharmacodynamics Assessment

Blood samples (4 mL) for assessment of free IgE serum concentration and blood samples (4 mL) for assessment of total IgE serum concentration will be taken before drug administration at the time points indicated in Table 1. The dates and times of IMP administration and the date and timepoint of each pharmacodynamic sample, will be recorded both on the source documentation and the CRF. Analysis for the measurement of total IgE and free IgE will be performed by the sponsor bioanalytical laboratory (GBT) using validated methods.

Details on sample handling, storage, shipment, and analysis are given in Appendix M.

8.3. Immunogenicity Testing

Two blood samples (5 mL each) for assessment of ADA response will be taken before drug administration at the time points indicated in Table 1.

Additionally, 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 at the relevant time point. The dates and times of IMP administration and the date and time point of each immunogenicity sample, will be recorded both on the source documentation and the CRF.

The detection and characterization of antibodies to TEV-45779 and XOLAIR will be performed using validated methods by or under the supervision of the sponsor.

Samples may be stored if permitted by the ICF and local regulations after the last patient's last visit for the study at a facility selected by the sponsor, to enable further analysis of immune responses to TEV-45779.

Details on sample handling, storage, shipment, and analysis are given in Appendix N.

9. STATISTICS

This section describes the statistical analysis as foreseen at the time of planning the study. Changes, additions, and further details about the analyses will be described in the statistical analysis plan (SAP). After finalization of the SAP, any additional analyses or changes to analyses that may be required will be fully disclosed in the clinical study report (CSR).

The statistical analysis of the study is planned to assess the biosimilarity (efficacy and safety) between TEV-45779 and XOLAIR, and to support the safety and immunogenicity assessment of a single switch from XOLAIR to TEV-45779.

9.1. Sample Size and Power Considerations

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, ie, 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] 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 from baseline in ISS7 at Week 12 using a 4-point assay, [redacted] (TEV-45779 and XOLAIR at 300 mg and 150 mg).
- [redacted]

Power assessment for the co-primary endpoint of relative potency of TEV-45779 and XOLAIR, as measured by change from baseline 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 9.5.1.1.1.

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

[redacted]

9.2. Analysis Sets

9.2.1. 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.

9.2.2. 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.

9.2.3. Modified Intent-to-Treat 1 Analysis Set

The 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.

9.2.4. Transition Intent-to-Treat Analysis Set

The transition intent-to-treat (TITT) analysis set will include all patients 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.

9.2.5. 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.

9.2.6. Transition Period Modified Intent-to-Treat 1 Analysis Set

The 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.

9.2.7. 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. Rules for assignment of treatment in case of actual treatment error will be provided in the SAP.

9.2.8. 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 the main treatment and transition period, regardless of the treatment to which they were randomized.

9.2.9. 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 (ie, 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 of the main treatment period for the analysis.

9.2.10. Pharmacokinetic Analysis Set

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

9.3. Data Handling Conventions

For all descriptive statistics, only the observed data from the patients will be used.

9.3.1. Handling Withdrawals and Missing Data

Data imputation is planned for the primary endpoint analysis, see Section 9.5 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 primary analysis. The ITT analysis set will be used for the primary analysis.

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 – If 4-7 daily scores are available for the calculation of the weekly score, the ISS7 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 (ie, 4-7 daily scores are missing), the ISS7 will be considered missing for that week.

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 9.4.1).

In the primary analysis, missing ISS7 at Week 12 will be imputed based on post-baseline assessments using multiple imputation under the MAR assumption (see Section 9.5.1.1); 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 (ie, 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 9.5.1.2 and Section 9.5.1.3.

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.

9.4. Study Population

The ITT analysis set (Section 9.2) will be used for all study population summaries unless otherwise specified. Summaries will be presented by treatment group and for all patients.

9.4.1. Patient Disposition

The number of patients screened, patients screened but not randomized, and patients in the main treatment period and the transition period will be summarized using descriptive statistics.

For the main treatment period, the summary will include: patients randomized (ITT analysis set), patients in the mITT, mITT1, safety, PK, and PP analysis sets, patients that withdraw up to Week 12, patients that withdraw after Week 12 and patients that complete the main treatment period.

For the transition period, the summary will include: patients randomized (TITT analysis set), patients in the TmITT and transition safety analysis sets, patients that withdraw during the transition period, and patients that complete the study.

Data from patients who withdraw from the study will also be summarized by reason for withdrawal as recorded in the disposition CRF using descriptive statistics.

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. In case of imbalances in withdrawal rates between treatment groups, further analysis of any differences with respect to baseline characteristics may be conducted as deemed necessary.

9.4.2. Demographic and Baseline Characteristics

Patient demographic and baseline characteristics, including but not limited to, medical history, prior medications and therapies, will be examined by treatment group and will be summarized using descriptive statistics based on the ITT, mITT and mITT1 analysis sets, as applicable.

Generally, for continuous variables, descriptive statistics (number [n], mean, SD, median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented if necessary.

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

9.5.1. 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 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.

9.5.1.1. Primary Efficacy Analysis

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 daily 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 data will be similar to the one used by the originator (see Section 2.1.1). Multiple imputation will be used for the missing ISS7 at Week 12 for the analysis of change from baseline (see Section 9.5.1.1.2 for details).

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 analysis of covariance (ANCOVA) with treatment group (2 levels: TEV-45779 300 mg and XOLAIR 300 mg), 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), 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 (see Section 9.2.1).

9.5.1.1.1. 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).

Refer to Appendix G for the technical details regarding relative potency and its CI estimation.

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

- Linearity: required but cannot be tested in a 4-point design.

- Parallelism: absence of significant deviations from parallelism of dose-response curves 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 β is not significantly different from zero, the data are consistent with a zero value for β and hence an infinite 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.

The macro to be used for the analysis is described briefly in Appendix G.

The relative potency 4-point assay will use an ANCOVA model with effect of product (2 levels: TEV-45779 and XOLAIR), dose on the log-scale (2 levels: log 150 and log 300), and their interaction (4 levels), baseline itch severity score, baseline weight and region (3 levels planned: Americas, Europe and Asia-Pacific) as covariates.

9.5.1.1.2. Missing Week 12 Itch Severity Score Multiple Imputation

The imputation rules below will be applied according to the region specific estimand. The change from baseline in ISS7 at Week 12 will be imputed:

- per the defined estimand for the FDA submission, for patients having a missing ISS7 at Week 12;
- per the defined estimand for the EMA submission, for patients discontinuing the treatment early or using any disallowed concomitant medication between randomization and Week 12 ISS7 assessment.

The change from baseline in ISS7 at Week 12 will be imputed using the predictive mean matching multiple imputation method (Heitjan and Little 1991, Schenker and Taylor 1996), under the MAR assumption 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 region (3 levels planned: Americas, Europe and Asia-Pacific) as covariates. Imputation will use available data from previous post baseline ISS7 scores. 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).

Primary analysis of relative potency will use only observed data.

9.5.1.2. 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 EU), 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 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

The following sensitivity analysis will be performed for the 4-points relative potency between TEV-45779 and XOLAIR

- The ANCOVA model in the %RELPOT macro run without baseline covariates

9.5.1.3. 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 data for change from baseline in the ISS7 at Week 12 will be imputed similarly to the primary analysis, except that in step 2 the monotone imputation model will be adjusted to different MNAR assumptions:

  - the change from baseline in the ISS7 in patients randomized to TEV-45779 300 mg with missing ISS7, will be imputed assuming the treatment effect is worsened by δ_1 compared to the patients who have no missing value (where $\delta_1 = 0$ to 4 or estimated treatment effect of TEV-45779 300 mg group, whichever is higher);
  - the change from baseline in the ISS7 in patients randomized to XOLAIR 300 mg with missing ISS7, will be imputed assuming the treatment effect is worsened by δ_2 compared to the patients who have no missing value (where $\delta_1 = 0$ 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 point".

- 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:

  - in the first test, missing values for the TEV-45779 300 mg group will be imputed assuming the treatment effect has worsened (ie, 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 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;
  - in the second test, missing values for the TEV-45779 300 mg group will be imputed assuming the treatment effect improved (ie, 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 -2.0 for the EMA submission.

  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), as in the primary analysis.

- primary analysis repeated on the mITT analysis set.

Other analyses:

- primary model repeated for the mITT1 analysis set (see Section 9.2.3) on observed data without multiple imputations
- primary model repeated for the PP analysis set (see Section 9.2.9) 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 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. No imputation will be carried out for this analysis.

Additional supplementary analyses to address missing data in the relative potency analysis will be provided in the SAP.

9.5.2. Secondary Endpoints

9.5.2.1. 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 UAS7 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 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.

9.5.2.2. 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.

9.5.2.3. Secondary Efficacy Analysis

No formal hypothesis testing is planned for the secondary efficacy and pharmacodynamic endpoints.

Descriptive statistics will be presented by treatment group. For descriptive purposes, 95% CIs for the difference in mean (for continuous variables) or proportion (for binary variables) between treatment groups will be presented.

9.5.2.4. Efficacy and Pharmacodynamic 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 150 mg or 300 mg). In addition, the difference and 95% CI for the difference between the XOLAIR/XOLAIR and XOLAIR/TEV-45779 groups at both doses will be presented.

Free and total IgE will be summarized by treatment and time point using descriptive statistics. Individual data will be listed.

The efficacy analyses in the transition period will be based on the TITT and TmITT analysis sets (see Section 9.2.4 and Section 9.2.5), as applicable.

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

9.6. Multiple Comparisons and Multiplicity

For the FDA submission, the above efficacy endpoint and the relative-potency endpoint of 2 dose levels (300 mg and 150 mg) of TEV-45779 and XOLAIR, as measured by change from baseline 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 efficacy similarity is demonstrated for the endpoint of change from baseline in ISS7 at Week 12 for TEV-45779 300 mg compared to XOLAIR 300 mg.

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

9.7. Safety Analysis

Safety analyses will be performed on the safety and transition period safety analyses sets (Sections 9.2.7 and 9.2.8, respectively).

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

Safety assessments and time points are provided in Table 1.

All adverse events will be coded using the MedDRA. Each patient will be counted only once in each preferred term or SOC category for the analyses of safety. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to test IMP/device (ie, reasonable possibility) (defined as related or with missing relationship) (overall and by severity), serious adverse events, and adverse events causing withdrawal from the study. Summaries for the main treatment period, transition period and overall treatment period will be presented as indicated below. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

Changes in laboratory and vital signs data will be summarized descriptively by treatment period. All values will be compared with predefined criteria to identify potentially clinically significant values or changes, and such values will be listed.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics by treatment period.

For continuous variables, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided. Descriptive summaries of serious adverse events, patient withdrawals due to adverse events, and potentially clinically significant abnormal values (clinical laboratory or vital signs) based on predefined criteria will be provided as well by treatment period.

If any patient dies during the study, a listing of deaths will be provided and all relevant information will be discussed in the patient narrative included in the CSR.

9.7.1. 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.

9.7.2. Safety Analysis in the Transition Period

Safety analyses in the transition period will be performed on the transition period safety analysis set (see Section 9.2.8 for definition). 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.

9.7.3. 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.

The analyses will be similar to the analyses of the main treatment period. Summaries will be presented by treatment group (TEV-45779, XOLAIR, further subdivided by dose 150 mg or 300 mg) and for all patients included in the analysis.

9.8. Pharmacokinetic Analysis

Omalizumab serum concentrations will be summarized by treatment and time point using descriptive statistics for all patients who have omalizumab serum concentration data for ≥1 time point.

Individual data will be listed.

9.9. Pharmacodynamic Analysis

Free and total IgE will be summarized by treatment and time point using descriptive statistics. Individual data will be listed.

9.10. Immunogenicity Analysis

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

If more than 5 patients develop treatment-related ADA anytime post-baseline, 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.

The effect of positive immunogenicity findings on efficacy and safety may be investigated, if applicable.

9.11. Planned Interim Analysis

No interim analysis is planned for this study.

9.12. Reporting Deviations from the Statistical Plan

Deviations from the statistical plan, along with the reasons for the deviations, will be described in protocol amendments, the SAP, the CSR, or any combination of these, as appropriate, and in accordance with applicable national, local, and regional requirements and regulations.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Refer to Appendix H for information regarding quality control and quality assurance. This includes information about protocol amendments, deviations, responsibilities of the investigator to study personnel, study monitoring, and audit and inspection.

Refer to Appendix O for the definition of a clinical product complaint and investigator responsibilities in the management of a clinical product complaint.

Details are given in the study reference manual.

11. COMPLIANCE STATEMENT

This study will be conducted in full accordance with the ICH Harmonised Tripartite Guideline, Guideline for GCP E6 and any applicable national and local laws and regulations (eg, Title 21 Code of Federal Regulations [21CFR] Parts 11, 50, 54, 56, 312, and 314, Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use). Any episode of noncompliance will be documented.

The investigator is responsible for performing the clinical study in accordance with this protocol and the applicable GCP guidelines referenced above for collecting, recording, and reporting the data accurately and properly. Agreement of the investigator to conduct and administer this clinical study in accordance with the protocol will be documented in separate clinical study agreements with the sponsor and other forms as required by national competent authorities in the country where each investigational center is located.

The investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the clinical study; and must ensure that trained personnel are immediately available in the event of a medical emergency. The investigator and the involved clinical study personnel must be familiar with the background and requirements of the study; and with the properties of the IMP as described in the IB or prescribing information.

The principal investigator at each investigational center has the overall responsibility for the conduct and administration of the clinical study at that investigational center and for contacts with study management, with the IEC/IRB, and with competent authorities.

See Appendix I for the ethics expectations of informed consent or assent, competent authorities and IEC and IRB, confidentiality regarding study patients, and requirements for registration of the clinical study.

12. DATA MANAGEMENT AND RECORD KEEPING

See Appendix P for information regarding data management and record keeping. This includes direct access to source data and documents, data collection, data quality control, and archiving of CRFs and source documents.

13. FINANCING AND INSURANCE

A separate clinical study agreement, including a study budget, will be signed between each principal investigator and the sponsor (or the CRO designated by the sponsor) before the IMP is delivered.

The patients in this clinical study are insured in accordance with applicable legal provisions. The policy coverage is subject to the full policy terms, conditions, extensions, and exclusions. Excluded from the insurance coverage are eg, damages to health, and worsening of previous existing disease that would have occurred or continued if the patient had not taken part in the clinical study.

The policy of Clinical Trials Insurance will be provided to the investigational centers by the sponsor.

For covered clinical studies (see 21CFR54), the investigator will provide the sponsor with financial information required to complete FDA 3454 form. Each investigator will notify the sponsor of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

14. PUBLICATION POLICY

See Appendix Q for information regarding the publication policy.

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16. SUMMARY OF CHANGES TO PROTOCOL

16.1. Amendment 04 Dated 15 February 2023

The primary reason for this amendment is to clarify details in the Study Protocol; add a method for calculating next visit for cases of out-of-window visits, align/clarify inclusion/exclusion criteria, and add the information of the Central Clinical Laboratory for India. All major changes to the protocol body are listed below in the table and are reflected in the synopsis, as applicable. Table 1 (Study Procedures and Assessments) has been revised to reflect changes described below. Minor editorial changes (typos, punctuation, etc) have been made to the protocol (and protocol synopsis, as appropriate).

Original text with changes shown	New wording	Reason/Justification for change
Sponsor Signature Page - Sponsor's Authorized Representative		
[redacted]	[redacted]	Personnel update
Section 1.1.2 TEV 45779 and Chronic Idiopathic Urticaria/Chronic Spontaneous Urticaria **Other sections affected by this change: Section 1.2.2.3 Safety and Immunogenicity, Section 1.3.2 Known and Potential Benefits and Risks of Reference Investigational Medicinal Product, Section 1.3.3 Overall Benefit and Risk Assessment for this Study**		
XOLAIR Summary of Product Characteristics ~~16/12/2021~~25/10/2021	XOLAIR Summary of Product Characteristics 25/10/2021	Updated as SmPC was revised
Section 1.2.1 Nonclinical Studies **Other section affected by this change: Section15 References**		
XOLAIR Product Monograph ~~8/9/2021~~1/11/2022	XOLAIR Product Monograph 1/11/2022	Updated as Product Monograph was revised
Section 1.2.2 Clinical Studies		
Clinical data for TEV-45779 are available from the pivotal pharmacokinetic/pharmacodynamic study TV45779-BE-10160 (report approval date: 25 November 2021). … ~~A blinded interim safety analysis was conducted after completion of the Day 29 visit (28 days post-dose; cut-off date: 19 April 2021)…~~	Clinical data for TEV-45779 are available from the pivotal pharmacokinetic/pharmacodynamic study TV45779-BE-10160 (report approval date: 25 November 2021).	Clarify study report completion
Section 1.2.2.3 Safety and Immunogenicity		
There were no deaths, other serious adverse events, or withdrawals due to adverse events, and no protocol defined adverse events of special interest (ie, anaphylaxis) during the study. There were 5 pregnancy cases reported in the TV45779-BE-10160 study, 3 in the TEV-45779 group, 1 in the XOLAIR EU group, and 1 in the XOLAIR US group. In 2 cases (1 each in the TEV-45779 and XOLAIR US groups), the pregnancy outcome was elective termination while in another case in the TEV-45779 group, the event of biochemical pregnancy was reported to have no viable	There were no deaths, other serious adverse events, or withdrawals due to adverse events, and no protocol defined adverse events of special interest (ie, anaphylaxis) during the study. There were 5 pregnancy cases reported in the TV45779-BE-10160 study, 3 in the TEV-45779 group, 1 in the XOLAIR EU group, and 1 in the XOLAIR US group. In 2 cases (1 each in the TEV-45779 and XOLAIR US groups), the pregnancy outcome was elective termination while in another case in the TEV-45779 group, the event of biochemical pregnancy was reported to have no viable	Update of safety information

Original text with changes shown	New wording	Reason/Justification for change
pregnancy. One case in the TEV-45779 group was considered as lost to follow up. One serious adverse event of spontaneous abortion was reported after completion of the study for a subject who received XOLAIR EU.~~i.e., anaphylaxis).~~ … Only a small percentage of ADA-positive subjects tested positive for neutralizing ADA during the study (1% to 9%), with no marked difference between groups.	pregnancy. One case in the TEV-45779 group was considered as lost to follow up. One serious adverse event of spontaneous abortion was reported after completion of the study for a subject who received XOLAIR EU. … Only a small percentage of ADA-positive subjects tested positive for neutralizing ADA during the study (1% to 9%), with no marked difference between groups.	
Section 2.1. Primary and Secondary Study Objectives and Endpoints **Other sections affected by this change: Section 9.1 Sample Size and Power Considerations, Section 9.5.1 Primary Endpoint, Section 9.5.1.1 Primary Efficacy Analysis, Section 9.6 Multiple Comparisons and Multiplicity**		
Relative potency of 2 dose levels (300 mg and 150 mg) 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.	Relative potency of 2 dose levels (300 mg and 150 mg) 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	Clarification
Section 2.1.1 Primary Estimand		
The relative potency of TEV-45779 and ~~US-licensed~~ 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, ~~US-licensed~~ XOLAIR 300 mg, and ~~US-licensed~~ XOLAIR 150 mg, in patients with CIU/CSU who remain symptomatic despite antihistamine (H1) treatment, regardless of treatment-related adverse events… primary endpoint of difference in mean change from baseline in weekly ISS7 at Week 12 between TEV-45779 300 mg and ~~US-licensed~~ XOLAIR 300 mg.	The 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, in patients with CIU/CSU who remain symptomatic despite antihistamine (H1) treatment, regardless of treatment-related adverse events… primary endpoint of difference in mean change from baseline in weekly ISS7 at Week 12 between TEV-45779 300 mg and XOLAIR 300 mg.	Deleted as both XOLAIR sourced from the EU and US can be used as reference product.
Section 3.1 General Study Design and Study Schematic Diagram		
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 India, Cetirizine is to be used as the single H1 antihistamine at stable and fixed doses, not exceeding label recommendations, as a uniform standard treatment regimen, throughout the entire study (Appendix T).	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 India, Cetirizine is to be used as the single H1 antihistamine at stable and fixed doses, not exceeding label recommendations, as a uniform standard treatment regimen, throughout the entire study (Appendix T).	Addition of new country specific information for India

<table>
<tr><th>Original text with changes shown</th><th>New wording</th><th>Reason/Justification for change</th></tr>
<tr><td colspan="3">Section 3.2 Planned Number of Patients and Countries</td></tr>
<tr><td>Approximately 600 patients (200:200:100:100 to TEV-45779 300 mg, XOLAIR 300 mg, TEV-45779 150 mg and XOLAIR 150 mg) will be randomized (also see Appendix S).</td><td>Approximately 600 patients (200:200:100:100 to TEV-45779 300 mg, XOLAIR 300 mg, TEV-45779 150 mg and XOLAIR 150 mg) will be randomized (also see Appendix S)</td><td>Cross-link to South Korea specific study information</td></tr>
<tr><td>The study is expected to start in quarter Q3 2021 and last until approximately Q2 2024~~Q3 2023~~.</td><td>The study is expected to start in quarter Q3 2021 and last until approximately Q2 2024.</td><td>Updated study timeline according to the latest information</td></tr>
<tr><td colspan="3">Section 3.5 Schedule of Study Procedures and Assessments
Other sections affected by this changes: Appendix B Study Procedures and Assessments by Visit</td></tr>
<tr><td>Table 1 - Rescue medication dispensation<table><tr><td>Rescue medication dispensation[s]</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr></table></td><td>Table 1 - Rescue medication dispensation<table><tr><td>Rescue medication dispensation[t]</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr></table></td><td>Corrected table information to clarify that rescue medication is dispensed at visits 1 and visits 2-12</td></tr>
<tr><td>Table 1 - insert new footnote “c”
…c In case of an out-of-window visit, the date of the next visit will be calculated based on the baseline date (V3) or will be scheduled at least 21 days apart.
~~cd~~ Any medical event relevant to eligibility…</td><td>Table 1 - insert new footnote “c”
… c In case of an out-of-window visit, the date of the next visit will be calculated based on the baseline date (V3) or or will be scheduled at least 21 days apart.
d Any medical event relevant to eligibility…</td><td>Added method of calculating the next visit for cases of out-of-window visits.
Updated footnote numbering accordingly.</td></tr>
<tr><td>Table 1 - footnote “o” update
~~n~~ o Additional laboratory parameters, such as FSH and β-HCG (see footnote ~~k~~n) or as applicable…performed locally. At V1, serum chemistry sample in non-fasting state may be acceptable.</td><td>Table 1 - footnote “o” update
o Additional laboratory parameters, such as FSH and β-HCG (see footnote n) or as applicable… performed locally. At V1, serum chemistry sample in non-fasting state may be acceptable.</td><td>Correct incorrect footnote reference and add clarification of blood sampling at visit 1</td></tr>
</table>

Original text with changes shown	New wording	Reason/Justification for change
Table 1 - footnote "r" update ~~q~~r Dispensation of rescue medication must be done at V1 in amount of maximum dose (3 tablets/day) until V2. At subsequent~~and at other~~ visits, patients have to return all unused rescue medication, the consumption from previous visit should be confirmed, and based on it further ~~as required;~~ dispensation should ~~on other visits will happen as needed to~~ ensure that subject has sufficient rescue medication to cover the period till the next subject visit ~~at max~~with a maximum dose.	**Table 1 - footnote "r" update** r Dispensation of rescue medication must be done at V1 in amount of maximum dose (3 tablets/day) until V2. At subsequent visits, patients have to return all unused rescue medication, the consumption from previous visit should be confirmed, and based on it further dispensation should ensure that subject has sufficient rescue medication to cover the period till the next subject visit with a maximum dose.	Clarification on dispensation of rescue medication
Section 4 Selection and Withdrawal of Patients		
Not applicable	Changes to inclusion or exclusion criteria are indicated below and detailed in Section 16	Added to emphasize that criteria have been updated
Section 4.1 Inclusion Criteria		
Inclusion Criteria "b" - CIS/CSU diagnosis for ≥3 months[4] [4] Diagnosis or symptoms leading to this diagnosis have to be present for ≥3◦months.	**Inclusion Criteria "b"** - CIS/CSU diagnosis for ≥3 months[4] [4] Diagnosis or symptoms leading to this diagnosis have to be present for ≥3◦months.	Added footnote for clarification on diagnosis criteria
Inclusion Criteria "c" Highly effective birth control methods are methods that can achieve a failure rate of less than 1% per year when used consistently and correctly ~~are considered~~ (see methods in Appendix J). ~~Such methods include:~~ ~~◦ Combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these should be initiated at least 7 days before the first dose of IMP.~~ ~~◦ Progestogen only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation; these should be initiated at least 7 days before the first dose of IMP.~~	**Inclusion Criteria "c"** Highly effective birth control methods are methods that can achieve a failure rate of less than 1% per year when used consistently and correctly (see such methods in Appendix J).	Referred to Appendix J for details on birth control methods

Original text with changes shown	New wording	Reason/Justification for change
~~○ Intrauterine device and intrauterine hormone releasing system need to be in place at least 2 months before the start of screening.~~ ~~○ Bilateral tubal occlusion or tubal ligation.~~ ~~○ Vasectomized partner provided he is the sole sexual partner and has received medical assessment of the surgical success.~~ ~~○ Sexual abstinence is only considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.~~ ~~Unacceptable birth control methods:~~ ~~○ Periodic abstinence (e.g., calendar, ovulation, symptothermal, post ovulation methods), and withdrawal are not acceptable methods of contraception (according to Medicines and Healthcare Products Regulatory Agency).~~		
Inclusion Criteria "d" [Revision 1] Male patients (including vasectomized men) with partners who are of childbearing potential (whether pregnant or not) must use condoms	**Inclusion Criteria "d"** [Revision 1] Male patients (including vasectomized men) with partners who are of childbearing potential (whether pregnant or not) must use condoms	Clarification that criteria was revised (ie, "with spermicide" deleted) during protocol amendment 3
Inclusion Criteria "f" …In particular, the patient must be willing and able to complete a ~~daily~~ symptom diary twice daily (morning and evening) for the duration of the study. The patients must have diary entries during at least 4 of the 7 days prior to randomization.	**Inclusion Criteria "f"** …In particular, the patient must be willing and able to complete a symptom diary twice daily (morning and evening) for the duration of the study. The patients must have diary entries during at least 4 of the 7 days prior to randomization.	Clarification on eDiary usage

Original text with changes shown	New wording	Reason/Justification for change
Section 4.2 Patient Exclusion Criteria		
Exclusion Criteria "l" Revision 1] Any H1 antihistamines at greater than approved doses use from 3 days after the start of screening	**Exclusion Criteria "l"** Revision 1] Any H1 antihistamines at greater than approved doses use from 3 days after the start of screening	Clarification that criteria was revised (from "…within 3 days prior…" to "…from 3 days after…") during protocol amendment 3
Exclusion Criteria "m" [Revision 1] Current malignancy, history of malignancy within the last 5 years, or currently under work up for suspected malignancy except non melanoma skin cancer that has been treated or excised and is considered resolved.	**Exclusion Criteria "m"** [Revision 1] Current malignancy, history of malignancy within the last 5 years, or currently under work up for suspected malignancy except non melanoma skin cancer that has been treated or excised and is considered resolved.	Clarification of exclusion criteria to aid with enrolment
Section 4.3 Withdrawal Criteria and Procedures for the Patient		
Patients who discontinue from IMP while remaining in the study are invited to continue safety follow-up per study schedule and to complete the remaining study visits and assessments ~~encouraged to complete end of treatment visit (of the main or transition period as applicable) procedures as soon as possible after receiving their last dose of IMP and to complete the remaining study visits and assessments~~ (with the exception of administration of IMP) including the EoS visit within the original time frames based on date of randomization.	Patients who discontinue from IMP while remaining in the study are invited to continue safety follow-up per study schedule and to complete the remaining study visits and assessments (with the exception of administration of IMP) including the EoS visit within the original time frames based on date of randomization.	Clarification for patients who discontinue from IMP
Section 5.2.3 Accountability		
…area in accordance with the labeled storage conditions or appropriate instructions with access limited to the unblinded ~~investigator and~~ authorized staff (eg, unblinded pharmacist, unblinded designee, IMP administrator) at the investigational center. The unblinded pharmacist, unblinded designee, or IMP...	…area in accordance with the labeled storage conditions or appropriate instructions with access limited to the unblinded authorized staff (eg, unblinded pharmacist, unblinded designee, IMP administrator) at the investigational center. The unblinded pharmacist, unblinded designee, or IMP...	Clarification on unblinded staff

Original text with changes shown	New wording	Reason/Justification for change
Section 5.5.1 Activity		
Patients will fast overnight prior to the morning of blood sampling for lipid profiling (at V1 non-fasting state before blood sampling may be acceptable).	Patients will fast overnight prior to the morning of blood sampling for lipid profiling (at V1 non-fasting state before blood sampling may be acceptable).	Clarification of blood sampling at visit 1
Section 5.9.1 Blinding and Unblinding		
During the main treatment period, the ~~S~~staff responsible for ~~pharmacokinetic and immunogenicity bioanalysis,~~ population pharmacokinetics, and/or the pharmacokinetics/pharmacodynamics model will be blinded ~~not have access to the patient treatment randomization prior to unblinding the study (before final DBL~~). The staff responsible for the pharmacokinetic, pharmacodynamics, and immunogenicity bioanalysis, will remain blinded to the subject treatment randomization during the main and transition treatment period. … After last patient last visit and DBL of the main treatment period, the sponsor will unblind the treatments for the analysis. Staff responsible for population pharmacokinetics, and/or the pharmacokinetics/pharmacodynamics model will receive access to the patient treatment randomization of the main treatment period (up to and including week 12;…	During the main treatment period, the staff responsible for population pharmacokinetics, and/or the pharmacokinetics/pharmacodynamics model will be blinded. The staff responsible for the pharmacokinetic, pharmacodynamics, and immunogenicity bioanalysis, will remain blinded to the subject treatment randomization during the main and transition treatment period. …After last patient last visit and DBL of the main treatment period, the sponsor will unblind the treatments for the analysis. Staff responsible for population pharmacokinetics, and/or the pharmacokinetics/pharmacodynamics model will receive access to the patient treatment randomization of the main treatment period (up to and including week 12;…	Clarification on blinded and unblinded staff
Section 6.1 Patient Symptom Diary		
The eDiary is to be completed twice a day (morning and evening) by the patient for the duration of the study. The eDiary will be given to the patient at the day -14 visit (V1).	The eDiary is to be completed twice a day (morning and evening) by the patient for the duration of the study. The eDiary will be given to the patient at the day -14 visit (V1).	Clarification on eDiary distribution and usage
Section 7.3 Pregnancy		
The investigator is not required to report patients who are found to be pregnant between screening (visit 1) and baseline (visit 3), provided no study drug (IMP) administrations were ~~protocol related procedures were~~ applied. These patients will be considered as screen failures.	The investigator is not required to report patients who are found to be pregnant between screening (visit 1) and baseline (visit 3), provided no study drug (IMP) administrations were applied. These patients will be considered as screen failures.	Clarification on reporting of patient pregnancies

Original text with changes shown	New wording	Reason/Justification for change
Section 7.5 Clinical Laboratory Tests		
A laboratory test result that is judged by the investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event (except at the initial screening visit, which will be captured as medical history), and monitored as described in Section 7.1.2.	A laboratory test result that is judged by the investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event (except at the initial screening visit, which will be captured as medical history), and monitored as described in Section 7.1.2.	Clarification that laboratory tests results at initial screening visit will be recorded under medical history
Section 9.5.1.3. Supplementary Analysis for the Primary Analysis		
Section 15 References		
XOLAIR Product Monograph. Revised 1/11/2022. Marketed by Novartis Pharmaceuticals Canada Inc.	XOLAIR Product Monograph. Revised 1/11/2022. Marketed by Novartis Pharmaceuticals Canada Inc.	Updated Product Monograph information
Appendix A Clinical Laboratories and Other Departments and Institutions		
Sponsor's Authorized Representative [redacted] Teva ratiopharm	**Sponsor's Authorized Representative** [redacted] Teva ratiopharm	Update personnel information
Legal Representative of the Sponsor in the EU Merckle GmbH Contact Person: [redacted] Merckle GmbH, Teva ratiopharm Graf-Arco-Strasse 3 89079 Ulm, Germany Tel: [redacted]	**Legal Representative of the Sponsor in the EU** Merckle GmbH Contact Person: [redacted] Merckle GmbH, Teva ratiopharm Graf-Arco-Strasse 3 89079 Ulm, Germany Tel: [redacted]	Update personnel information

Original text with changes shown		New wording		Reason/Justification for change
Sponsor's Medical Expert/Contact Point Designated by the Sponsor for Further Information on the Study	EU Medical Monitor [redacted] ICON ~~PRA Health Sciences~~ Gottlieb-Daimler-Strasse 10 68165 Mannheim, Germany Tel: [redacted] Medical monitoring support center contact information: Americas: [redacted] (toll-free) or direct at: [redacted] EAPA: [redacted] ~~PRA Health Sciences has been acquired by ICON plc, creating the world's most advanced healthcare intelligence and clinical research organization~~	**Sponsor's Medical Expert/Contact Point designated by the Sponsor for Further Information on the Study**	EU Medical Monitor [redacted] ICON Gottlieb-Daimler-Strasse 10 68165 Mannheim, Germany Tel: [redacted] Medical monitoring support center contact information: Americas: [redacted] (toll-free) or direct at: [redacted] EAPA: [redacted]	Update of contact information
Central Clinical Laboratory <u>(except India)</u>	ACM Medical Laboratory, Inc. 160 Elmgrove Park Rochester New York 14624, USA Tel: [redacted]	**Central Clinical Laboratory (except India)**	ACM Medical Laboratory, Inc. 160 Elmgrove Park Rochester New York 14624, USA Tel: [redacted]	Update on Clinical Laboratory for India

Original text with changes shown	New wording	Reason/Justification for change
Not applicable	**Central Clinical Laboratory India** Metropolis Healthcare Limited Plot No. 103 Road No. 12 MIDC Andheri (E) Mumbai – 400 093 Maharashtra, India	Addition of Central Clinical Laboratory for India
Appendix B Study Procedures and Assessments by Visit		
1. Procedures for Screening (Visits 1 and 2, Up to 3-week Period) **a. Visit 1 (Day -14 [-7/+2 days])** • dispense ~~and check~~ electronic Patient Symptom Diary (eDiary) ~~including UAS~~ • ...clinical laboratory tests: – serum chemistry tests (at V1, serum chemistry sample in non-fasting state may be acceptable) – serum hematology tests…	**1. Procedures for Screening (Visits 1 and 2, Up to 3-week Period)** **a. Visit 1 (Day -14 [-7/+2 days])** • •dispense electronic Patient Symptom Diary (eDiary) • …clinical laboratory tests: – serum chemistry tests (at V1, serum chemistry sample in non-fasting state may be acceptable) – serum hematology tests…	Clarification
7. Procedures During Follow-up Period (Visits 10 through 13) **b. Procedures During Visit 13 (day 281 ±3 days) (End of Study/Early Termination Visit)** • clinical laboratory tests: – serum chemistry – serum hematology – urinalysis • obtain blood sample for ADAs • ~~dispensation of rescue medication (if needed)~~	**7. Procedures During Follow-up Period (Visits 10 through 13)** **b. Procedures During Visit 13 (day 281 ±3 days) (End of Study/Early Termination Visit)** • clinical laboratory tests: – serum chemistry – serum hematology – urinalysis • obtain blood sample for ADAs	Updated to be in line with Table 1

Original text with changes shown	New wording	Reason/Justification for change
Appendix J Birth Control Methods and Pregnancy Testing		
Highly effective birth control methods in females • Combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these should be initiated at least ~~3 months before IMP administration~~ 7 days before the first dose of IMP. • Progestogen-only hormonal contraception (oral, injectable, or implantable) associated with inhibition of ovulation; these should be initiated at least ~~3 months before IMP administration~~ 7 days before the first dose of IMP. • Intrauterine device or intrauterine hormone-releasing system need to be in place at least ~~3 months before IMP administration~~ 2 months before the start of screening. • Bilateral tubal occlusion (for hysteroscopic "Essure®" a hysterosalpingogram is required 3 months post procedure to assess surgical success) or tubal ligation. • Vasectomized partner provided he is the sole sexual partner and has received medical assessment of the surgical success.	**Highly effective birth control methods in females** • Combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these should be initiated at least 7 days before the first dose of IMP. • Progestogen-only hormonal contraception (oral, injectable, or implantable) associated with inhibition of ovulation; these should be initiated at least 7 days before the first dose of IMP. • Intrauterine device or intrauterine hormone-releasing system need to be in place at least 2 months before the start of screening. • Bilateral tubal occlusion (for hysteroscopic "Essure®" a hysterosalpingogram is required 3 months post procedure to assess surgical success) or tubal ligation. • Vasectomized partner provided he is the sole sexual partner and has received medical assessment of the surgical success.	Aligned with previous information included in Section 4.1 Inclusion Criteria bullet c. Now only refer to Appendix J for details on birth control methods.
Unacceptable birth control methods: Periodic abstinence (eg, calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female condom and male condom should not be used together. **Male contraception:** Male patients (including vasectomized men) with ~~if their~~ partners are of childbearing potential (whether pregnant or not) must always use ~~a~~ condoms prior to IMP administration and until 20 weeks after last IMP dose.	**Unacceptable birth control methods:** Periodic abstinence (eg, calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female condom and male condom should not be used together. **Male contraception:** Male patients (including vasectomized men) with partners of childbearing potential (whether pregnant or not) must always use condoms prior to IMP administration and until 20 weeks after last IMP dose.	Aligned with previous information included in Section 4.1 Inclusion Criteria bullet c. Now only refer to Appendix J for details on birth control methods.

Original text with changes shown	New wording	Reason/Justification for change
Appendix L List of Prohibited Medications		
…will be discontinued from study treatment; under certain circumstances, a patient may be eligible to remain in the study when taking prohibited concomitant medications - such cases should be discussed with, and approved by, the medical monitor. I~~i~~f a patient has received…	…will be discontinued from study treatment; under certain circumstances, a patient may be eligible to remain in the study when taking prohibited concomitant medications - such cases should be discussed with, and approved by, the medical monitor. If a patient has received…	Clarification on using concomitant medications
Appendix T Additional Information to the Protocol for India		
Not applicable	For India, Cetirizine is to be used as the single H1 antihistamine at stable and fixed doses, not exceeding label recommendations, as a uniform standard treatment regimen, throughout the entire study according to Section 3.1.	New appendix added. Country specific instructions for the use of H1antihistamine in India

16.2. Administrative Letter 07 Dated 19 December 2022

ADMINISTRATIVE LETTER 07

Study number: TV45779-IMB-30086

Clinical Study Protocol with Amendment 03

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,

Approval date 10 May 2022

IND number: 145915; EudraCT number: 2021-001796-17

19 DEC 2022

Dear Investigator:

The purpose of this Administrative Letter is to document the decision of the Global Clinical Trial (GCT) Division, Central Drugs Standard Control Organization (CDSCO) of Ministry of Health and Family Welfare, New Dehli, India, concerning the conduct of Study TV45779-IMB-30086 in India.

The study is approved under File No. CT/22/000099 and permission is granted by the Central Licensing Authority to conduct clinical trial with the following conditions: "the H1-antihistamines (preferably the second generation H1-antihistamines in the approved dosage regimen) should be used as standard care and it shall be uniform across all the study sites in the country".

For India, the sponsor decided to use Cetirizine as the single H1 antihistamine at stable and fixed doses, not exceeding label recommendations, as a uniform standard treatment regimen, throughout the entire study according to Protocol Section 3.1.

These changes will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

Please feel free to contact [redacted] if you have any questions or concerns regarding this letter.

Sincerely,

DocuSigned by:

[redacted]

Cc: [redacted]

16.3. Administrative Letter 06 Dated 20 October 2022

ADMINISTRATIVE LETTER 06

Study number: TV45779-IMB-30086

Clinical Study Protocol with Amendment 03

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,

Approval date 10 May 2022

IND number: 145915; EudraCT number: 2021-001796-17

20 OCT 2022

Dear Investigator:

The purpose of this Administrative Letter is to document involvement of the laboratory Metropolis Healthcare Limited as the Central Clinical Laboratory for India.

As per protocol for Study TV45779-IMB-30086 (APPENDIX A), the Central Clinical Laboratory is:

- ACM Medical Laboratory, Inc., USA

ACM Medical Laboratory, Inc. has a laboratory in India with which they partner:

- Metropolis Healthcare Limited, India

Clinical laboratory tests for Indian sites will be performed at Metropolis Healthcare Limited in India. Accordingly, all collected samples such as clinical laboratory tests (ie, serum chemistry, hematology, and urinalysis), pharmacokinetics, pharmacodynamics and immunogenicity samples will be sent from the Indian sites to Metropolis Healthcare Limited.

Table 1 below summarizes the addition of the Indian Central Clinical Laboratory to APPENDIX A of the study protocol. The actual changes to the text are shown (revisions and additions are shown in bold and underline).

Table 1: Updates to APPENDIX A - Central Clinical Laboratory sites

Central Clinical Laboratory (except India)	ACM Medical Laboratory, Inc. 160 Elmgrove Park Rochester New York 14624, USA Tel: [redacted]
Central Clinical Laboratory (India	**Metropolis Healthcare Limited** **Plot No. 103** **Road No. 12** **MIDC** **Andheri (E)** **Mumbai – 400 093** **Maharashtra, India**

These changes will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

Please feel free to contact [redacted] if you have any questions or concerns regarding this letter.

Sincerely,

DocuSigned by:

[redacted]

Cc: [redacted]

16.4. Administrative Letter 05 Dated 01 August 2022

ADMINISTRATIVE LETTER 05

Study number: TV45779-IMB-30086

Clinical Study Protocol with Amendment 03

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,

Approval date 10 May 2022

IND number: 145915; EudraCT number: 2021-001796-17

01 AUG 2022

The purpose of this letter is to provide correction of discrepancies in protocol amendment 03 and align APPENDIX J. BIRTH CONTROL METHODS AND PREGNANCY TESTING with the information in Inclusion Criterion c of the protocol synopsis and Section 4.1

The actual changes to the text in APPENDIX J (italics) are shown below (revisions and additions are shown in bold and underlined; deletions are shown in strikethrough):

Highly effective birth control methods in females:

Highly effective birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered. Such methods include the following:

- *Combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these should be initiated at least ~~3 months before IMP administration~~ **7 days before the first dose of IMP**.*
- *Progestogen-only hormonal contraception (oral, injectable, or implantable) associated with inhibition of ovulation; these should be initiated at least ~~3 months before IMP administration~~ **7 days before the first dose of IMP**.*
- *Intrauterine device or intrauterine hormone-releasing system need to be in place at least ~~3 months before IMP administration~~ **2 months before the start of screening**.*
- *Bilateral tubal occlusion (for hysteroscopic "Essure®" a hysterosalpingogram is required 3 months post procedure to assess surgical success) **or tubal ligation**.*
- ***Vasectomized partner provided he is the sole sexual partner and has received medical assessment of the surgical success.***
- *Sexual abstinence is only considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.*

Teva Pharmaceuticals 145 Brandywine Parkway | West Chester, PA 19380 | Tel [redacted] www.tevapharm.com

These changes will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

Please feel free to contact [redacted] or [redacted] if you have any questions or concerns regarding this letter.

Sincerely,

DocuSigned by:

[redacted]

Cc: [redacted]

Teva Pharmaceuticals 145 Brandywine Parkway | West Chester, PA 19380 | Tel. [redacted] www.tevapharm.com

16.5. Amendment 03 Dated 10 May 2022

The primary reason for this amendment is to clarify details in the Study Protocol: number of ADA blood samples, align Inclusion Criterion in the protocol synopsis with those in the corresponding section of the protocol (Section 4.1), align Exclusion Criterion l with Inclusion Criterion b, clarify that COVID-19 testing at screening is mandatory. In addition, Appendix S ADDITIONAL INFORMATION TO THE PROTOCOL FOR SOUTH KOREA was added. All major changes to the protocol body are listed below in the table and are reflected in the synopsis, as applicable. Table 1 (Study Procedures and Assessments) has been revised to reflect changes described below. Minor editorial changes (typos, punctuation, etc) have been made to the protocol (and protocol synopsis, as appropriate).

Original text with changes shown	New wording	Reason/Justification for change
CLINICAL STUDY PROTOCOL SYNOPSIS and Section 3.1. General Study Design and Study Schematic Diagram		
The total duration of the study is up to 42 weeks.	The total duration of the study is up to 43 weeks.	Adding: up to 3 weeks of Screening period + 24 weeks of study treatment + 16 Follow Up
CLINICAL STUDY PROTOCOL SYNOPSIS. Inclusion criteria.		
f. …The patients must have diary entries during 4 of the 7 days prior to randomization.	f. …The patients must have diary entries during at least 4 of the 7 days prior to randomization.	To align Inclusion Criterion f in the protocol synopsis with Inclusion Criterion f in protocol section 4.1.
CLINICAL STUDY PROTOCOL SYNOPSIS, 9.4.2. Demographic and Baseline Characteristics and 9.7. SAFETY ANALYISIS		
CLINICAL STUDY PROTOCOL SYNOPSIS Changes in laboratory, ~~electrocardiogram (ECG),~~ and vital signs data will be summarized descriptively by treatment period. Descriptive summaries of serious adverse events, patient withdrawals due to adverse events, and potentially clinically significant abnormal values (clinical laboratory, ~~ECG~~ or vital signs) based on predefined criteria will be provided as well by treatment period. **9.4.2. Demographic and Baseline Characteristics** Patient demographic and baseline characteristics, including but not limited to, medical history, prior medications and therapies, ~~and ECG findings,~~ will be …. **9.7. SAFETY ANALYISIS**	**CLINICAL STUDY PROTOCOL SYNOPSIS** Changes in laboratory and vital signs data will be summarized descriptively by treatment period. Descriptive summaries of serious adverse events, patient withdrawals due to adverse events, and potentially clinically significant abnormal values (clinical laboratory or vital signs) based on predefined criteria will be provided as well by treatment period. **9.4.2. Demographic and Baseline Characteristics** Patient demographic and baseline characteristics, including but not limited to, medical history, prior medications and therapies, will be ….. **9.7. SAFETY ANALYISIS** Changes in laboratory and vital signs data will be summarized descriptively by treatment period…..	No detailed ECG data are captured in the database; thus, references to statistical analysis of ECG parameters were omitted from the protocol.

Original text with changes shown	New wording	Reason/Justification for change
Changes in laboratory, ~~ECG~~ and vital signs data will be summarized descriptively by treatment period….. Descriptive summaries of serious adverse events, patient withdrawals due to adverse events, and potentially clinically significant abnormal values (clinical laboratory, ~~ECG~~ or vital signs) based on predefined criteria will be provided as well by treatment period.	Descriptive summaries of serious adverse events, patient withdrawals due to adverse events, and potentially clinically significant abnormal values (clinical laboratory or vital signs) based on predefined criteria will be provided as well by treatment period.	
3.4 Stopping Rules for the Study		
• Additional criteria for pausing enrollment can be found in the IDMC charter.	• Additional criteria for pausing enrollment are: – A death for which the cause is judged to be related to the study drug by the treating investigator. – A life-threatening SAE judged to be related to the study drug by the treating investigator. – Any combination of 4 occurrences of Grade 3 or higher (per Common Terminology Criteria for Adverse Events [CTCAE] grading) toxicities that are assessed to be related to the study drug by the investigator. – For the same Preferred Term, 2 occurrences of Grade 3 or higher (per CTCAE grading) toxicities that are assessed to be related to the study drug by the investigator. – Any combination of 4 occurrences of a clinically significant Grade 3 or higher (per CTCAE grading) laboratory abnormality for different laboratory parameters assessed to be related to the study drug by the investigator. – Two occurrences of a clinically significant Grade 3 or higher (per CTCAE grading) laboratory abnormality for the same laboratory parameter that are assessed to be related to the study drug by investigator.	Reintroduction of recruitment stopping rules from DMC charter, without mentioning this document, since it should not be available to PIs.
3.5 Schedule of Study Procedures and Assessments		

Original text with changes shown	New wording	Reason/Justification for change
	Added: Medical history: any medical event relevant to eligibility and further participation should be collected and reported in source documents and CRF (eg, completely cured non-melanoma skin malignancy, hysterectomy, allergic diseases or any other significant medical event).	To clear things to report in medical history
4.1 INCLUSION CRITERIA AND APPENDIX J		
4.1 Inclusion criteria d. Male patients (including vasectomized) with partners who are of childbearing potential (whether pregnant or not) must use condoms ~~with spermicide~~ prior to IMP administration and until 20 weeks after last IMP dose. **Appendix J** **Male contraception:** Male patients must always use a condom ~~with spermicide~~ including vasectomized men if their partners are of childbearing potential. ~~The sponsor will provide condoms and spermicide at each visit to encourage further adherence to the contraceptive measures recommended in the study.~~	**Inclusion criteria** d. Male patients (including vasectomized) with partners who are of childbearing potential (whether pregnant or not) must use condoms prior to IMP administration and until 20 weeks after last IMP dose. **Male contraception:** Male patients must always use a condom including vasectomized men if their partners are of childbearing potential.	In light of the new knowledge that condoms with spermicide may not be available in all countries
Section 4.2. Exclusion Criterion l		
Any H1 antihistamines at greater than approved doses use within 3 days prior to the start of screening.	Any H1 antihistamines at greater than approved doses use from 3 days after the start of screening.	To align Exclusion Criterion l with Inclusion Criterion b,
5.5.1. Activity		
	Added: Blood donation is forbidden for the duration of the study.	To add this restriction where it belongs.

Original text with changes shown	New wording	Reason/Justification for change
5.6. Prior and Concomitant Medication or Therapy		
Any prior or concomitant medication (including prior CIU/CSU medication), or procedure a patient has had from 4 weeks before screening through the end of the study will be recorded in the source documentation and in the CRF. Trade name and international… Prohibited and restricted medications are listed in Appendix L.	Any prior or concomitant medication (including prior CIU/CSU medication), or procedure a patient has had from 4 weeks before screening through the end of the study will be recorded in the source documentation and in the CRF. Also, any prior intake of IMP and omalizumab (and any anti-IgE medications) before screening or treatment with an investigational agent within 30 days or longer depending on half-life (>5 half-lives) before screening needs to be recorded in the source documentation and in the CRF. Trade name and international... The list of prohibited medications and guidance rules are located in Appendix L.	Protocol was updated with requirements for reporting medical history To align with exclusion criteria e and f
7.1.5.2. Expectedness		
In this study, the reference safety information (RSI) ~~for TEV-45779~~ for determination of suspected serious adverse reaction is included in the IB… ~~The RSI of XOLAIR for this study is the USPI.~~ The sponsor's GPSP will determine the expectedness for all serious adverse events.	In this study, the reference safety information (RSI) for determination of suspected serious adverse reaction is included in the IB… The sponsor's Global Patient Safety and Pharmacovigilance (GPSP) will determine the expectedness for all serious adverse events.	Eventually, the safety team might want to switch to SmPC as the RSI, since it could be modified in the IB revision without making changes to the protocol.
Section 7.5.2.3. (Coronavirus Disease 2019 Testing)		
7.5.2.3. 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. COVID 19 testing will be performed locally ~~(if available) or centrally (if not available locally)~~ and reported in the CRF.	7.5.2.3. COVID-19 testing will be performed at screening (V1). In addition, the patient should be tested 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 and reported in the CRF.	To clarify that COVID-19 testing at screening (V1) is mandatory and that testing will only be performed locally.
8.3 Immunogenicity Testing		

Original text with changes shown	New wording	Reason/Justification for change
Blood samples (5 mL) for assessment of anti-drug antibody (ADA) response will be taken before drug administration at the time points indicated in Table 1.	Two blood samples (5 mL each) for assessment of anti-drug antibody (ADA) response will be taken before drug administration at the time points indicated in Table 1.	The volume of ADA blood samples should be increased for the purpose of possibly requested extended ADA analyses. This would increase the total blood volume in the study to 255 mL.
Table 1		
	Lettering for footnotes was changed from c onwards	A footnote had to be introduced for "Medical and surgical history" as letter c
	Rescue medication dispensation[q] (X added at V1) [q] Dispensation of rescue medication must be done at V1 and at other visits as required; dispensation on other visits will happen as needed to ensure that subject has sufficient rescue medication to cover the period till the next subject visit at max dose.	The Protocol is not specific about the expected timing for dispensation of rescue medication and it may be assumed it must be done at the baseline visit and also when it is required.
m. COVID-19 testing to be performed at screening, and the patient should be tested 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. COVID-19 testing to be performed at V1. In addition, the patient should be tested 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.	To clarify that COVID-19 testing at screening (V1) is mandatory and that testing will only be performed locally.
Table 5, footnote		
~~All injection site findings will be captured as adverse events and must be recorded and reported as specified in Section 7.1.5.~~	Injection site findings will not be captured as adverse events unless they fulfill characteristics that are beyond those in the specified forms/scales (eg, necrosis, abscess,	Injection site findings don't need to be

Original text with changes shown	New wording	Reason/Justification for change
	etc) or fulfill seriousness criteria and then they must be recorded and reported as specified in Section 7.1.	captured generally as adverse events
APPENDIX M		
~~**Specimen Sampling and Handling**~~ ~~For serum collection, samples will be collected in vacutainer tubes containing no anticoagulant and allowed to set at room temperature for between 1 and 1.5 hours to allow for serum separation to occur. Samples will then be centrifuged (2000 g, approximately 10 minutes, at 4 to 8°C). Separated serum (at least 1 mL) will be transferred in approximately equal portions into 2 opaque, labeled, polypropylene tubes (Sets A and B). The 2 aliquots (Set A and Set B) will be prepared for each analysis purpose i.e. for PK, for Total IgE and for free IgE.~~ ~~Labels for samples should include study number, patient randomization number, period, nominal collection time, Set A or B, and indication that they are PK samples or Total IgE samples or free IgE samples. Samples will be stored at a temperature -80°C (nominal) in an upright position until they are shipped to the central laboratory. If a -80°C (nominal) freezer is not available at the investigational site, serum samples will be stored at -20°C and should be transferred to -80°C (nominal) within the timeframe that the bioanalytical assays stability data at -20°C supports.~~ ~~**Shipment and Analysis of Samples**~~ ~~Serum samples for all patients will be shipped from the investigational center to the central laboratory, in dry ice with a temperature data logger. The central laboratory will be notified before the shipment of the samples and the shipping information will be sent when the samples are shipped. Primary and backup samples (Set A and Set B) are not to be sent in the same shipment. An electronic file containing sample collection dates will be emailed to the central laboratory and the sponsor's representatives from bioanalytical departments for each shipment.~~ ~~All samples will be stored at -80°C (nominal) in an upright position at the central laboratory until they are shipped to the bioanalytical laboratory (GBT) for analysis. The bioanalytical laboratory (GBT) will be notified before the shipment of the samples and the shipping information will be sent when the samples are shipped. All samples~~	Instructions for sampling, handling and shipment of the pharmacokinetics and pharmacodynamics samples are described in the TV45779-IMB-30086 Laboratory Manual. Samples should not be shipped on a holiday. Samples are not to arrive on the Israel weekend or a holiday. Samples will be analyzed using an appropriate validated method. Timing of the initiation of sample analysis will be determined by the management of bioanalytical laboratory responsible for the bioanalysis while keeping the study blinding, if any, intact.	Instructions for sampling, handling and shipment of the pharmacokinetics, and pharmacodynamics samples were modified and are described in detail in the latest version of the TV45779-IMB-30086 Laboratory Manual.

Original text with changes shown	New wording	Reason/Justification for change
~~should be shipped in dry ice with a temperature data logger. Primary and backup samples (Set A and Set B) are not to be sent in the same shipment. An electronic file containing sample collection dates will be emailed to the bioanalytical laboratory representatives for each shipment.~~ ~~Set A samples will be transported with a temperature data logger and frozen with dry ice sufficient for 4 days, by next-day courier to the bioanalytical laboratory (GBT).~~ ~~Set B samples will be sent to the same laboratory as that for Set A samples on a subsequent day by next-day courier.~~ ~~Instructions as to the disposition of the Set B samples will be provided by the sponsor.~~ Samples should not be shipped on a holiday. Samples are not to arrive on the Israel weekend or a holiday. Samples will be analyzed using an appropriate validated method. Timing of the initiation of sample analysis will be determined by the management of bioanalytical laboratory responsible for the bioanalysis while keeping the study blinding, if any, intact.		
APPENDIX N		
~~For serum collection, samples will be collected in vacutainer tubes containing no anticoagulant and allowed to set at room temperature for between 1 and 1.5 hours to allow for serum separation to occur. Samples will then be centrifuged (2000 g, approximately 10 minutes, at 4 to 8°C). Separated serum (at least 1 mL) will be transferred in approximately equal portions into 2 opaque, labeled, polypropylene tubes (Sets A and B).~~ ~~Labels for samples should include study number, patient randomization number, period, nominal collection time, Set A or Set B, and indication that they are anti-drug antibody (ADA) samples. Samples will be stored at –80°C (nominal) in an upright position until they are shipped to the central laboratory. If a –80°C (nominal) freezer is not available at the investigational site, serum samples will be stored at –20°C and should be transferred to –80°C (nominal) within the timeframe that the bioanalytical assays stability data at –20°C supports.~~	Instructions for sampling, handling and shipment of the immunogenicity samples are described in the TV45779-IMB-30086 Laboratory Manual. Samples should not be shipped on a holiday. Samples are not to arrive on the Israel weekend or a holiday. Samples will be analyzed using an appropriate validated method. Timing of the initiation of sample analysis will be determined by the management of bioanalytical laboratory responsible for the bioanalysis while keeping the study blinding, if any, intact.	Instructions for sampling, handling and shipment of the immunogenicity samples were modified and are described in detail in the latest version of the TV45779-IMB-30086 Laboratory Manual.

Original text with changes shown	New wording	Reason/Justification for change
~~**Shipment and Analysis of Samples**~~ ~~Serum samples for all patients will be shipped from the investigational center to the central laboratory, in dry ice with a temperature data logger. The central laboratory will be notified before the shipment of the samples and the shipping information will be sent when the samples are shipped. Primary and backup samples (Set A and Set B) are not to be sent in the same shipment. An electronic file containing sample collection dates will be emailed to the central laboratory and the sponsor's representatives from bioanalytical departments for each shipment.~~ ~~All samples will be stored at -80°C (nominal) in an upright position at central laboratory until they are shipped to the bioanalytical laboratory (GBT) for analysis. The bioanalytical laboratory (GBT) will be notified before the shipment of the samples and the shipping information will be sent when the samples are shipped. All samples to shipped in dry ice with temperature data logger. Primary and backup samples (Set A and Set B) are not to be sent in the same shipment. An electronic file containing sample collection dates will be emailed to the bioanalytical laboratory representatives for each shipment.~~ ~~Set A samples will be transported with a temperature data logger and frozen with dry ice sufficient for 4 days, by next-day courier to the bioanalytical laboratory (GBT).~~ ~~Set B samples will be sent to the same laboratory as that for Set A samples on a subsequent day by next-day courier. Instructions as to the disposition of the Set B samples will be provided by the sponsor.~~ Samples should not be shipped on a holiday. Samples are not to arrive on the Israel weekend or a holiday. Samples will be analyzed using an appropriate validated method. Timing of the initiation of sample analysis will be determined by the management of bioanalytical laboratory responsible for the bioanalysis while keeping the study blinding, if any, intact.		
APPENDIX S (NEW). ADDITIONAL INFORMATION TO THE PROTOCOL FOR SOUTH KOREA		

Original text with changes shown	New wording	Reason/Justification for change
	The sponsor sought advice for the study protocol regarding detailed study design and statistical analysis from the FDA (Type 2 meetings, 2020, 2021) and the EMA (Scientific Advice Meeting, 2020, SA Follow Up, 2020). The EMA agreed essentially to the study design proposed by the sponsor. Later, the FDA requested a different study design with at least 600 patients, inclusion of arms with 150 mg doses of TEV-45779 or XOLAIR and an additional co-primary endpoint of relative potency of 2 dose levels. Harmonization of study design according to the FDA requests was not accepted by the EMA. The sponsor incorporated the different requests into the study design. Therefore, the study protocol contains two statistical approaches for FDA and EMA, respectively. In this study, patients will be randomly assigned to 1 of the 4 treatment arms and may receive 150 mg or 300 mg doses of TEV-45779 or XOLAIR. Thus, patients from a specific country will be randomized to all treatment arms. Patients from South Korea will be part of the whole study population. Their data will be pooled and analyzed with the data from all study patients. There will be 1 primary analysis according to FDA criteria and 1 according to EMA criteria. The results of both analyses will be completely reported in the Clinical Study Report. As this is an investigational medicinal product, Teva has not determined at this time if a Marketing Authorization Application (MAA) will be submitted to the Ministry for Food and Drug Safety (MFDS). In the event that an MAA is submitted to the MFSD, Teva will determine the successfulness of this study result in South Korea by using EMA criteria as specific criteria for South Korea.	New additional information for South Korea

16.6. Administrative Letter 04 dated 23 February 2022

ADMINISTRATIVE LETTER 04

Study number: TV45779-IMB-30086

Clinical Study Protocol with Amendment 02

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

version date 23 November 2021

IND number: 145915; EudraCT number: 2021-001796-17

23 FEB 2022

The purpose of this letter is to provide clarification to the study protocol for South Korea, through the inclusion of the following information in APPENDIX S. ADDITIONAL INFORMATION TO THE PROTCOL FOR SOUTH KOREA:

The sponsor sought advice for the the study protocol regarding detailed study design and statistical analysis from the FDA (Type 2 meetings, 2020, 2021) and the EMA (Scientific Advice Meeting, 2020, SA Follow Up, 2020).
The EMA agreed essentially to the study design proposed by the sponsor.
Later, the FDA requested a different study design with at least 600 patients, inclusion of arms with 150 mg doses of TEV-45779 or XOLAIR and an additional co-primary endpoint of relative potency of 2 dose levels.

Harmonization of study design according to the FDA requests was not accepted by the EMA. The sponsor incorporated the different requests into the study design. Therefore, the study protocol contains two statistical approaches for FDA and EMA, respectively.

In this study, patients will be randomly assigned to 1 of the 4 treatment arms and may receive 150 mg or 300 mg doses of TEV-45779 or XOLAIR. Thus, patients from a specific country will be randomized to all treatment arms.

Patients from South Korea will be part of the whole study population. Their data will be pooled and analyzed with the data from all study patients.

There will be 1 primary analysis according to FDA criteria and 1 according to EMA criteria. The results of both analyses will be completely reported in the Clinical Study Report.

As this is an investigational medicinal product, Teva has not determined at this time if a Marketing Authorization Application (MAA) will be submitted to the Ministry for Food and Drug Safety (MFDS). In the event that an MAA is submitted to the MFSD, Teva will determine the successfulness of this study result in South Korea by using EMA criteria as specific criteria for South Korea.

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These changes will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

Please feel free to contact [redacted] if you have any questions or concerns regarding this letter.

Sincerely,

DocuSigned by:

[redacted]

[redacted]

Cc: [redacted]

Teva Pharmaceuticals 145 Brandywine Parkway | West Chester, PA 19380 | Tel. [redacted] | www.tevapharm.com

16.7. Administrative Letter 03 Dated 28 January 2022

ADMINISTRATIVE LETTER 03

Study number: TV45779-IMB-30086

Clinical Study Protocol with Amendment 02

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

version date 23 November 2021

IND number: 145915; EudraCT number: 2021-001796-17

28 JAN 2022

Dear Investigator:

The purpose of this letter is to clarify details in the Study Protocol:

1. The volume of ADA blood samples should be increased for the purpose of possibly requested extended ADA analyses. This would increase the total blood volume in the study to 255 mL, which complies with the total blood volume of "approximately 250 mL" as already covered by the Study Protocol (section 5.10. Total Blood Volume). In Study Protocol, section 8.3. (Immunogenicity Testing) relative to "IMP administration", the following sentence will be changed:

   "**Two** blood samples (5 mL **each**) for assessment of anti-drug antibody (ADA) response will be taken before drug administration at the time points indicated in Table 1."

2. Correction of a discrepancy to align Inclusion Criterion f in the protocol synopsis with Inclusion Criterion f in protocol section 4.1. Inclusion Criterion f in the protocol synopsis should read:

   "The patients must have diary entries during **at least** 4 of the 7 days prior to randomization."

3. Correction of a discrepancy to align Exclusion Criterion l with Inclusion Criterion b, 4th bullet point. This will affect exclusion criteria l in the Protocol synopsis and section 4.2. Exclusion Criterion l should read:

   "Any H1 antihistamines at greater than approved doses use ~~within~~ **from** 3 days ~~prior to~~ **after** the start of screening."

4. Clarification that COVID-19 testing at screening is mandatory. Table 1, footnote m and section 7.5.2.3. (Coronavirus Disease 2019 Testing) should read:

   "COVID-19 testing will be performed at screening**. In addition,** ~~and~~ **the patient should be tested** at any other time point during the study if the patient exhibits clinical

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symptoms that may indicate COVID-19 infection."

These changes will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

Please feel free to contact [redacted] if you have any questions or concerns regarding this letter.

Sincerely,

DocuSigned by:

31-Jan-2022 | 10:01 GMT [redacted]

Cc: [redacted]

Teva Pharmaceuticals, Inc. 145 Brandywine Parkway | West Chester, PA 19380 | Tel [redacted] www.tevapharm.com

16.8. Amendment 02 Dated 23 November 2021

The primary reason for this amendment is to clarify patient inclusion criteria, blinded statistical analysis and safety related activities such as study stop criteria, patient withdrawal criteria, add screening visit window and concomitant medication use. All major changes to the protocol body are listed below in the table and are reflected in the synopsis, as applicable. Table 1 (Study Procedures and Assessments) has been revised to reflect changes described below. Minor editorial changes (typos, punctuation, etc) have been made to the protocol (and protocol synopsis, as appropriate).

Original text with changes shown	New wording	Reason/Justification for change
Title Page		
Teva Pharmaceuticals ~~Development~~, Inc. 400 Interpace Parkway, Building A, Parsippany, NJ 07054, United States of America Similar changes have been applied to other text in this section	Teva Pharmaceuticals, Inc. 400 Interpace Parkway, Building A, Parsippany, NJ 07054, United States of America	Change in Sponsor name
Section 1.1.2 TEV-45779 and Chronic Idiopathic Urticaria/Chronic Spontaneous Urticaria		
… ~~CIU~~CSU in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment (XOLAIR Prescribing Information ~~11/2020~~7/2021).	… CSU in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment (XOLAIR Prescribing Information 7/2021).	Update of term from previously used CIU to new term CSU; update of the prescribing information publication date.
Section 1.1.2 TEV-45779 and Chronic Idiopathic Urticaria/Chronic Spontaneous Urticaria (other sections affected by this change: section 1.2.1, 1.2.2.3, 1.3.2, 1.3.3, 15)		
… ~~(XOLAIR Prescribing Information 11/2020)~~ (XOLAIR Prescribing Information 7/2021).	… (XOLAIR Prescribing Information 7/2021).	Update of the prescribing information publication date in multiple sections.
Section 1.2.2 Clinical Studies		
~~The~~Clinical data for TEV-45779 are available from the pivotal pharmacokinetic/pharmacodynamic study ~~of TEV-45779 (~~Study TV45779-BE-10160~~) started in December 2020~~. This first-in-human study ~~is~~was a phase I, single dose, 3-arm, parallel-group study in subjects with serum IgE levels of <100 IU/mL to demonstrate pharmacokinetic biosimilarity between TEV-45779 150 mg and XOLAIR 150 mg sourced from the US (US-licensed XOLAIR) and XOLAIR 150 mg sourced from the EU (EU-approved XOLAIR), and to evaluate pharmacodynamics based on total and free IgE. ~~All subjects (N=228) have been dosed with TEV-45779, XOLAIR (US) or XOLAIR (EU).~~ A total of 228 healthy subjects were enrolled into the study: 75 subjects were randomized to receive a single sc injection of TEV-	Clinical data for TEV-45779 are available from the pivotal pharmacokinetic/pharmacodynamic study TV45779-BE-10160. This first-in-human study was a phase I, single dose, 3-arm, parallel-group study in subjects with serum IgE levels of <100 IU/mL to demonstrate pharmacokinetic biosimilarity between TEV-45779 150 mg and XOLAIR 150 mg sourced from the US (US-licensed XOLAIR) and XOLAIR 150 mg sourced from the EU (EU-approved XOLAIR), and to evaluate pharmacodynamics based on total and free IgE. A total of 228 healthy subjects were enrolled into the study: 75 subjects were randomized to receive a single sc injection	Update section with new PK/PD information.

Original text with changes shown	New wording	Reason/Justification for change
45779, 76 subjects to XOLAIR EU, and 77 subjects to XOLAIR US. Blood sampling for PK, PD and ADA assessment and routine safety visits occurred up to 126 days after study drug administration. A blinded interim safety analysis was conducted after completion of the Day 29 visit (28 days post-dose; cut-off date: 19 April 2021). ~~The adverse events and other blinded~~ Overall, 218 (96%) subjects completed the study. From the 10 subjects who withdrew from the study: 7 subjects were in the TEV-45779 group, 1 subject in the XOLAIR EU group, and 2 subjects in the XOLAIR US group. The most frequent reason for withdrawal was lost to follow-up, which occurred in 4 subjects in the TEV-45779 group and 1 subject in the XOLAIR US group. A further 3 subjects were withdrawn due to pregnancy (2 in the TEV-45779 group and 1 subject in the XOLAIR EU group), and 2 subjects withdrew voluntarily (1 subject in each of the TEV-45779 and XOLAIR US groups). 1.2.2.1. Pharmacokinetics Omalizumab serum concentrations were measured in serum samples for up to 126 days after administration of TEV-45779, XOLAIR US, or XOLAIR EU using a validated assay. All 3 groups had a similar mean omalizumab serum concentration-time profile. Pharmacokinetic similarity was demonstrated between TEV-45779 and XOLAIR US, TEV-45779 and XOLAIR EU, and XOLAIR US and XOLAIR EU: for each of the 2 co-primary endpoints (Cmax and AUC0-∞), the 90% confidence intervals (CI) for the GMRs were fully contained within the pre-defined limits of 0.8000 to 1.2500. Evaluation of the secondary pharmacokinetic parameters (time to maximum observed drug concentration [tmax], percentage extrapolated area under the concentration-time curve [%AUCext], apparent total body clearance [CL/F], apparent volume of distribution [Vz/F], terminal elimination rate constant [λz] and	of TEV-45779, 76 subjects to XOLAIR EU, and 77 subjects to XOLAIR US. Blood sampling for PK, PD and ADA assessment and routine safety visits occurred up to 126 days after study drug administration. A blinded interim safety analysis was conducted after completion of the Day 29 visit (28 days post-dose; cut-off date: 19 April 2021). Overall, 218 (96%) subjects completed the study. From the 10 subjects who withdrew from the study: 7 subjects were in the TEV-45779 group, 1 subject in the XOLAIR EU group, and 2 subjects in the XOLAIR US group. The most frequent reason for withdrawal was lost to follow-up, which occurred in 4 subjects in the TEV-45779 group and 1 subject in the XOLAIR US group. A further 3 subjects were withdrawn due to pregnancy (2 in the TEV-45779 group and 1 subject in the XOLAIR EU group), and 2 subjects withdrew voluntarily (1 subject in each of the TEV-45779 and XOLAIR US groups). 1.2.2.1. Pharmacokinetics Omalizumab serum concentrations were measured in serum samples for up to 126 days after administration of TEV-45779, XOLAIR US, or XOLAIR EU using a validated assay. All 3 groups had a similar mean omalizumab serum concentration-time profile. Pharmacokinetic similarity was demonstrated between TEV-45779 and XOLAIR US, TEV-45779 and XOLAIR EU, and XOLAIR US and XOLAIR EU: for each of the 2 co-primary endpoints (Cmax and AUC0-∞), the 90% confidence intervals (CI) for the GMRs were fully contained within the pre-defined limits of 0.8000 to 1.2500. Evaluation of the secondary pharmacokinetic parameters (time to maximum observed drug concentration [tmax], percentage extrapolated area under the concentration-time curve [%AUCext], apparent total body clearance [CL/F], apparent volume of distribution [Vz/F], terminal	

Original text with changes shown	New wording	Reason/Justification for change
terminal elimination half-life [t½]) and partial AUCs supports that the pharmacokinetics of the 3 treatments are similar. 1.2.2.2. Pharmacodynamics Pharmacodynamic similarity was evaluated comparing the change of free and total IgE in serum following drug administration. TEV-45779, XOLAIR EU, and XOLAIR US had similar mean free IgE and total IgE concentration time profiles for both total and free IgE. For each pharmacodynamic parameter evaluated (negative AUEC of free IgE change from baseline, positive AUEC of total IgE change from baseline, Cmin,IgE,free, and Cmax,IgE,total), the results were descriptively similar for each treatment group. 1.2.2.3. Safety and immunogenicity The proportion of subjects reporting adverse events and treatment-related adverse events was low and similar between treatment groups. All adverse events were mild or moderate in severity. There were no deaths, other serious adverse events, or withdrawals due to adverse events, and no protocol defined adverse events of special interest (ie, anaphylaxis). There were no findings of clinical importance in any treatment group for vital signs, ECGs, or clinical laboratory data. Local tolerability at the injection site was good following sc administration of each treatment, with no clinically meaningful differences between the groups. Anti-drug antibody formation occurred during the study for 30 to 40% of subjects in each group, with no substantial difference between TEV-45779, XOLAIR EU, and XOLAIR US. ADA had returned to baseline levels at the last sampling point, 126 days post dose. Only a small percentage of ADA-positive subjects tested positive for neutralizing ADA during the study. The adverse events and other safety data observed after dosing of 228 healthy subjects are in line with the known safety profile of XOLAIR (~~XOLAIR Prescribing Information 11/2020~~ XOLAIR Prescribing Information 7/2021; XOLAIR Summary of Product Characteristics 08/2020) and also with events expected in a healthy study population.	elimination rate constant [λz] and terminal elimination half-life [t½]) and partial AUCs supports that the pharmacokinetics of the 3 treatments are similar. 1.2.2.2. Pharmacodynamics Pharmacodynamic similarity was evaluated comparing the change of free and total IgE in serum following drug administration. TEV-45779, XOLAIR EU, and XOLAIR US had similar mean free IgE and total IgE concentration time profiles for both total and free IgE. For each pharmacodynamic parameter evaluated (negative AUEC of free IgE change from baseline, positive AUEC of total IgE change from baseline, Cmin,IgE,free, and Cmax,IgE,total), the results were descriptively similar for each treatment group. 1.2.2.3. Safety and immunogenicity The proportion of subjects reporting adverse events and treatment-related adverse events was low and similar between treatment groups. All adverse events were mild or moderate in severity. There were no deaths, other serious adverse events, or withdrawals due to adverse events, and no protocol defined adverse events of special interest (ie, anaphylaxis). There were no findings of clinical importance in any treatment group for vital signs, ECGs, or clinical laboratory data. Local tolerability at the injection site was good following sc administration of each treatment, with no clinically meaningful differences between the groups. Anti-drug antibody formation occurred during the study for 30 to 40% of subjects in each group, with no substantial difference between TEV-45779, XOLAIR EU, and XOLAIR US. ADA had returned to baseline levels at the last sampling point, 126 days post dose. Only a small percentage of ADA-positive subjects tested positive for neutralizing ADA during the study. The adverse events and other safety data observed after dosing of 228 healthy subjects are in line with the known safety profile of XOLAIR (XOLAIR Prescribing	

Original text with changes shown	New wording	Reason/Justification for change
Clinical data on omalizumab, the reference product, have been published in the scientific literature (Rivière et al 2011) and in the XOLAIR US Prescribing Information (USPI) (XOLAIR Prescribing Information 11/2020),(XOLAIR Prescribing Information 7/2021), EU Summary of Product Characteristics (SmPC) (XOLAIR Summary of Product Characteristics 08/2020), and Canadian Consumer Information Leaflet (XOLAIR Consumer Information 04/2017). Since TEV 45779 is being developed as a biosimilar candidate to XOLAIR, the clinical findings for TEV 45779 are expected to be similar to those of XOLAIR, particularly the safety, pharmacokinetic, pharmacodynamic, immunogenicity response, and efficacy profiles. Further information can be found in the current version of the TEV-45779 IB.	Information 7/2021; XOLAIR Summary of Product Characteristics 08/2020) and also with events expected in a healthy study population. Clinical data on omalizumab, the reference product, have been published in the scientific literature (Rivière et al 2011) and in the XOLAIR US Prescribing Information (USPI) (XOLAIR Prescribing Information 7/2021), EU Summary of Product Characteristics (SmPC) (XOLAIR Summary of Product Characteristics 08/2020), and Canadian Consumer Information Leaflet (XOLAIR Consumer Information 04/2017). Since TEV-45779 is being developed as a biosimilar candidate to XOLAIR, the clinical findings for TEV-45779 are expected to be similar to those of XOLAIR, particularly the safety, pharmacokinetic, pharmacodynamic, immunogenicity response, and efficacy profiles. Further information can be found in the current version of the TEV-45779 IB.	
Section 1.3.1 Known and Potential Benefits and Risks of TEV045779		
~~To date (19 April 2021) no~~No safety concerns have been observed in Study TV45779-BE-10160 (Section 1.2.2). Since TEV 45779 is being developed as a proposed biosimilar to XOLAIR, treatment risks with TEV 45779 are anticipated based on the safety information for the use of XOLAIR in the US and EU.	No safety concerns have been observed in Study TV45779-BE-10160 (Section 1.2.2). Since TEV 45779 is being developed as a proposed biosimilar to XOLAIR, treatment risks with TEV 45779 are anticipated based on the safety information for the use of XOLAIR in the US and EU.	Remove the reference date of information as the date would always be the protocol approval date.
Section 3.1 General Study Design and Study Schematic Diagram (other sections affected by this change: section 5.8)		
… Patients in the 300 mg groups will receive 2 sc injections of 150 mg IMP whereas patients in the 150 mg groups will receive 1 sc injection of 150 mg IMP and an additional placebo injection in order to administer 2 injections per dosing in all groups and, thereby, ensure ~~patients continue to be blinded~~ maintaining of the blind to treatment. …	… Patients in the 300 mg groups will receive 2 sc injections of 150 mg IMP whereas patients in the 150 mg groups will receive 1 sc injection of 150 mg IMP and an additional placebo injection in order to administer 2 injections per dosing in all groups and, thereby, ensure maintaining of the blind to treatment. …	Generalize the need to maintain the treatment blind - not only for the patient. Correction of reference visit for the dosing level

Original text with changes shown	New wording	Reason/Justification for change
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 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.	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 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.	
Section 3.4 Stopping Rules for the Study		
During the conduct of the study, serious adverse events will be reviewed (Section 7.1.5) as they are reported from the investigational centers to identify safety concerns. The study may be terminated by the sponsor for any reason at any time. For example, the sponsor should terminate the study in the event of: • New toxicological or pharmacological findings or safety issues invalidate the earlier positive benefit risk assessment. • Discontinuation of the development of the IMP. • Additional criteria for pausing enrollment can be found in the IDMC charter. ~~If any of the below mentioned criteria are met, enrollment will be paused for a safety review by the IDMC (Section 5.9.2):~~ ~~• A death for which the cause is judged to be related to the study drug by the treating investigator;~~ ~~• A life-threatening serious adverse event judged to be related to the study drug by the treating investigator;~~ ~~• 2 occurrences of Grade 3 or higher (per Common Terminology Criteria for Adverse Events [CTCAE] grading) adverse events that are assessed to be related to the study drug by the investigator;~~	During the conduct of the study, serious adverse events will be reviewed (Section 7.1.5) as they are reported from the investigational centers to identify safety concerns. The study may be terminated by the sponsor for any reason at any time. For example, the sponsor should terminate the study in the event of: • New toxicological or pharmacological findings or safety issues invalidate the earlier positive benefit risk assessment. • Discontinuation of the development of the IMP. • Additional criteria for pausing enrollment can be found in the IDMC charter. If the whole study or arms of the study will be stopped, the patients that are terminated early will be followed according to Withdrawal Criteria and Procedures for the Patient (Section 4.3).	Remove these stopping criteria from the protocol and refer the reader to the IDMC charter. This will allow modifying stopping criteria without requiring a protocol amendment.

Original text with changes shown	New wording	Reason/Justification for change
~~• 2 occurrences of a clinically significant Grade 3 or higher (per CTCAE grading) laboratory abnormality assessed to be related to the study drug by the investigator.~~ If the whole study or arms of the study will be stopped, the patients that are terminated early will be followed according to Withdrawal Criteria and Procedures for the Patient (Section 4.3).		
Section 3.5 Schedule of Study Procedures and Assessments		
Table 1: Study Procedures and Assessments		
See new wording column	Table 1 has been revised as described below: The visit window for V2 (week -1) was changed from 0 days to -2 days	Add a visit window to V2 for scheduling flexibility
… [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 … [d] 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. … ~~g~~[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 ~~not~~ have ~~any missing~~ diary entries during at least 4 of the 7 days prior to randomization on day 1.	… [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 … [d] 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. … [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.	Specify the minimal interval between V1 and V2 since the windows all for a very short interval and also clarify the 3 days required for patients that adjust their H1 antihistamines during screening; IMP injection sites to be aligned with the pharmacy manual and update to new eDiary compliance requirements. Footnotes were relabeled to remain consistent with the table and the body of the protocol
Section 4.1 Patient Inclusion Criteria		

Original text with changes shown	New wording	Reason/Justification for change
See new wording column	Footnote added to inclusion criteria b (bullet 2): Refer to Section 9.3.1 for handling of missing data for daily and weekly scores.	eDiary compliance was changed and now allows missing data as part of this inclusion criteria instead of the original full 7 days

Original text with changes shown	New wording	Reason/Justification for change
… b. Diagnosis of CIU/CSU refractory to H1 antihistamines at the time of randomization, as defined by all of the following: - The presence of itch and wheals for ≥8 consecutive weeks at any time prior to enrollment despite current use of H1 antihistamine treatment during this time period. - Weekly urticaria activity score (UAS7; sum of the daily number of wheals score and itch severity score over 7 days) ≥16 (range 0 42) and itch component of UAS7 ≥8 (range 0 21) during 7 days prior to randomization. - Urticaria activity score (UAS) ≥4 assessed by a clinician on ≥1 of the screening visit days. - Patients must have been on an approved dose of an H1 antihistamine for CIU/CSU for ≥3 consecutive days immediately prior to the start of screening and must document current use on the day of the initial screening visit, OR, have their H1 antihistamine for CIU/CSU adjusted to an approved dose during the first 3 days of screening and have their adjusted use documented at the end of the dose adjustment. - CIU/CSU diagnosis for ≥3 months. … c. Bilateral tubal occlusion or tubal ligation. … d. Male patients (including vasectomized) with partners who are of childbearing potential (whether pregnant or not) must use condoms with spermicide prior to IMP administration and until 20 weeks after last IMP dose. … f. Must be willing and able to comply with study requirements and procedures as specified in this protocol. In particular, the patient must be willing and able to complete a daily symptom diary for the duration of the study. The patients must ~~not~~ have ~~any missing~~ diary entries during at least 4 of the 7 days prior to randomization.	… b. Diagnosis of CIU/CSU refractory to H1 antihistamines at the time of randomization, as defined by all of the following: - The presence of itch and wheals for ≥8 consecutive weeks at any time prior to enrollment despite current use of H1 antihistamine treatment during this time period. - Weekly urticaria activity score (UAS7; sum of the daily number of wheals score and itch severity score over 7 days) ≥16 (range 0 42) and itch component of UAS7 ≥8 (range 0 21) during 7 days prior to randomization. - Urticaria activity score (UAS) ≥4 assessed by a clinician on ≥1 of the screening visit days. - Patients must have been on an approved dose of an H1 antihistamine for CIU/CSU for ≥3 consecutive days immediately prior to the start of screening and must document current use on the day of the initial screening visit, OR, have their H1 antihistamine for CIU/CSU adjusted to an approved dose during the first 3 days of screening and have their adjusted use documented at the end of the dose adjustment. - CIU/CSU diagnosis for ≥3 months. … c. Bilateral tubal occlusion or tubal ligation. … d. Male patients (including vasectomized) with partners who are of childbearing potential (whether pregnant or not) must use condoms with spermicide prior to IMP administration and until 20 weeks after last IMP dose. … f. Must be willing and able to comply with study requirements and procedures as specified in this protocol. In particular, the patient must be willing and able to complete a daily symptom diary for the duration of the study. The patients must have diary entries during at least 4 of the 7 days prior to randomization.	Allow H1 histamine adjustments during the screening period in consideration of any patients who will be on higher that approved treatment doses at screening; extend the highly effective birth control methods and align type of male condom with appendix J ; Adjust eDiary Compliance requirements for determining patient eligibility.

Original text with changes shown	New wording	Reason/Justification for change
Section 4.2. Exclusion Criteria		
… f. Previous treatment with omalizumab or other Anti-IgE therapy within a year prior to the start of screening. …	… f. Previous treatment with omalizumab or other Anti-IgE therapy within a year prior to the start of screening. …	Clarify specific exclusion criteria, aligned with appendix L
Section 4.3. Withdrawal Criteria and Procedures for the Patient		
… 4. Patient takes prohibited concomitant medications as defined in this protocol (see appendix L). Under certain circumstances, a patient may be eligible to remain in the study when taking prohibited concomitant medications - such cases should be discussed with, and approved by, the medical monitor. … 8. A female patient has a confirmation of pregnancy during the study from a positive serum pregnancy test.	… 4. Patient takes prohibited concomitant medications as defined in this protocol (see appendix L). Under certain circumstances, a patient may be eligible to remain in the study when taking prohibited concomitant medications - such cases should be discussed with, and approved by, the medical monitor. … 8. A female patient has a confirmation of pregnancy during the study from a positive serum pregnancy test.	Modify the withdrawal criteria due to use of conmeds – allowing patients to continue is study under certain circumstances. Specifying the withdrawal rule due to pregnancy as required by the Czech Republic CA.
Section 4.5. Re-screening		
~~Patients may not be re-screened.~~ A patient who is screened but not enrolled (eg, because inclusion and exclusion criteria were not met or enrollment did not occur within the specified time) may be considered for re-screening 1 time if there is a change in the patient's medical background or other relevant change. (Note: the medical monitor should approve re-screening after review of the enabling reasons.) If the patient is re-screened, a new informed consent form (ICF) will need to be signed and all study assessments will need to be repeated.	A patient who is screened but not enrolled (eg, because inclusion and exclusion criteria were not met or enrollment did not occur within the specified time) may be considered for re-screening 1 time if there is a change in the patient's medical background or other relevant change. (Note: the medical monitor should approve re-screening after review of the enabling reasons.) If the patient is re-screened, a new informed consent form (ICF) will need to be signed and all study assessments will need to be repeated.	Allow one re-screening of a patient who previously screen failed and the process for obtaining this approval.
Section 5.1. Investigational Medicinal Products Used in the Study		
Table 2: Investigational Medicinal Products Used in the Study		
See new wording column	Table 2 has been revised as described below: Manufacturer of the reference drug XOLAIR was changed from ~~Novartis AG Forum 1, Novartis Campus, CH 4056 Basel, Switzerland~~	Update the reference drug manufacturer address.

Original text with changes shown	New wording	Reason/Justification for change
	to Novartis Pharma GmbH, Roonstrasse 25, D-90429, Nuremberg, Germany.	
Section 5.8. Randomization nd Blinding		
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). Patients in the 150 mg groups will receive an additional placebo injection in order to administer 2 injections per dosing in all groups and, thereby, ensure ~~patients continue to be blinded~~ maintaining of the blind to treatment. At Week 12, prior to receiving their fourth dose of study medication, patients in the XOLAIR treatment group will be re-randomized 1:1 to receive 3 additional doses of XOLAIR (at the same dose level as prior to re-randomization) or switch to 3 doses of TEV 45779 (at the same dose level as prior to re-randomization) for the transition period. All patients in the TEV 45779 group will continue to receive TEV 45779 during the transition period at the same dose level as prior to re-randomization. During the ~~study~~ main treatment period, the sponsor, investigators (~~and~~ including other site staff involved in study assessments) and patients will be blinded to the treatment assignment of all patients. To ~~maintain~~ assure continued blinding to the treatment ~~assignment,~~ assignments after the main treatment period, re-randomization ~~process~~ will be performed for all patients, including ~~the~~ patients in the TEV 45779 group (although only patients in the XOLAIR arm will actually be re randomized while patients in the TEV 45779 group will continue to receive TEV 45779 in the transition period). The randomization will be implemented using a Randomization and Trial Supply Management (RTSM) system. Further details on unblinding during the transition and follow-up periods are provided in Section 5.9.1.	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). Patients in the 150 mg groups will receive an additional placebo injection in order to administer 2 injections per dosing in all groups and, thereby, ensure maintaining of the blind to treatment. At Week 12, prior to receiving their fourth dose of study medication, patients in the XOLAIR treatment group will be re-randomized 1:1 to receive 3 additional doses of XOLAIR (at the same dose level as prior to re-randomization) or switch to 3 doses of TEV 45779 (at the same dose level as prior to re-randomization) for the transition period. All patients in the TEV 45779 group will continue to receive TEV 45779 during the transition period at the same dose level as prior to re-randomization. During the main treatment period, the sponsor, investigators (including other site staff involved in study assessments) and patients will be blinded to the treatment assignment of all patients. To assure continued blinding to the treatment assignments after the main treatment period, re-randomization will be performed for all patients, including patients in the TEV 45779 group (although only patients in the XOLAIR arm will actually be re randomized while patients in the TEV 45779 group will continue to receive TEV 45779 in the transition period). The randomization will be implemented using a Randomization and Trial Supply Management (RTSM) system. Further details on unblinding during the transition and follow-up periods are provided in Section 5.9.1.	Correct how the blinding and randomization is performed and differentiate between sponsor and non-sponsor blinding.
Section 5.9.1 Blinding and Unblinding		

Original text with changes shown	New wording	Reason/Justification for change
… In order to ensure additional patient blinding, a blindfold with an additional pillow at chest level (or similar device) will be used during the IMP injection as a shield to hide the IMP from the patient. 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. Staff responsible for pharmacokinetic and immunogenicity bioanalysis, population pharmacokinetics, and/or pharmacokinetics/pharmacodynamics model will not have access to the patient treatment randomization prior to unblinding the study (before final DBL). During the transition period, the sponsor, investigators (and other site staff involved in study assessments) and patients will be blinded to the randomized treatment of patients who received XOLAIR US in the main treatment period and are re randomized for the transition period. ~~Before final database lock (DBL), staff responsible for pharmacokinetic and immunogenicity bioanalysis will not have access to the patient treatment randomization.~~ After last patient last visit and DBL of the main treatment period, the sponsor will unblind the treatments for the analysis of the main treatment period (up to and including week 12; not including fourth IMP dose and assessments following the fourth dose). A full CSR may be prepared with all data up to week 12 (end of main treatment phase procedures). Only after completion of the study (after Week 40), final DBL and formal request to unblind from the sponsor statistician, will the study be fully unblinded and analyzed. The results will be reported separately in a CSR addendum, including any updates to the safety analysis of the main treatment period. If a full CSR is	… In order to ensure additional patient blinding, a blindfold with an additional pillow at chest level (or similar device) will be used during the IMP injection as a shield to hide the IMP from the patient. 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. Staff responsible for pharmacokinetic and immunogenicity bioanalysis, population pharmacokinetics, and/or pharmacokinetics/pharmacodynamics model will not have access to the patient treatment randomization prior to unblinding the study (before final DBL). During the transition period, investigators (and other site staff involved in study assessments) and patients will remain blinded to the randomized treatment of patients who received XOLAIR in the main treatment period and are re-randomized for the transition period. After last patient last visit and DBL of the main treatment period, the sponsor will unblind the treatments for the analysis of the main treatment period (up to and including week 12; not including fourth IMP dose and assessments following the fourth dose). A full CSR may be prepared with all data up to week 12 (end of main treatment phase procedures). Only after completion of the study (after Week 40), final DBL and formal request to unblind from the sponsor statistician, will the study be fully unblinded and analyzed. The results will be reported separately in a CSR addendum, including any updates to the safety analysis of the main treatment period. If a full CSR is not prepared after the main treatment period, then the full study results will be analyzed in a single CSR after end of study.	Clarify the IMP injection site. Reinstate the analysis of the main treatment period based on newly available FDA input. Remove redundant section that is already detailed two paragraphs above.

Original text with changes shown	New wording	Reason/Justification for change
not prepared after the main treatment period, then the full study results will be analyzed in a single CSR after end of study. …	…	
Section 9.2.9. Per-Protocol Analysis Set		
… 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 of the main treatment period for the analysis. ~~of the main treatment period~~.	… 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 of the main treatment period for the analysis.	Clarify the unblinding language to refer to the main treatment period only; as this analysis is related to week 12 data.
Section 9.3.1. Handling Withdrawals and Missing Data		
… To account for ~~the~~ missing itch severity, wheal or urticaria activity 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.	… To account for missing itch severity, wheal or urticaria 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 – If 4-7 daily scores are available for the calculation of the weekly score, the ISS7 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 (ie, 4-7 daily scores are missing), the ISS7 will be considered missing for that week.	Describe use of this strategy beyond the itch severity score and also in support of the newly added footnote to inclusion criteria b.
Section 9.11. Planned Interim Analysis		
~~An interim analysis (IA) may be conducted after all subjects have completed the main treatment period in order to facilitate Teva's decision regarding additional studies in the clinical development program for TEV-45779 prior to the completion of the current study. If performed, the IA will not have any impact on the conduct and analyses of this study. The IA will be conducted by an external Independent Statistician while keeping Teva and the~~	No interim analysis is planned for this study.	Remove the interim analysis and replace with a final analysis for efficacy in other sections.

Original text with changes shown	New wording	Reason/Justification for change
~~study team blinded. No actual numeric results or data will be shared with Teva and the study team. The only information that will be provided to Teva by the Independent Statistician is the Yes/No result for each co-primary comparison for FDA and EMA biosimilarity assessment (see Section 9.5.1.1 for details). As the IA does not introduce any inflation to the Type I error rate of the final analysis of the study, no adjustments of the nominal significance level are required.~~ No interim analysis is planned for this study.		
APPENDIX A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS		
[redacted] ICON PRA Health Sciences Gottlieb-Daimler-Strasse 10 68165 Mannheim, Germany Tel: [redacted] Medical monitoring support center contact information: Americas: [redacted] (toll-free) or direct at: [redacted] EAPA: [redacted] PRA Health Sciences has been acquired by ICON plc, creating the world's most advanced healthcare intelligence and clinical research organization. … [redacted] -Coordinating Investigator [redacted]	[redacted] ICON PRA Health Sciences Gottlieb-Daimler-Strasse 10 68165 Mannheim, Germany Tel: [redacted] Medical monitoring support center contact information: Americas: [redacted] (toll-free) or direct at: [redacted] EAPA: [redacted] PRA Health Sciences has been acquired by ICON plc, creating the world's most advanced healthcare intelligence and clinical research organization. … Coordinating Investigator [redacted]	Update table in the following sections, including changes to some of the role titles: - Sponsor's Medical Expert - Coordinating Investigator - RTSM - Trial Supply Vendors

Original text with changes shown	New wording	Reason/Justification for change
[redacted] … ~~Interactive Voice Recognition System~~ Randomization and Trial Supply Management (RTSM) System … ~~Non US sites~~ Secondary Labeling and Distribution Almac Clinical Services (Almac Group Limited) 20 Seagoe Industrial Estate, Craigavon, BT63 5QD, Northern Ireland, UK [redacted] Tel: [redacted] ~~US Sites~~ Secondary Labeling and Distribution Actavis Laboratories UT, Inc 577 Chipeta Way Salt Lake City, UT 84108, USA [redacted] Tel: [redacted]	[redacted] … Randomization and Trial Supply Management (RTSM) System … Secondary Labeling and Distribution Almac Clinical Services (Almac Group Limited) 20 Seagoe Industrial Estate, Craigavon, BT63 5QD, Northern Ireland, UK [redacted] Tel: [redacted] Secondary Labeling and Distribution Actavis Laboratories UT, Inc 577 Chipeta Way Salt Lake City, UT 84108, USA [redacted] Tel: [redacted]	
APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT		
1. Procedures for Screening (Visits 1 and 2, Up to 3 week Period)		
The screening visit (visits 1 and 2) will take place not more than ~~18~~ 21 days before the baseline visit (visit 3). The interval between V1 and V2 should be at least 5 days; patients that require a 3-day	The screening visit (visits 1 and 2) will take place not more than 21 days before the baseline visit (visit 3). The interval between V1 and V2 should be at least 5 days; patients that require a 3-day adjustment period to reach an approved	Describe new interval requirements between V1 and V2 and 3-day adjustment to normal dose

Original text with changes shown	New wording	Reason/Justification for change
adjustment period to reach an approved dose of their H1 antihistamine treatment will need an interval of at least 8 days. … b. Visit 2 (Day -7-2 days) …	dose of their H1 antihistamine treatment will need an interval of at least 8 days. … b. Visit 2 (Day -7-2 days) …	which is now part of the screening process. Add a 2 day window to allow V2 scheduling flexibility.
APPENDIX L: LIST OF PROHIBITED MEDICATIONS		
See new wording column	• First column (Trade Name) was deleted • INN / Formulation columns updated as follows: - INN: Omalizumab or other Anti-IgE therapies - INN: Dupilumab, Benralizumab / Formulation: Injection (sc) - INN: Dapsone, Sulfasalazine / Formulation: Injection (sc) - INN: Cyclosporine, Tacrolimus, Mycophenolate / Formulation: Systemic or cutaneous (topical)	The medication trade name is not useful considering the numerous countries and variations. Add/update with new prohibited medications based on current clinical understanding.
… Routine (daily or every other day during 5 or more consecutive days) doses of the following medications within 30 days prior to day 14: systemic or cutaneous (topical) corticosteroids (prescription or over the counter), hydroxychloroquine, methotrexate, cyclosporine, ~~or~~ cyclophosphamide, Tacrolimus, mycophenolate, dapsone, or sulfasalazine. … Omalizumab or other anti-IgE therapy within 1 year prior to screening. … Any H1 antihistamines at greater than approved doses ~~within~~ from 3 days ~~prior~~ after start of screening ~~to day 14~~. …	… Routine (daily or every other day during 5 or more consecutive days) doses of the following medications within 30 days prior to day 14: systemic or cutaneous (topical) corticosteroids (prescription or over the counter), hydroxychloroquine, methotrexate, cyclosporine, cyclophosphamide, Tacrolimus, mycophenolate, dapsone, or sulfasalazine. … Omalizumab or other anti-IgE therapy within 1 year prior to screening. … Any H1 antihistamines at greater than approved doses from 3 days after start of screening. …	Add/update with new prohibited medications based on current clinical understanding. Clarify when H1 antihistamines are prohibited to be aligned with updated inclusion criteria b.

Original text with changes shown	New wording	Reason/Justification for change
APPENDIX R: CTCAE GRADING SCALE		
See new wording column	The CTCAE Grading Scale will be provided as a separate document.	Eliminate the need to print out the entire CTCAE grading scale as part of the protocol.

16.9. Administrative Letter 02 Dated 10 November 2021

ADMINISTRATIVE LETTER 02

Study number: TV45779-IMB-30086

Clinical Study Protocol with Amendment 01

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

version date 11 June 2021

IND number: 145915; EudraCT number: 2021-001796-17

10 NOV 2021

Dear Investigator:

The purpose of this letter is to clarify details in the Study Protocol on the injection site for the investigational medicinal products (IMP).

1. In Study Protocol Synopsis (Investigational Medicinal Products: Dose, Pharmaceutical Form, Route of Administration, and Administration Rate), section 5.9.1 (Blinding and Unblinding), and Table 1, "Study Procedures and Assessments" footnote c. relative to "IMP administration", the following statement will be added:

   "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."

These changes will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

Please feel free to contact [redacted] if you have any questions or concerns regarding this letter.

Sincerely,

10-Nov-2021 | 11:03 GMT

[redacted]

DocuSigned by:

[redacted]

Cc: [redacted]

Teva Pharmaceuticals, Inc. 145 Brandywine Parkway | West Chester, PA 19380 | Tel. [redacted] www.tevapharm.com

16.10. Administrative Letter 01 Dated 11 June 2021

ADMINISTRATIVE LETTER 01

Study number: TV45779-IMB-30086

Clinical Study Protocol with Amendment 01

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

version date 11 June 2021

IND number: 145915; EudraCT number: 2021-001796-17

25 OCT 2021

Dear Investigator:

The purpose of this letter is to clarify details in the Study Protocol on patient eligibility to join the study and the screening period prior to enrollment.

1. In Study Protocol Synopsis and Protocol Section 4.1 "Patient Inclusion Criteria", criterion f. and Table 1, "Study Procedures and Assessments" footnote g. relative to "Patient Symptom Diary (eDiary)" it is stated that "The patients must not have any missing diary entries in the 7 days prior to randomization."

   The Sponsor would like to modify this inclusion criteria so that it now states "The patients must **~~not have any missing~~ have at least 1** diary **~~entry entries~~** in **4 of** the 7 days prior to randomization."

2. Table 1, "Study Procedures and Assessments", "Allowed time window (days)" for the V2 screening visit is currently zero. A visit window of "**-2**" days will be added.

   APPENDIX B, 1, b., the section header will e changed to "b. Visit 2 (Day -7 **[-2 Days]**)"

These changes will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

Please feel free to contact [redacted] if you have any questions or concerns regarding this letter.

Sincerely,

[redacted]

Cc: [redacted]

Teva Pharmaceuticals, Inc. 145 Brandywine Parkway | West Chester, PA 19380 | Tel. [redacted] | www.tevapharm.com

16.11. Amendment 01 Dated 11 June 2021

The primary reason for this amendment is to implement changes based on feedback on the protocol received from a BPD Type 2 meeting with the FDA (BPD Type 2 Meeting Written Responses 2021). All major changes to the protocol body are listed below in the table and are reflected in the synopsis, as applicable. Table 1 (Study Procedures and Assessments) has been revised to reflect changes described below. Minor editorial changes (typos, punctuation, etc) have been made to the protocol (and protocol synopsis, as appropriate).

Original text with changes shown	New wording	Reason/Justification for change
Coordinating Investigator Agreement		
Coordinating Investigator: [redacted] **Title:** [redacted] **Address of Investigational Center:** [redacted] **Tel**: [redacted]	**Coordinating Investigator**: [redacted] **Title:** [redacted] **Address of Investigational Center:** [redacted] **Tel:** [redacted]	Added name and contact details of Coordinating Investigator
1. INTRODUCTION AND BACKGROUND INFORMATION		
Section 1.2.2; other sections affected by this change: Section 1.3.1		
The pivotal pharmacokinetic/pharmacodynamic study of TEV-45779 (Study TV45779-BE-10160) started in December 2020. This first-in-human study is a single dose, 3-arm, parallel-group study in subjects with serum IgE levels of <100 IU/mL to demonstrate pharmacokinetic biosimilarity between TEV-45779 150 mg and XOLAIR 150 mg sourced from the US (US-licensed XOLAIR) and XOLAIR 150 mg sourced from the EU (EU-approved XOLAIR), and to evaluate pharmacodynamics based on total and free IgE. ~~To date (18 April 2021), a~~All subjects (N=228) have been dosed with TEV-45779, XOLAIR (US) or XOLAIR (EU)~~ and no safety concerns have been observed~~. A blinded interim safety analysis was conducted after completion of the Day 29 visit (28 days post-dose; cut-off date: 19 April 2021). The adverse events and other blinded safety data observed after dosing of 228 healthy subjects are in line with the known safety profile of XOLAIR (XOLAIR Prescribing Information 11/2020; XOLAIR Summary of Product Characteristics 08/2020) and also with events expected in a healthy study population.	The pivotal pharmacokinetic/pharmacodynamic study of TEV-45779 (Study TV45779-BE-10160) started in December 2020. This first-in-human study is a single dose, 3-arm, parallel-group study in subjects with serum IgE levels of <100 IU/mL to demonstrate pharmacokinetic biosimilarity between TEV-45779 150 mg and XOLAIR 150 mg sourced from the US (US-licensed XOLAIR) and XOLAIR 150 mg sourced from the EU (EU-approved XOLAIR), and to evaluate pharmacodynamics based on total and free IgE. All subjects (N=228) have been dosed with TEV-45779, XOLAIR (US) or XOLAIR (EU). A blinded interim safety analysis was conducted after completion of the Day 29 visit (28 days post-dose; cut-off date: 19 April 2021). The adverse events and other blinded safety data observed after dosing of 228 healthy subjects are in line with the known safety profile of XOLAIR (XOLAIR Prescribing Information 11/2020; XOLAIR Summary of Product Characteristics 08/2020) and also with events expected in a healthy study population.	Updated to provide the most recent information available.
2. STUDY OBJECTIVES AND ENDPOINTS		
Section 2.1; other sections affected by this change: Sections 3.5 (Table 1), 9.5.2.1, and 9.5.2.2		

Original text with changes shown	New wording	Reason/Justification for change
additional secondary efficacy endpoint for the main period: • Change from baseline in the overall dermatology life quality index (DLQI) score at Week 12 *additional secondary efficacy endpoints for the main and transition period:* • Change from Week 12 in the overall DLQI score at Week 24 • Change from Week 12 in the overall DLQI score at Week 40	*additional secondary efficacy endpoint for the main period:* • Change from baseline in the overall dermatology life quality index (DLQI) score at Week 12 *additional secondary efficacy endpoints for the main and transition period:* • Change from Week 12 in the overall DLQI score at Week 24 • Change from Week 12 in the overall DLQI score at Week 40	Added DLQI as an additional secondary efficacy parameter for the main and transition period
Section 2.1.2		
2.1.2 Justification of Primary Endpoint and Equivalence Margins … 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 9.5.1.1) 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	**2.1.2 Justification of Primary Endpoint and Equivalence Margins** … 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 9.5.1.1) 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	Added justification for equivalence margins chosen

Original text with changes shown	New wording	Reason/Justification for change
and worse in only 2.0 score points than the reference product if similarity could be demonstrated. **Co-primary endpoint** The co-primary endpoint for the FDA submission is the relative potency of TEV-45779 and XOLAIR (using a 4-point assay with a margin of [0.5, 2.0]), as recommended by the FDA in their written response to the Biological Product Development (BPD) Type 2 meeting (BPD Type 2 Meeting Written Responses 2020). …	worse in only 2.0 score points than the reference product if similarity could be demonstrated. **Co-primary endpoint** The co-primary endpoint for the FDA submission is the relative potency of TEV-45779 and XOLAIR (using a 4-point assay with a margin of [0.5, 2.0]), as recommended by the FDA in their written response to the Biological Product Development (BPD) Type 2 meeting (BPD Type 2 Meeting Written Responses 2020). …	
3. STUDY DESIGN		
Section 3.1		
… Throughout the entire study, patients should remain on a ~~stable~~single H1 antihistamine at stable and fixed doses not exceeding label recommendations as the standard treatment regimen. ….	… 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. ….	Clarified H1 antihistamine standard treatment
Section 3.4		
~~There are no formal rules for early termination of this study.~~ During the conduct of the study, serious adverse events will be reviewed (Section 7.1.5) as they are reported from the investigational centers to identify safety concerns. The study may be terminated by the sponsor for any reason at any time. For example, the sponsor should terminate the study in the event of: • New toxicological or pharmacological findings or safety issues invalidate the earlier positive benefit-risk assessment. • Discontinuation of the development of the IMP. If any of the below mentioned criteria are met, enrollment will be paused for a safety review by the IDMC (Section 5.9.2):	During the conduct of the study, serious adverse events will be reviewed (Section 7.1.5) as they are reported from the investigational centers to identify safety concerns. The study may be terminated by the sponsor for any reason at any time. For example, the sponsor should terminate the study in the event of: • New toxicological or pharmacological findings or safety issues invalidate the earlier positive benefit-risk assessment. • Discontinuation of the development of the IMP. If any of the below mentioned criteria are met, enrollment will be paused for a safety review by the IDMC (Section 5.9.2): • A death for which the cause is judged to be related to the study drug by the treating investigator;	Revised to include formal rules to pause enrollment for a DMC safety review

Original text with changes shown	New wording	Reason/Justification for change
• A death for which the cause is judged to be related to the study drug by the treating investigator; • A life-threatening serious adverse event judged to be related to the study drug by the treating investigator; • 2 occurrences of Grade 3 or higher (per Common Terminology Criteria for Adverse Events [CTCAE] grading) adverse events that are assessed to be related to the study drug by the investigator; • 2 occurrences of a clinically significant Grade 3 or higher (per CTCAE grading) laboratory abnormality assessed to be related to the study drug by the investigator. If the whole study or arms of the study will be stopped, the patients that are terminated early will be followed according to Withdrawal Criteria and Procedures for the Patient (Section 4.3).	• A life-threatening serious adverse event judged to be related to the study drug by the treating investigator; • 2 occurrences of Grade 3 or higher (per Common Terminology Criteria for Adverse Events [CTCAE] grading) adverse events that are assessed to be related to the study drug by the investigator; • 2 occurrences of a clinically significant Grade 3 or higher (per CTCAE grading) laboratory abnormality assessed to be related to the study drug by the investigator. If the whole study or arms of the study will be stopped, the patients that are terminated early will be followed according to Withdrawal Criteria and Procedures for the Patient (Section 4.3).	
Section 3.5 (Table 1); other sections affected by this change: Appendix B		
Timepoints for DLQI completion: Baseline, Week 12, Week 24, Week 40 *Additional timepoint for weight measurement: Baseline*	*Timepoints for DLQI completion: Baseline, Week 12, Week 24, Week 40* *Additional timepoint for weight measurement: Baseline*	Added timepoints for DLQI completion and additional timepoint for weight measurement
[e] 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.	[e] 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.	Added new footnote to detail the observation of patients after IMP administration
[j] Note that stool ova and parasite evaluation should be performed on day -7 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	[j] Note that stool ova and parasite evaluation should be performed on day -7 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	Added clarification for footnote j

Original text with changes shown	New wording	Reason/Justification for change
some countries), the test can be done at Visit 1 or at an unscheduled visit shortly after Visit 1 and the preceding eosinophil count can be done locally.	some countries), the test can be done at Visit 1 or at an unscheduled visit shortly after Visit 1 and the preceding eosinophil count can be done locally.	
4. SELECTION AND WITHDRAWAL OF PATIENTS		
Section 4.3		
Each patient is free to withdraw from the study or discontinue from IMP at any time, without prejudice to their continued care. Patients must be withdrawn from the study if any of the following events occur: 1. Patient withdraws consent or requests withdrawal from the study or discontinuation from IMP for any reason. 2. Patient develops an illness that would interfere with his/her continued participation. 3. Patient is noncompliant with the study procedures and assessments in the opinion of the investigator. 4. Patient takes prohibited concomitant medications as defined in this protocol. 5. The sponsor requests withdrawal of the patient. 6. Patients experiencing anaphylaxis (Section 7.1.6) have to be discontinued from IMP. 7. Patient experiences an adverse event or other medical condition which indicates to the investigator that continued participation is not in the best interest of the patient. Patients who discontinue from IMP while remaining in the study are encouraged to complete end of treatment visit (of the main or transition period as applicable) procedures as soon as possible after receiving their last dose of IMP and to complete the remaining study visits and assessments (with the exception of administration of IMP) including the EoS visit within the original time frames based on date of randomization. The investigator should determine the reason for and the date of discontinuation of study treatment and record this information in both the source documentation and	Each patient is free to withdraw from the study or discontinue from IMP at any time, without prejudice to their continued care. Patients must be withdrawn from the study if any of the following events occur: 1. Patient withdraws consent or requests withdrawal from the study or discontinuation from IMP for any reason. 2. Patient develops an illness that would interfere with his/her continued participation. 3. Patient is noncompliant with the study procedures and assessments in the opinion of the investigator. 4. Patient takes prohibited concomitant medications as defined in this protocol. 5. The sponsor requests withdrawal of the patient. 6. Patients experiencing anaphylaxis (Section 7.1.6) have to be discontinued from IMP. 7. Patient experiences an adverse event or other medical condition which indicates to the investigator that continued participation is not in the best interest of the patient. Patients who discontinue from IMP while remaining in the study are encouraged to complete end of treatment visit (of the main or transition period as applicable) procedures as soon as possible after receiving their last dose of IMP and to complete the remaining study visits and assessments (with the exception of administration of IMP) including the EoS visit within the original time frames based on date of randomization. The investigator should determine the reason for and the date of discontinuation of study treatment and record this information in both the source documentation and the CRF. The patient	Revised withdrawal criteria and procedures to include IMP discontinuation due to anaphylaxis

Original text with changes shown	New wording	Reason/Justification for change
the CRF. The patient should not be considered withdrawn from the study due to interruption or discontinuation of IMP. Patients should be treated with standard of care after withdrawal from or termination of the study as appropriate. …	should not be considered withdrawn from the study due to interruption or discontinuation of IMP. Patients should be treated with standard of care after withdrawal from or termination of the study as appropriate. …	
5. TREATMENT		
Section 5.2.3; other Sections affected by this change: Section 5.9.1		
… During the main and transition treatment period, ~~site and sponsor representatives~~the persons who are involved in receipt, storage, distribution, administration, return, and accountability of IMP will be unblinded as the IMPs differ in appearance: these persons will not be involved in the conduct of any study procedures or assessments. …	… 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 as the IMPs differ in appearance: these persons will not be involved in the conduct of any study procedures or assessments. …	Revised to include reason why persons dealing with IMP are not blinded
Sections 5.8 and 5.9.1		
5.8 Randomization and Blinding … All patients in the TEV-45779 group will continue to receive TEV-45779 during the transition period at the same dose level as prior to randomization. During the study~~ main treatment period,~~ the sponsor, investigators (and other site staff involved in study assessments) and patients will be blinded to the treatment assignment of all patients. To maintain blinding ~~of the patients and investigators (and other site staff involved in study assessments)~~ to the treatment assignment~~ of all patients during the entire study, and to maintain blinding of the sponsor until the main treatment period is unblinded~~, the re-randomization process will be performed for all patients, including the patients in the TEV-45779 group (although only patients in the XOLAIR arm will actually be re-randomized while patients in the TEV-45779 group will continue to receive TEV-45779 in the transition period). The	**5.8 Randomization and Blinding** … All patients in the TEV-45779 group will continue to receive TEV-45779 during the transition period at the same dose level as prior to randomization. During the study, the sponsor, investigators (and other site staff involved in study assessments) and patients will be blinded to the treatment assignment of all patients. To maintain blinding to the treatment assignment, the re-randomization process will be performed for all patients, including the patients in the TEV-45779 group (although only patients in the XOLAIR arm will actually be re-randomized while patients in the TEV-45779 group will continue to receive TEV-45779 in the transition period). The randomization will be implemented using a Randomization and Trial Supply Management (RTSM) system. **5.9. Maintenance of Randomization and Blinding** **5.9.1. Blinding and Unblinding**	Revised to reflect omission of unblinded analysis of the main treatment period after Week 12

Original text with changes shown	New wording	Reason/Justification for change
randomization will be implemented using a Randomization and Trial Supply Management (RTSM) system. **5.9. Maintenance of Randomization and Blinding** **5.9.1. Blinding and Unblinding** … Before database lock (DBL), staff responsible for pharmacokinetic and immunogenicity bioanalysis will not have access to the patient treatment randomization. ~~After the last visit of the last patient of the main treatment period and DBL for this period and following the formal request of the sponsor statistician, the sponsor will unblind the treatments for the analysis of the main treatment period (up to and including Week 12).~~ ~~During the transition period, the sponsor, investigators (and other site staff involved in study assessments) and patients will be blinded to the randomized treatment and dose of patients who received XOLAIR in the main treatment period and are re-randomized at the beginning of the transition period.~~Only after completion of the study (after Week 40), DBL and formal request to unblind from the sponsor statistician, will the ~~transition period and the follow-up~~study be fully unblinded and analyzed. …	… 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), DBL and formal request to unblind from the sponsor statistician, will the study be fully unblinded and analyzed. …	
Section 5.9.1		
… The IMP will be prepared in a separate room by the non-blinded person (eg, pharmacist or designee). <u>The blinding will be maintained during the transportation from and to the dosing room.</u> ~~This person will place the respective syringes from the original box in a neutral container provided by the sponsor to transfer the study medication from the pharmacy/storage area to the dosing room.~~ Dosing will be performed by a non-blinded staff member in the dosing room. ~~Once dosing is complete, the study medication is placed back~~	… The IMP will be prepared in a separate room by the non-blinded person (eg, pharmacist or designee). The blinding will be maintained during the transportation from and to the dosing room. Dosing will be performed by a non-blinded staff member in the dosing room. The original IMP packaging and syringes should not be visible when the patient or any other blinded study team member enters the room. …	Revised to allow country-specific procedures for maintaining the blinding during transportation to and from the dosing room

Original text with changes shown	New wording	Reason/Justification for change
~~into this neutral container to return to the pharmacy/storage area for any post-dose assessments on the syringes.~~ The original IMP packaging and syringes should not be visible when the patient or any other blinded study team member enters the room. …		
Section 5.9.2; other Sections affected by this change: Section 3.1		
~~There will be no Data Monitoring Committee in this study.~~ 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 (eg, efficacy data) if deemed necessary. The IDMC will perform a safety review if any of the pausing criteria listed in Section 3.4 is met. The specific details regarding the IDMC sessions will be outlined in the IDMC charter. The IDMC will be composed of 2 independent physicians with expertise in the relevant therapeutic field and an independent statistician. The IDMC chairperson will communicate with the sponsor in regard to issues resulting from the conduct and clinical aspects of the study. The sponsor will work closely with the committee to provide the necessary data for review. 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.	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 (eg, efficacy data) if deemed necessary. The IDMC will perform a safety review if any of the pausing criteria listed in Section 3.4 is met. The specific details regarding the IDMC sessions will be outlined in the IDMC charter. The IDMC will be composed of 2 independent physicians with expertise in the relevant therapeutic field and an independent statistician. The IDMC chairperson will communicate with the sponsor in regard to issues resulting from the conduct and clinical aspects of the study. The sponsor will work closely with the committee to provide the necessary data for review. 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.	Revised to include plans for IDMC
6. ASSESSMENT OF EFFICACY		
Section 6.3		
Added new Section 6.3: 6.3. Dermatology Life Quality Index	*Added new Section 6.3:* 6.3. Dermatology Life Quality Index	Added to include description of DLQI

Original text with changes shown	New wording	Reason/Justification for change
The Dermatology Life Quality Index (DLQI) will be performed at the time points detailed in Table 1. The DLQI consists of 10 questions concerning patients' perception of the impact of skin diseases on different aspects of their health-related quality of life over the last week (Finlay and Khan 1994; further information is available at: https://www.cardiff.ac.uk/medicine/resources/quality-of-life-questionnaires/dermatology-life-quality-index). The DLQI is calculated by adding the score of each question, resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. A score higher than 10 indicates that the patient's life is being severely affected by their skin disease.	The Dermatology Life Quality Index (DLQI) will be performed at the time points detailed in Table 1. The DLQI consists of 10 questions concerning patients' perception of the impact of skin diseases on different aspects of their health-related quality of life over the last week (Finlay and Khan 1994; further information is available at: https://www.cardiff.ac.uk/medicine/resources/quality-of-life-questionnaires/dermatology-life-quality-index). The DLQI is calculated by adding the score of each question, resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. A score higher than 10 indicates that the patient's life is being severely affected by their skin disease.	
7. ASSESSMENT OF SAFETY		
Section 7.1.3		
~~The severity of each adverse event must be recorded as 1 of the following:~~ ~~**Mild:** No limitation of usual activities.~~ ~~**Moderate:** Some limitation of usual activities.~~ ~~**Severe:** Inability to carry out usual activities.~~ The severity of each adverse event, including clinical laboratory adverse events, will be graded according to CTCAE (Appendix R). The severity of each adverse event must be recorded as 1 of the following: • Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. • Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). (Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).	~~The severity of each adverse event must be recorded as 1 of the following:~~ ~~**Mild:** No limitation of usual activities.~~ ~~**Moderate:** Some limitation of usual activities.~~ ~~**Severe:** Inability to carry out usual activities.~~ The severity of each adverse event, including clinical laboratory adverse events, will be graded according to CTCAE (Appendix R). The severity of each adverse event must be recorded as 1 of the following: • Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. • Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). (Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).	Revised to include CTCAE scale for grading of adverse events

Original text with changes shown	New wording	Reason/Justification for change
• Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL. (Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden). • Grade 4: Life-threatening consequences; urgent intervention indicated. • Grade 5: Death related to adverse event.	• Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL. (Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden). • Grade 4: Life-threatening consequences; urgent intervention indicated. • Grade 5: Death related to adverse event.	
Section 7.1.6		
Anaphylaxis will be considered a protocol-defined adverse event of special interest (PDAESI). Anaphylaxis is described as highly likely when any 1 of the following 3 criteria based on the 2006 Joint National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN) Second Symposium on Anaphylaxis are fulfilled (Sampson et al 2006): … The process for reporting this PDAESI is the same as that for reporting a serious adverse event (see Section 7.1.5.3). In the event of suspected anaphylaxis while the patient is at the site during the 2-hour observation period following drug administration, vital signs should be collected and a physical examination (brief or full, at the discretion of the investigator) performed. Blood samples to test omalizumab serum concentration and ADA formation should be collected if possible. Collection of blood samples to test tryptase and/or histamine levels are encouraged if available locally at the time of the suspected hypersensitivity event. Other assessments may be performed at the discretion of the investigator. As a precaution, each site should have a resuscitation medication/equipment (at a minimum according to local regulations) nearby. Information about all suspected anaphylaxis and hypersensitivity events will be recorded on	Anaphylaxis will be considered a protocol-defined adverse event of special interest (PDAESI). Anaphylaxis is described as highly likely when any 1 of the following 3 criteria based on the 2006 Joint National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN) Second Symposium on Anaphylaxis are fulfilled (Sampson et al 2006): ... The process for reporting this PDAESI is the same as that for reporting a serious adverse event (see Section 7.1.5.3). In the event of suspected anaphylaxis while the patient is at the site during the 2-hour observation period following drug administration, vital signs should be collected and a physical examination (brief or full, at the discretion of the investigator) performed. Blood samples to test omalizumab serum concentration and ADA formation should be collected if possible. Collection of blood samples to test tryptase and/or histamine levels are encouraged if available locally at the time of the suspected hypersensitivity event. Other assessments may be performed at the discretion of the investigator. As a precaution, each site should have a resuscitation medication/equipment (at a minimum according to local regulations) nearby. Information about all suspected anaphylaxis and hypersensitivity events will be recorded on	Added instructions regarding the handling of potential anaphylaxis cases

Original text with changes shown	New wording	Reason/Justification for change
the Suspected Anaphylaxis CRF, which is based on the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis (Sampson et al 2006). Patients should be instructed to contact the investigator or seek appropriate medical support (eg, in an emergency room) should they experience any signs or symptoms indicative of anaphylaxis after leaving the site.	the Suspected Anaphylaxis CRF, which is based on the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis (Sampson et al 2006). Patients should be instructed to contact the investigator or seek appropriate medical support (eg, in an emergency room) should they experience any signs or symptoms indicative of anaphylaxis after leaving the site.	
Section 7.10; other sections affected by this change: Section 3.5 (Table 1)		
… The assessments will be performed at 20, 60 and 120 minutes after dosing (Table 1). …	… The assessments will be performed at 20, 60 and 120 minutes after dosing (Table 1). …	Updated assessment times
… All injection site findings will ~~not~~ be captured as adverse events unless they fulfill characteristics that are beyond those in the specified forms/scales (eg, necrosis, abscess, etc.) or fulfill seriousness criteria and ~~then~~ must be recorded and reported as specified in Section 7.1.5.	… All injection site findings will be captured as adverse events unless they fulfill characteristics that are beyond those in the specified forms/scales (eg, necrosis, abscess, etc.) or fulfill seriousness criteria and must be recorded and reported as specified in Section 7.1.5.	Revised to capture all injection site findings as adverse events
9. STATISTICS		
Section 9.5.1.1, other Sections affected by this change: Sections 9.5.1.1.1 and 9.5.1.1.2 and Appendix G		
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), 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). …	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), 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). …	Added region as a covariate

Original text with changes shown	New wording	Reason/Justification for change
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), 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).	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), 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).	
Section 9.5.1.3		
… Additional supplementary analyses to address missing data in the relative potency analysis will be provided in SAP.	… Additional supplementary analyses to address missing data in the relative potency analysis will be provided in SAP.	Clarification
Section 9.11		
9.11 Planned Interim Analysis An interim analysis (IA) may be conducted after all subjects have completed the main treatment period in order to facilitate Teva's decision regarding additional studies in the clinical development program for TEV-45779 prior to the completion of the current study. If performed, the IA will not have any impact on the conduct and analyses of this study. The IA will be conducted by an external Independent Statistician while keeping Teva and the study team blinded. No actual numeric results or data will be shared with Teva and the study team. The only information that will be provided to Teva by the Independent Statistician is the Yes/No result for each co-primary comparison for FDA and EMA biosimilarity assessment (see Section 9.5.1.1 for details). As the IA does not introduce any inflation to the	**9.11 Planned Interim Analysis** An interim analysis (IA) may be conducted after all subjects have completed the main treatment period in order to facilitate Teva's decision regarding additional studies in the clinical development program for TEV-45779 prior to the completion of the current study. If performed, the IA will not have any impact on the conduct and analyses of this study. The IA will be conducted by an external Independent Statistician while keeping Teva and the study team blinded. No actual numeric results or data will be shared with Teva and the study team. The only information that will be provided to Teva by the Independent Statistician is the Yes/No result for each co-primary comparison for FDA and EMA biosimilarity assessment (see Section 9.5.1.1 for details). As the IA does not introduce any inflation to the Type I error rate of the final	Deleted previous Section 9.11 due to omission of unblinded analysis of main treatment period after Week 12 and added new Section 9.11 to present plans regarding blinded interim analysis

Original text with changes shown	New wording	Reason/Justification for change
Type I error rate of the final analysis of the study, no adjustments of the nominal significance level are required.	analysis of the study, no adjustments of the nominal significance level are required.	
APPENDIX E. URTICARIA ACTIVITY SCORE; same changes made in APPENDIX F. IN CLINIC URTICARIA ACTIVITY SCORE		
		Revised format of table
APPENDIX L. LIST OF PROHIBITED MEDICATIONS		
		Clarification

APPENDIX A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS

Sponsor's Authorized Representative	[redacted] [redacted] Teva ratiopharm
Legal Representative of the Sponsor in the EU	Merckle GmbH Contact Person: [redacted] [redacted] Merckle GmbH, Teva ratiopharm Graf-Arco-Strasse 3 89079 Ulm, Germany Tel: [redacted]
Sponsor's Medical Expert/Contact Point Designated by the Sponsor for Further Information on the Study	EU Medical Monitor [redacted] ICON Gottlieb-Daimler-Strasse 10 68165 Mannheim, Germany Tel: [redacted] Medical monitoring support center contact information: Americas: [redacted] (toll-free) or direct at: [redacted] EAPA: [redacted]
Coordinating Investigator	[redacted]
Contract Research Organization	PHARMACEUTICAL RESEARCH ASSOCIATES Inc. 4130 ParkLake Avenue, Suite 400 Raleigh, NC 27612, USA
Central Clinical Laboratory (except India)	ACM Medical Laboratory, Inc. 160 Elmgrove Park Rochester New York 14624, USA Tel: [redacted]
Central Clinical Laboratory India	Metropolis Healthcare Limited Plot No. 103

	Road No. 12 MIDC Andheri (E) Mumbai – 400 093 Maharashtra, India
Randomization and Trial Supply Management (RTSM) System	Perceptive eClinical Limited d/b/a Calyx with offices at Castle Wharf 4 Canal Street Nottingham, United Kingdom NG1 7EH [redacted] Tel: [redacted]
Bioanalytical Pharmacokinetics, Pharmacodynamics, and Immunogenicity Evaluation	[redacted] Biologics, Assays & Technology (GBT) Teva Pharmaceutical Industries, Ltd. 19 Giborey Israel Street Sapir Industrial Zone Netanya, Israel 4250419 Tel: [redacted]
Trial Supply vendors	Secondary Labeling and Distribution Almac Clinical Services (Almac Group Limited) 20 Seagoe Industrial Estate, Craigavon, BT63 5QD, Northern Ireland, UK [redacted] Tel: [redacted] Secondary Labeling and Distribution Actavis Laboratories UT, Inc 577 Chipeta Way Salt Lake City, UT 84108, USA [redacted] Tel: [redacted]

APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT

1. **Procedures for Screening (Visits 1 and 2, Up to 3-week Period)**

The screening visit (visits 1 and 2) will take place not more than 21 days before the baseline visit (visit 3). 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.

a. Visit 1 (Day -14 [-7/+2 days])

The following procedures will be performed:

- obtain signed and dated informed consent before any study-related procedures are performed
- demographics
- medical and surgical history
- document prior medication and treatment history
- review inclusion and exclusion criteria
- inquire about adverse events
- inquire about COVID-19 status
- complete Physician's (in-clinic) assessment of UAS
- dispense electronic Patient Symptom Diary (eDiary)
- comprehensive physical examination
- height and weight
- ECG; 12-lead
- vital signs measurement
- obtain blood sample for free and total IgE
- inform patients of study restrictions and compliance requirements
- clinical laboratory tests:
  - serum chemistry tests (at V1, serum chemistry sample in non-fasting state may be acceptable)
  - serum hematology tests
  - urinalysis
  - COVID-19 testing
- dispensation of rescue medication

b. Visit 2 (Day -7 [-2 days])

The following procedures will be performed at visit 2:

- document prior medication and treatment history
- review inclusion and exclusion criteria
- inquire about adverse events
- inquire about COVID-19 status (if patient exhibits clinical symptoms that may indicate COVID-19 infection, COVID-19 testing will be performed locally)
- complete Physician's (in-clinic) assessment of UAS (it should be completed prior to reviewing the diary entries of the patients)
- check eDiary including UAS
- stool ova and parasite evaluation (only for patients with an eosinophil count >2× the ULN on day -14 and risk factors for parasitic disease)
- clinical laboratory tests:
  - Urine β-HCG (only for women of childbearing potential). If the urine pregnancy test result is positive a serum pregnancy test should be performed by the central laboratory.
- dispensation of rescue medication (if needed)

2. **Procedures During Baseline Visit for Main Treatment Period (Visit 3, Day 1)**

Patients who meet the inclusion and exclusion criteria at visit 2 will continue to visit 3, when baseline assessments will be conducted.

The following procedures will be performed at visit 3, prior to IMP administration:

- review inclusion and exclusion criteria
- assign randomization/treatment numbers and enter in CRF
- weight
- inquire about adverse events
- inquire about concomitant medication, including rescue medication
- inquire about COVID-19 status (if patient exhibits clinical symptoms that may indicate COVID-19 infection, COVID-19 testing will be performed locally)
- complete Physician's (in-clinic) assessment of UAS (it should be completed prior to reviewing the diary entries of the patients and must be completed prior to administration of IMP)
- check eDiary including UAS
- complete DLQI
- physical examination (abbreviated to detect changes in symptoms of CIU/ CSU)
- vital signs measurement
- obtain blood sample for free and total IgE

- obtain blood sample for pharmacokinetics
- clinical laboratory tests:
  - serum chemistry tests
  - serum hematology tests
  - urinalysis
- obtain blood sample for ADAs
- dispensation of rescue medication (if needed)

Patients will have IMP administered by qualified site staff. The following procedure will be performed at visit 3, during the 2-hour observation period following IMP administration:

- local tolerability
- record device-related adverse events

3. **Procedures During Main Treatment Period (Visits 4 through 5)**

   a. Visit 4 (Day 29 ±3 days)

   The following procedures will be performed, prior to IMP administration:

   - inquire about adverse events
   - inquire about concomitant medication, including rescue medication
   - inquire about COVID-19 status (if patient exhibits clinical symptoms that may indicate COVID-19 infection, COVID-19 testing will be performed locally)
   - complete Physician's (in-clinic) assessment of UAS (it should be completed prior to reviewing the diary entries of the patients and must be completed prior to administration of IMP)
   - check eDiary including UAS
   - physical examination (abbreviated to detect changes in symptoms of CIU/CSU)
   - vital signs measurement
   - obtain blood sample for free and total IgE
   - obtain blood sample for pharmacokinetics
   - obtain blood sample for ADAs
   - dispensation of rescue medication (if needed)

   Patients will have IMP administered by qualified site staff. The following procedure will be performed at visit 4, during the 2-hour observation period following IMP administration:

   - local tolerability
   - record device-related adverse events

   b. Visit 5 (Day 57 ±3 days)

The following procedures will be performed, prior to IMP administration:

- inquire about adverse events
- inquire about concomitant medication, including rescue medication
- inquire about COVID-19 status (if patient exhibits clinical symptoms that may indicate COVID-19 infection, COVID-19 testing will be performed locally)
- complete Physician's (in-clinic) assessment of UAS (it should be completed prior to reviewing the diary entries of the patients and must be completed prior to administration of IMP)
- check eDiary including UAS
- physical examination (abbreviated to detect changes in symptoms of CIU/CSU)
- vital signs measurement
- obtain blood sample for free and total IgE
- obtain blood sample for pharmacokinetics
- dispensation of rescue medication (if needed)

Patients will have IMP administered by qualified site staff. The following procedure will be performed at visit 5, during the 2-hour observation period following IMP administration:

- local tolerability
- record device-related adverse events

4. **Procedures During Visit 6 (Day 85 +3 days) (End of Main Treatment Period Visit/Baseline Transition Period)**

   The following procedures will be performed at visit 6, prior to IMP administration:

   - randomization for the transition period. Patients in the XOLAIR treatment groups will be re-randomized in a 1:1 ratio to receive 3 additional doses of XOLAIR or switch to 3 doses of TEV-45779 at the same dose, in the transition period. Patients who were initially randomized to TEV-45779 will continue to receive TEV-45779 at the same dose; however, to maintain blinding, the re-randomization process will be performed for all patients (although only patients in the XOLAIR arm will actually be re-randomized)
   - inquire about adverse events
   - inquire about concomitant medication, including rescue medication
   - inquire about COVID-19 status (if patient exhibits clinical symptoms that may indicate COVID-19 infection, COVID-19 testing will be performed locally)
   - complete Physician's (in-clinic) assessment of UAS (it should be completed prior to reviewing the diary entries of the patients and must be completed prior to administration of IMP)
   - check eDiary including UAS

- complete DLQI
- physical examination (abbreviated to detect changes in symptoms of CIU/CSU) and body weight
- 12-lead ECG
- vital signs measurement
- obtain blood sample for free and total IgE
- obtain blood sample for pharmacokinetics
- clinical laboratory tests:
  - serum chemistry tests
  - serum hematology tests
  - urinalysis
  - urine β-HCG (only for women of childbearing potential). If the urine pregnancy test result is positive a serum pregnancy test should be performed by the central laboratory
- obtain blood sample for ADAs
- dispensation of rescue medication (if needed)

Patients will have IMP administered by qualified site staff. The following procedure will be performed at visit 6, during the 2-hour observation period following IMP administration:

- local tolerability
- record device-related adverse events

5. **Procedures During Transition Period (Visits 7 through 8)**

a. Visit 7 (day 113 ±3 days)

The following procedures will be performed, prior to IMP administration:

- inquire about adverse events
- inquire about concomitant medications, including rescue medication
- inquire about COVID-19 status (if patient exhibits clinical symptoms that may indicate COVID-19 infection, COVID-19 testing will be performed locally)
- complete Physician's (in-clinic) assessment of UAS (it should be completed prior to reviewing the diary entries of the patients and must be completed prior to administration of IMP)
- check eDiary including UAS
- physical examination (abbreviated to detect changes in symptoms of CIU/CSU)
- vital signs measurement

- obtain blood sample for free and total IgE
- obtain blood sample for pharmacokinetics
- dispensation of rescue medication (if needed)

Patients will have IMP administered by qualified site staff. The following procedure will be performed at visit 7, during the 2-hour observation period following IMP administration:

- local tolerability
- record device-related adverse events

b. Visit 8 (Day 141 ±3 days)

The following procedures will be performed, prior to IMP administration:

- inquire about adverse events
- inquire about concomitant medications, including rescue medication
- inquire about COVID-19 status (if patient exhibits clinical symptoms that may indicate COVID-19 infection, COVID-19 testing will be performed locally)
- complete Physician's (in-clinic) assessment of UAS (it should be completed prior to reviewing the diary entries of the patients and must be completed prior to administration of IMP)
- check eDiary including UAS
- physical examination (abbreviated to detect changes in symptoms of CIU/CSU)
- vital signs measurement
- obtain blood sample for free and total IgE
- obtain blood sample for pharmacokinetics
- dispensation of rescue medication (if needed)

Patients will have IMP administered by qualified site staff. The following procedure will be performed at visit 8, during the 2-hour observation period following IMP administration:

- local tolerability
- record device-related adverse events

6. **Procedures During Visit 9 (Day 169 ±3 days) (End of Treatment Visit)**

The following procedures will be performed:

- inquire about adverse events
- inquire about concomitant medication, including rescue medication
- inquire about COVID-19 status (if patient exhibits clinical symptoms that may indicate COVID-19 infection, COVID-19 testing will be performed locally)

- complete Physician's (in-clinic) assessment of UAS (it should be completed prior to reviewing the diary entries of the patients)
- check eDiary including UAS
- complete DLQI
- physical examination (abbreviated to detect changes in symptoms of CIU/CSU)
- 12-lead ECG
- vital signs measurement
- obtain blood sample for free and total IgE
- obtain blood sample for pharmacokinetics
- clinical laboratory tests:
  - serum chemistry tests
  - serum hematology tests
  - urinalysis
  - urine β-HCG (only for women of childbearing potential). If the urine pregnancy test result is positive a serum pregnancy test should be performed by the central laboratory
- obtain blood sample for ADAs
- dispensation of rescue medication (if needed)

7. **Procedures During Follow-up Period (Visits 10 through 13)**

   a. Visit 10 (Day 197 ±3 days), Visit 11 (day 225 ±3 days), and Visit 12 (day 253 ±3 days)

   The following procedures will be performed:

   - inquire about adverse events
   - inquire about concomitant medication, including rescue medication
   - inquire about COVID-19 status (if patient exhibits clinical symptoms that may indicate COVID-19 infection, COVID-19 testing will be performed locally)
   - complete Physician's (in-clinic) assessment of UAS (it should be completed prior to reviewing the diary entries of the patients)
   - check eDiary including UAS
   - physical examination (abbreviated to detect changes in symptoms of CIU/CSU)
   - vital signs measurement
   - obtain blood sample for free and total IgE
   - obtain blood sample for pharmacokinetics

- dispensation of rescue medication (if needed)

b. Procedures During Visit 13 (day 281 ±3 days) (End of Study/Early Termination Visit)

The following procedures will be performed:

- inquire about adverse events
- inquire about concomitant medication, including rescue medication
- inquire about COVID-19 status (if patient exhibits clinical symptoms that may indicate COVID-19 infection, COVID-19 testing will be performed locally)
- complete Physician's (in-clinic) assessment of UAS (it should be completed prior to reviewing the diary entries of the patients)
- check eDiary including UAS
- complete DLQI
- physical examination (abbreviated to detect changes in symptoms of CIU/CSU) and body weight
- 12-lead ECG
- vital signs measurement
- obtain blood sample for free and total IgE
- obtain blood sample for pharmacokinetics
- clinical laboratory tests:
  - serum chemistry
  - serum hematology
  - urinalysis
- obtain blood sample for ADAs

8. **Unscheduled Visits**

An unscheduled visit may be performed at any time during the study at the patient’s request and as deemed necessary by the investigator. The date and reason for the unscheduled visit will be recorded on the CRF as well as any other data obtained from procedures and assessments.

Procedures performed during unscheduled visits include:

- vital signs measurement
- inquire about adverse events
- inquire about COVID-19 status (if patient exhibits clinical symptoms that may indicate COVID-19 infection, COVID-19 testing will be performed locally)
- inquire about concomitant medication

- inform patients of study restrictions and compliance requirements

Other procedures and assessments may be performed at the discretion of the investigator.

APPENDIX C. MANAGEMENT OF STUDY ACTIVITIES DURING CORONAVIRUS DISEASE 2019 OUTBREAKS

This appendix addresses the modifications set-up for managing study conduct during Coronavirus disease 2019 (COVID-19) outbreaks.

The changes will be effective in the event of an emergency situation (eg, COVID-19 outbreaks); when the situation at specific sites/countries allows the return to regular study activities, this appendix will be void for those sites/countries.

The following sections of the protocol are affected:

Section 1.3.1 Known and Potential Benefits and Risks of TEV-45779

In the event of an emergency situation (eg, COVID-19 outbreaks), the sponsor, in close collaboration with the investigators, will determine if the benefit-risk assessment remains positive as a whole, and will assess any additional risks on a patient-by-patient basis. The measures outlined in this appendix are aimed at further mitigating the additional risks in an emergency situation.

Section 3.1 General Study Design and Study Schematic Diagram; Section 3.5 Schedule of Study Procedures and Assessments

In the event of an emergency situation (eg, COVID-19 outbreaks), in case a patient cannot return to the clinic for the scheduled visits (eg, due to quarantine, isolation, patient's concern, active COVID-19 infection, or closure of the site clinic) remote assessment of safety via telephone and/or videoconference (VC), with VC being the preferred method, may be allowed.

Modifications to other procedures and assessments (ECG, laboratory sample collection [including pharmacokinetics, pharmacodynamics, and immunogenicity] etc.) may be performed per implemented contingency measures according to sponsor instructions and the corresponding manual. For example, if central laboratory samples cannot be collected for safety assessments, sites may have patients visit a local reference laboratory or dispatch a home health nurse to perform the assessments, but only after consultation with the sponsor; see Section 7 and Section 8 below for details.

If pharmacokinetics, pharmacodynamics, and immunogenicity samples cannot be collected at site, sites may use a home health nurse to collect these blood samples, but only after consultation with the sponsor; see Section 7 and Sections 7.5-7.10 below for details.

If a patient does not continue in the study due to site closure, the patient status should be NOT COMPLETED DUE TO: 'Other' 'COVID-19 logistical reasons prevented patient's continuation in the study'.

These measures will be implemented on a case-by-case basis, and only when and where they are warranted due to the emergency situation. Preferably, the original protocol instructions will be followed whenever the new instructions are not required.

Section 4.3 Withdrawal Criteria and Procedures for the Patient

If a patient exhibits clinical symptoms that may indicate COVID-19 infection after entering the study, the patient should be tested for active COVID-19. If the patient tests positive for active

COVID-19, he/she may continue for scheduled visits when recovered (ie, tests negative for active COVID-19 infection).

Section 6 Assessment of Efficacy

In the event of an emergency situation (eg, COVID-19 outbreaks), in case a patient cannot return to the clinic for the scheduled visits (eg, due to quarantine, isolation, patient's concern, active COVID-19 infection, or closure of the site clinic), Physician's Assessment of Urticaria Assessment Score should be evaluated if another location might be used after consultation and approval by the sponsor.

These measures will be implemented on a case-by-case basis, and only when and where they are warranted due to the emergency situation. Preferably, the full protocol instructions will be followed whenever the modified instructions are not required.

Section 7. Assessment of Safety

In the event of an emergency situation (eg, COVID-19 outbreaks), in case a patient cannot return to the clinic for the scheduled visits (eg, due to quarantine, isolation, patient's concern, active COVID-19 infection, or closure of the site clinic), remote assessment of safety (as well as inquiries regarding adverse events and use of concomitant medication) via telephone call and/or VC, with VC being the preferred method, may be allowed. The results will be directly entered into the CRF per the usual process.

Modifications to other procedures and assessments (ECG, laboratory sample collection, pharmacokinetic sampling, etc.) may be performed per implemented contingency measures according to sponsor instructions. For example, if central laboratory samples cannot be collected for safety assessments, sites may have patients visit a local reference laboratory or dispatch a home health nurse to perform the assessments, but only after consultation with the sponsor.

These measures will be implemented on a case-by-case basis, and only when and where they are warranted due to the emergency situation. These measures will not be implemented for patients known to be COVID-19 infectious. Preferably, the original protocol instructions will be followed unless the instructions in this appendix are implemented by the sponsor.

Section 7.5 Clinical Laboratory Tests

If central laboratory samples cannot be collected for safety assessments, sites may have patients visit a local reference laboratory or arrange a home health visit to perform the assessments after discussion with and approval by the sponsor. If any patient has clinical laboratory samples collected at a local laboratory, the site will be responsible for collection of reference ranges from that laboratory.

Section 7.6 Physical Examinations; Section 7.8 Vital Signs; Section 7.9 Electrocardiography; Section 7.10 Assessment of Local Tolerability and Pain

At-home health visits may be used to perform safety assessments such as physical examinations, vital signs, ECG, and local tolerability to determine any new adverse events.

Section 8 Assessment of Pharmacokinetics, Pharmacodynamics, and Immunogenicity

If pharmacokinetic, pharmacodynamic, and immunogenicity samples cannot be collected due to limitations in ability to carry out the procedure or limitations in storage and shipments, the

samples will not be collected for those respective visits. Study samples collected from confirmed COVID-19 positive patients during the study, with confirmation either before or after the sample collection, will be kept at the central laboratory and will not be shipped to Teva bioanalytical laboratories nor analyzed. Teva bioanalytical laboratories will be informed within approximately 1 week of any COVID-19 positive patients confirmed after samples being collected.

Section 10 Quality Control and Quality Assurance; Appendix H Quality Control and Quality Assurance

Deviations from the study conduct due to emergency situations (eg, COVID-19 outbreaks), including implemented contingency measures and their impact (eg, patient discontinuation from the study, alternative procedures used to collect critical safety and/or efficacy data, etc.), will be described in the appropriate sections of the CSR as applicable.

APPENDIX D. PATIENT DIARY

The patient diary will be provided as a separate document.

APPENDIX E. URTICARIA ACTIVITY SCORE

Wheals (Hives)		Pruritus (Itch)	
Score	**Criteria**	**Score**	**Criteria**
0	None	0	None
1	Mild (1-6 hives/12 hours)	1	Mild
2	Moderate (7-12 hives/12 hour)	2	Moderate
3	Intense (>12 hives/12 hour)	3	Severe

The score is the sum of the wheals (hives) score and pruritus (itch) score.

APPENDIX F. IN-CLINIC URTICARIA ACTIVITY SCORE

Pruritus		Number of Hives	
Score	**Criteria**	**Score**	**Criteria**
0	None	0	None
1	Mild: minimal awareness, easily tolerated	1	1= 1-6
2	Moderate: definite awareness, bothersome but tolerable	2	2= 7-12
3	Severe: difficult to tolerate	3	3= >12

The score is the sum of the pruritus score and number of hives score.

APPENDIX G. RELATIVE POTENCY

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:

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

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 ANCOVA model is estimated in order to verify the required assumptions. The treatment effect is decomposed into the effects of product, dose on the log-scale and their interaction.

Baseline itch severity score, baseline weight and region (3 levels planned: Americas, Europe and Asia-Pacific) 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.

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): (aR– aT) / b. Its confidence limits can be obtained based on the other results from the model.

APPENDIX H. QUALITY CONTROL AND QUALITY ASSURANCE

Protocol Amendments and Protocol Deviations

Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IEC/ IRB and national and local competent authorities, as applicable, except when necessary to address immediate safety concerns to the patients or when the change involves only non-substantial logistics or administration. The principal investigator at each investigational center, the coordinating investigator (if applicable), and the sponsor will sign the protocol amendment.

Important Protocol Deviations

Any deviation from the protocol that affects, to a significant degree, (a) the safety, physical, or mental integrity of the patients in the study and/or (b) the scientific value of the study will be considered an important protocol deviation. Important protocol deviations may include non-adherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion and exclusion criteria, primary objective variable criteria, or GCP guidelines; noncompliance to IMP administration; use of prohibited medications. Important protocol deviations will be identified and recorded in the patient's source. All important protocol deviations will be reported to the responsible IEC/IRB, as required.

When an important protocol deviation is reported, the sponsor will determine whether to withdraw the patient from the study or permit the patient to continue in the study, with documented approval from the medical expert. The decision will be based on ensuring the safety of the patient and preserving the integrity of the study.

Changes in the inclusion and exclusion criteria of the protocol are **not** prospectively granted by the sponsor. If investigational center personnel learn that a patient who did not meet protocol inclusion and exclusion criteria was entered in a study, they must immediately inform the sponsor of the important protocol deviation. If such patient has already completed the study or has withdrawn early, no action will be taken but the deviation will be recorded.

Information to Study Personnel

The investigator is responsible for giving information about the study to all personnel members involved in the study or in any element of patient management, both before starting the study and during the course of the study (eg, when new personnel become involved). The investigator must ensure that all study personnel are qualified by education, experience, and training to perform their specific task. These study personnel members must be listed on the investigational center authorization form, which includes a clear description of each personnel member’s responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study personnel, including the investigator, and for ensuring they comply with the protocol.

Study Monitoring

To ensure compliance with GCP guidelines, the study monitor or representative is responsible for ensuring that patients have signed the ICF and the study is conducted according to applicable

Standard Operating Procedures (SOP)s, the protocol, and other written instructions and regulatory guidelines.

The study monitor is the primary association between the sponsor and the investigator. The main responsibilities of the study monitors are to visit the investigator before, during, and after the study to ensure adherence to the protocol, that all data are correctly and completely recorded and reported, and that informed consent is obtained and recorded for all patients before they participate in the study and when changes to the consent form are warranted, in accordance with IEC/IRB approvals.

The study monitors will contact the investigator and visit the investigational center according to the monitoring plan. The study monitor will be permitted to review and verify the various records (CRFs and other pertinent source data records, including specific electronic source document relating to the study) to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded.

As part of the supervision of study progress, other sponsor personnel may, on request, accompany the study monitor on visits to the investigational center. The investigator and assisting personnel must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected during the course of these monitoring visits or provided in follow-up written communication.

In case of an emergency situation (eg, the COVID-19 pandemic), where study monitors may not be able to access the investigational centers for on-site visits, investigational centers will be monitored remotely, where allowed, and in accordance with local regulations.

Audit and Inspection

The sponsor may audit the investigational center to evaluate study conduct and compliance with protocols, SOPs, GCP guidelines, and applicable regulatory requirements. The sponsor’s Global Clinical Quality Assurance, independent of Global Specialty Development, is responsible for determining the need for (and timing of) an investigational center audit.

The investigator must accept that competent authorities and sponsor representatives may conduct inspections and audits to verify compliance with GCP guidelines.

In case of an emergency situation (eg, the COVID-19 pandemic), where auditors may not be able to access the investigational centers for on-site visits, investigational centers will be audited remotely, where allowed and in accordance with local regulations.

APPENDIX I. ETHICS

Informed Consent

The investigator, or a qualified person designated by the investigator, should fully inform the patient of all pertinent aspects of the study, including the written information approved by the IEC/ IRB. All written and oral information about the study will be provided in a language as nontechnical as practical to be understood by the patient. The patient should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. The above should be detailed in the source documents.

Written informed consent will be obtained from each patient before any study specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The patient's willingness to participate in the study will be documented in the ICF, which will be signed and personally dated by the patient and by the person who conducted the informed consent discussion. The investigator will keep the original ICFs, and copies will be given to the patients. It will also be explained to the patients that they are free to refuse participation in the study and free to withdraw from the study at any time without prejudice to future treatment.

Adult patients with a legally acceptable representative should provide informed consent according to national and local requirements.

Competent Authorities and Independent Ethics Committees/Institutional Review Boards

Before this study starts, the protocol will be submitted to the national competent authority and to the respective IEC/IRB for review. As required, the study will not start at a given investigational center before the IEC/IRB and competent authority (as applicable) for the investigational center give written approval or a favorable opinion.

Confidentiality Regarding Study Patients

The investigator must ensure that the privacy of the patients, including their identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the sponsor, patients will be identified not by their names, but by an identification number.

Personal medical information may be reviewed for the purpose of patient safety or for verifying data in the source and the CRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the sponsor, Global Quality Assurance (GCA), or competent authorities. Personal medical information will always be treated as confidential.

Registration of the Clinical Study

In compliance with national and local regulations and in accordance with Teva standard procedures, this clinical study will be registered on trials registry websites.

APPENDIX J. BIRTH CONTROL METHODS AND PREGNANCY TESTING

DEFINITIONS

Women of childbearing potential are defined as:

- Not surgically (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile nor clinically diagnosed infertile (documentation required) as assessed by a physician
- Not postmenopausal

Postmenopausal women are defined as:

- 1 year postmenopausal (no menses for 12 months without an alternative medical cause plus an increased concentration of FSH of more than 35 IU/L) in women not using hormonal contraception or hormonal replacement therapy

DESCRIPTION OF DIFFERENT BIRTH CONTROL METHODS

Highly effective birth control methods in females:

Highly effective birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered. Such methods include the following:

- Combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these should be initiated at least 7 days before the first dose of IMP.
- Progestogen-only hormonal contraception (oral, injectable, or implantable) associated with inhibition of ovulation; these should be initiated at least 7 days before the first dose of IMP.
- Intrauterine device or intrauterine hormone-releasing system need to be in place at least 2 months before the start of screening.
- Bilateral tubal occlusion (for hysteroscopic "Essure®" a hysterosalpingogram is required 3 months post procedure to assess surgical success) or tubal ligation.
- Vasectomized partner provided he is the sole sexual partner and has received medical assessment of the surgical success.
- Sexual abstinence is **only** considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.

Unacceptable birth control methods:

Periodic abstinence (eg, calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female condom and male condom should not be used together.

Male contraception:

Male patients (including vasectomized men) with partners of childbearing potential (whether pregnant or not) must always use condoms prior to IMP administration and until 20 weeks after last IMP dose.

Vasectomy:

Use of contraceptive methods also applies to vasectomized men.

Pregnant female partners of male study participants:

Male study participants must use condoms during intercourse if their female partners are pregnant.

APPENDIX K. LOST TO FOLLOW-UP

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the investigational center.

The following actions must be taken if a patient fails to return to the investigational center for a required study visit:

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

APPENDIX L. LIST OF PROHIBITED MEDICATIONS

INN	Formulation
Omalizumab or other Anti-IgE therapies	Injection (sc)
Dupilumab, Benralizumab	Injection (sc)
Corticosteroids	Systemic or cutaneous (topical)
Hydroxychloroquine	Systemic or cutaneous (topical)
Methotrexate	Systemic or cutaneous (topical)
Dapsone, Sulfasalazine	Systemic or cutaneous (topical)
Cyclosporine, Tacrolimus, Mycophenolate	Systemic or cutaneous (topical)
Cyclophosphamide	Systemic or cutaneous (topical)
Doxepin	Tablet (or other if applicable)
Leukotriene receptor antagonists (montelukast, zafirlukast, pranlukast)	Tablet (or other if applicable)
H2 antagonists (cimetidin, ranitidin, famotidin, nizatidin, roxatidin, lafutidin)	Tablet, granules, suspension, injection (iv)

INN=international nonproprietary name; iv=intravenous; sc=subcutaneous

Prior to the screening visit (-14 days) and during the study, the following medications and treatments will be restricted:

- Routine (daily or every other day during 5 or more consecutive days) doses of the following medications within 30 days prior to day -14: systemic or cutaneous (topical) corticosteroids (prescription or over-the-counter), hydroxychloroquine, methotrexate, cyclosporine, cyclophosphamide, Tacrolimus, mycophenolate, dapsone, or sulfasalazine.
- Routine (daily or every other day during 5 or more consecutive days) doses of doxepin within 14 days prior to day -14.
- Omalizumab or other anti-IgE therapy within 1 year prior to screening.
- Any LTRAs (montelukast or zafirlukast) or H2 blockers within 7 days prior to day -14.
- Any H1 antihistamines at greater than approved doses from 3 days after start of screening.
- Either intravenous IgG or plasmapheresis within 30 days prior to day -14.
- Treatment with an investigational agent within 30 days or longer depending on half-life (>5 half-lives) prior to the start of screening.

Patients who receive any excluded therapy during screening should be considered a screening failure. Patients who receive any excluded therapy after randomization will be discontinued from study treatment; under certain circumstances, a patient may be eligible to remain in the study when taking prohibited concomitant medications - such cases should be discussed with, and

approved by, the medical monitor. If a patient has received at least 1 dose of omalizumab following enrollment, the patient should be followed for safety for the remainder of the study.

Patients taking either LTRAs or H2 blockers for diseases other than CIU (eg, asthma or gastroesophageal reflux disease, respectively) will be permitted to continue their use during the study. These diseases must be recorded as part of the medical history collected during the screening period. Inhaled asthma controllers, including corticosteroids, are also permitted during the study.

Appendix M. PHARMACOKINETICS AND PHARMACODYNAMICS SAMPLES

Instructions for sampling, handling and shipment of the pharmacokinetics and pharmacodynamics samples are described in the TV45779-IMB-30086 Laboratory Manual.

Samples should not be shipped on a holiday. Samples are not to arrive on the Israel weekend or a holiday.

Samples will be analyzed using an appropriate validated method. Timing of the initiation of sample analysis will be determined by the management of bioanalytical laboratory responsible for the bioanalysis while keeping the study blinding, if any, intact.

APPENDIX N. IMMUNOGENICITY SAMPLES

Instructions for sampling, handling and shipment of the immunogenicity samples are described in the TV45779-IMB-30086 Laboratory Manual.

Samples should not be shipped on a holiday. Samples are not to arrive on the Israel weekend or a holiday.

Samples will be analyzed using an appropriate validated method. Timing of the initiation of sample analysis will be determined by the management of bioanalytical laboratory responsible for the bioanalysis while keeping the study blinding, if any, intact.

APPENDIX O. PRODUCT COMPLAINTS

I. Clinical Product Complaints/Device Deficiency

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical IMP supplies or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to:

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling, etc.)
- defective components
- missing or extra units (eg, primary container is received at the investigational center with more or less than the designated number of units inside)
- incorrect packaging, or incorrect or missing labeling/labels
- unexpected or unanticipated taste or odor, or both
- device not working correctly or appears defective in some manner

Each investigational center will be responsible for reporting a possible clinical product complaint by completing the product complaint form provided by Teva and emailing it to clinical.productcomplaints@tevapharm.com within 48 hours of becoming aware of the issue.

For complaints involving a device/combination product or other retrievable item, it is required that the device/combination product (or item) be sent back to the sponsor for investigative testing whenever possible. For complaints involving an IMP, all relevant samples (eg, the remainder of the patient's IMP supply) should be sent back to the sponsor for investigative testing whenever possible.

Product Complaint Information Needed from the Investigational Center

In the event that the product complaint form cannot be completed, the investigator will provide the following information, as available:

- investigational center number and principal investigator name
- name, phone number, and address of the source of the complaint
- clinical protocol number
- patient identifier (patient study number) and corresponding visit numbers, if applicable
- patient number, bottle, and kit numbers (if applicable) for double-blind or open-label studies
- product available for return Yes/No
- product was taken or used according to protocol Yes/No
- description or nature of complaint

- device deficiency associated with adverse event Yes/No
- device deficiency associated serious adverse event Yes/No *
- device deficiency that could lead to a serious adverse event Yes/No *
- clinical supplies unblinded (for blinded studies) Yes/No
- date and name of person receiving the complaint

Note: Reporting a product complaint must not be delayed even if not all the required information can be obtained immediately. Known information must be reported immediately. The sponsor will collaborate with the investigator to obtain any outstanding information.

*Please refer to Table 6 and Table 7.

Handling of Investigational Medicinal Product(s) at the Investigational Center(s)

The investigator is responsible for retaining the product in question in a location separate from the investigator's clinical study supplies. The sponsor may request that the investigator returns the product for further evaluation and/or analysis. If this is necessary, the clinical study monitor or designee will provide the information needed for returning the IMP or device.

If it is determined that the investigational center must return all IMP or devices, the sponsor will provide the information needed to handle the return.

The integrity of the randomization code and corresponding blinded clinical supplies will be maintained whenever possible. A serious adverse event or the potential for a product quality problem existing beyond the scope of the complaint may be a reason to unblind the clinical supplies for an affected patient, if applicable.

Adverse Events or Serious Adverse Events Associated with a Product Complaint

If there is an adverse event or serious adverse event due to product complaint, the protocol should be followed for recording and reporting (Section 7.1.2 and Section 7.1.5.3, respectively).

Documenting a Product Complaint

The investigator will record in the source documentation a description of the product complaint, the initial determination whether the deficiency could have led to a serious adverse event (Section II), and any actions taken to resolve the complaint and to preserve the safety of the patient. Once the complaint has been investigated by the sponsor and the investigator, if necessary, an event closure letter may be sent to the investigational center where the complaint originated or to all investigational centers using the product.

Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study.

II. Assessment of Device Performance

Device performance will be assessed by device deficiencies and product complaints.

A device deficiency is defined as any inadequacy of an investigational medical device or combination product with respect to its identity, quality, durability, reliability, usability, safety, or performance (Figure 3). This definition includes malfunctions, use errors, inadequate labeling

(eg, unintelligible label, incorrect expiry date), and product complaints that are related to the IMP.

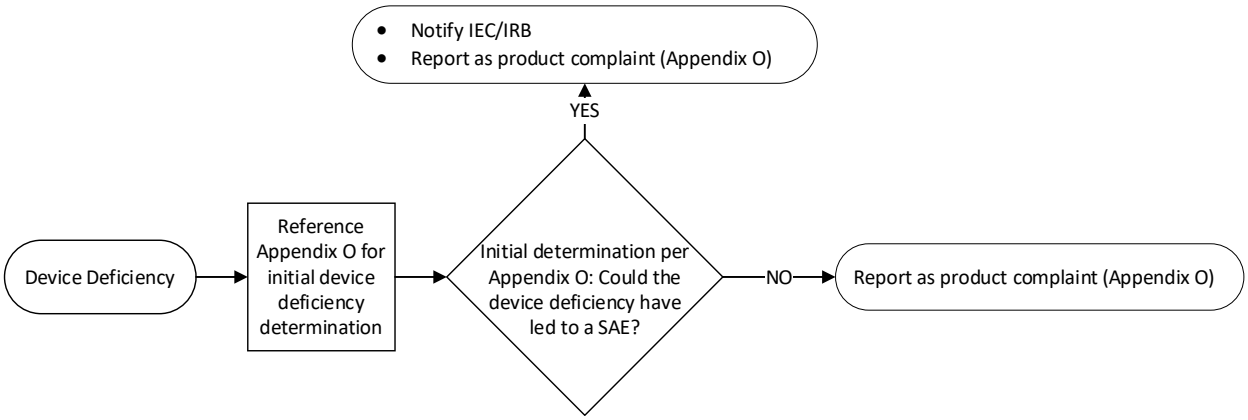
The investigator should use Table 6 and Table 7 to help make an initial determination whether the device deficiency could have led to a serious adverse event and include this assessment in the product complaint form.

Device deficiencies with potential serious adverse device effect are defined as deficiencies that might have led to a serious adverse device effect if (Figure 3):

- suitable action had not been taken (or)
- intervention had not been made (or)
- if circumstances had been less fortunate

These device deficiencies shall be reported to the IEC/IRB by the investigator and to the regulatory authorities by the sponsor according to the national and local regulations.

Figure 3: Decision Tree for Device Deficiencies



IEC=Independent Ethics Committee; IRB=Institutional Review Board; SAE=serious adverse event

Table 6: Potential Use-Related Deficiencies That Could Lead to Serious Adverse Events

Use Step	Use Error	Potential Hazard Situation	Potential Harm
Store the product in the appropriate storage location	Failure to store product between 2°C and 8°C	Injection of Degraded or Expired Drug	Injury or impairment requiring professional medical intervention to patient or third party
Check the product name	Failure to identify the product name	Injection of Wrong Drug	Death to patient or third party
Check the product dose	Failure to identify the dose	Overdose	Injury or impairment requiring professional medical intervention to patient or third party
Check the product expiration date	Failure to check the expiration date	Injection of Degraded or Expired Drug	Injury or impairment requiring professional medical intervention to patient or third party
Allow the product to come to room temperature	Failure to allow the product to come to room temperature prior to use	Injection of Degraded or Expired Drug	Injury or impairment requiring professional medical intervention to patient or third party
Remove the syringe from the packaging	Failure to grasp syringe properly when removing from packaging.	Damaged device.	Injury or impairment requiring professional medical intervention to patient or third party
Inspect the syringe	Failure to check the drug color and quality.	Injection of Degraded or Expired Drug	Injury or impairment requiring professional medical intervention to patient or third party
Choose an injection site	Failure to select an acceptable injection site that is consistent with subcutaneous injection	Injection to Wrong Depth – Intramuscular or Intradermal	Injury or impairment requiring professional medical intervention to patient or third party
Clean the injection site	Failure to clean the injection site prior to use	Improper Aseptic or Disinfection Technique	Permanent impairment or life-threatening injury to patient or third party
Pinch the skin	Failure to pinch the skin adequately to achieve the intended injection depth	Injection to Wrong Depth – Intramuscular or Intradermal	Injury or impairment requiring professional medical intervention to patient or third party
Insert the needle into the pinched skin	Failure to manipulate the syringe to be at 90 degrees	Injection to Wrong Depth - Intramuscular or Intradermal	Injury or impairment requiring professional medical intervention to patient or third party

Table 6: Potential Use-Related Deficiencies That Could Lead to Serious Adverse Events (Continued)

Use Step	Use Error	Potential Hazard Situation	Potential Harm
Insert the needle into the pinched skin	Failure to avoid inserting the needle through clothing.	Improper Aseptic or Disinfection Technique	Permanent impairment or life-threatening injury to patient or third party
Inject the product	Failure to push the plunger rod all the way down to activate the needle shield.	Needle Stick Injury - Used Needle	Permanent impairment or life-threatening injury to patient or third party
Release the plunger rod	Failure to release the plunger rod to deploy the needle shield.	Needle Stick Injury - Used Needle	Permanent impairment or life-threatening injury to patient or third party
Inspect the injection site	Failure to avoid rubbing the injection site.	Improper Aseptic or Disinfection Technique	Permanent impairment or life-threatening injury to patient or third party
Dispose of the used product	Failure to avoid putting the cap back on the needle. Failure to dispose of syringe in the intended location.	Needle Stick Injury - Used Needle	Permanent impairment or life-threatening injury to patient or third party

Table 7: Potential Design Related Deficiencies That Could Lead to Serious Adverse Events

Device Component	Failure Mode	Potential Hazard Situation	Harm
Syringe assembly	Cannot push plunger rod to deliver drug without an extremely forceful push.	Damaged or inoperable device	Injury or impairment requiring professional medical intervention to patient or third party
Syringe assembly	Syringe assembly appears damaged and inoperable.	Damaged or inoperable device	Injury or impairment requiring professional medical intervention to patient or third party
Syringe assembly	Drug product leaks.	Breach of container closure integrity or other sterile barrier	Permanent impairment or life- threatening injury to patient or third party
Rigid Needle Shield	The rigid shell detaches from the elastomer when user removes the RNS.	Damaged or inoperable device	Injury or impairment requiring professional medical intervention to patient or third party
Rigid Needle Shield	The RNS cannot be removed from the needle.	Damaged or inoperable device	Injury or impairment requiring professional medical intervention to patient or third party
Rigid Needle Shield	The RNS detaches from the needle during shipping and storage.	Breach of container closure integrity or other sterile barrier	Permanent impairment or life- threatening injury to patient or third party
Rigid Needle Shield	Needle tip punctures the RNS.	Breach of container closure integrity or other sterile barrier	Permanent impairment or life- threatening injury to patient or third party
Needle	Needle has blunted or otherwise damaged tip	Damaged or inoperable device	Injury or impairment requiring professional medical intervention to patient or third party
Needle	Needle deforms when attempting insertion into patient's skin.	Damaged or inoperable device	Injury or impairment requiring professional medical intervention to patient or third party
Needle	Needle clogged	Damaged or inoperable device	Injury or impairment requiring professional medical intervention to patient or third party
Needle Safety Device	The NSD activates prematurely.	Damaged or inoperable device	Injury or impairment requiring professional medical intervention to patient or third party

Table 7: Potential Design Related Deficiencies That Could Lead to Serious Adverse Events (Continued)

Device Component	Failure Mode	Potential Hazard Situation	Harm
Needle Safety Device	The NSD does not fully shield the needle after activation.	Needle Stick Injury - Used Needle	Permanent impairment or life- threatening injury to patient or third party
Needle Safety Device	The activated NSD is overridden to expose a used needle.	Needle Stick Injury - Used Needle	Permanent impairment or life- threatening injury to patient or third party
Needle Safety Device	The NSD does not activate post-injection.	Needle Stick Injury - Used Needle	Permanent impairment or life- threatening injury to patient or third party
Tamper Seal	Carton closure seal is not adhered to carton or broken.	Tampered Product	Injury or impairment requiring professional medical intervention to patient or third party
Carton	Carton is damaged	Damaged or inoperable device	Injury or impairment requiring professional medical intervention to patient or third party
Labeling	Critical information missing or incomplete	Exposure to toxic substance or degraded drug	Injury or impairment requiring professional medical intervention to patient or third party

APPENDIX P. DATA MANAGEMENT AND RECORD KEEPING

Direct Access to Source Data and Documents

All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the CRF. Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

If data are processed from other institutions or by other means (eg, clinical laboratory, central image center, or electronic diary data) the results will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management).

The medical experts, study monitors, auditors, IEC/ IRB, and inspectors from competent authority (or their agents) will be given direct access to source data and documents (eg, medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that patient confidentiality is maintained in accordance with national and local requirements.

The investigator must maintain the original records (ie, source documents) of each patient's data at all times. The investigator must maintain a confidential patient identification list that allows the unambiguous identification of each patient.

Data Collection

Data will be collected using CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in 21 Code of Federal Regulations (CFR) Part 11 (USA) and documents of other concerned competent authorities. Before using the CDMS, it will be fully validated and all users will receive training on the system and study-specific training. After they are trained, users will be provided with individual system access rights.

Data will be collected at the investigational center by appropriately designated and trained personnel, and CRFs must be completed for each patient who provided informed consent. Patient identity should not be discernible from the data provided on the CRF.

If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary data, electronic patient-reported outcome [ePRO] tablet), these data will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management). All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the CRF. Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

For patients who enter a study but do not meet entry criteria, at a minimum, data for screening failure reason, demography, and adverse events from the time of informed consent will be entered in the CRF.

Data Quality Control

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Oversight will be carried out as described in the sponsor's SOPs for clinical studies. Day to day data management tasks for this study are delegated to a contract organization, and these functions may be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the sponsor before the start of data management activities.

Data will be verified by the study monitor, using the data source, and reviewed by data management using both automated logical checks and manual review. Data identified as erroneous, or data that are missing, will be referred to the investigational center for resolution through data queries. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed. Data from external sources will be compared with the information available in the CDMS and any discrepancies will be queried.

Applicable terms will be coded according to the coding conventions for this study.

At the conclusion of the study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgment that all data have been captured and confirmed as accurate. All data collected will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

Archiving of Case Report Forms and Source Documents

Sponsor Responsibilities

The original CRFs will be archived by the sponsor. Investigational center-specific CRFs will be provided to the respective investigational centers for archiving.

Investigator Responsibilities

The investigator must maintain all written and electronic records, accounts, notes, reports, and data related to the study and any additional records required to be maintained under country, state/province, or national and local laws, including, but not limited to:

- full case histories
- signed informed consent forms
- patient identification lists
- CRFs for each patient on a per-visit basis
- data from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary)
- safety reports
- financial disclosure reports/forms
- reports of receipt, use, and disposition of the IMP
- copies of all correspondence with sponsor, the IEC/IRB, and any competent authority

The investigator will retain all records related to the study and any additional records required, as indicated by the protocol and according to applicable laws and regulations, until the CRO or sponsor notifies the institution in writing that records may be destroyed. If, after 25 years from study completion, or earlier in the case of the investigational center closing or going out of business, the investigator reasonably determines that study record retention has become unduly burdensome, and sponsor has not provided written notification of destruction, then the investigator may submit a written request to sponsor at least 60 days before any planned disposition of study records. After receipt of such request, the sponsor may make arrangements for appropriate archival or disposition, including requiring that the investigator deliver such records to the sponsor. The investigator shall notify the sponsor of any accidental loss or destruction of study records.

APPENDIX Q. PUBLICATION POLICY

All unpublished information given to the investigator by the sponsor shall not be published or disclosed to a third party without the prior written consent of the sponsor.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results: "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (ICMJE 2019). Publication of the results will occur in a timely manner according to applicable regulations. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual investigational center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work.
- Drafting the work or revising it critically for important intellectual content.
- Final approval of the version to be published.
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The publications committee established by the sponsor will oversee this process. Additional publications may follow. Policies regarding the publication of the study results are defined in the financial agreement.

No patent applications based on the results of the study may be made by the investigator nor may assistance be given to any third party to make such an application without the written authorization of the sponsor.

APPENDIX R. CTCAE GRADING SCALE

The CTCAE Grading Scale will be provided as a separate document.

APPENDIX S. ADDITIONAL INFORMATION TO THE PROTOCOL FOR SOUTH KOREA

The sponsor sought advice for the study protocol regarding detailed study design and statistical analysis from the FDA (Type 2 meetings, 2020, 2021) and the EMA (Scientific Advice Meeting, 2020, SA Follow Up, 2020).

The EMA agreed essentially to the study design proposed by the sponsor.

Later, the FDA requested a different study design with at least 600 patients, inclusion of arms with 150 mg doses of TEV-45779 or XOLAIR and an additional co-primary endpoint of relative potency of 2 dose levels.

Harmonization of study design according to the FDA requests was not accepted by the EMA.

The sponsor incorporated the different requests into the study design. Therefore, the study protocol contains two statistical approaches for FDA and EMA, respectively.

In this study, patients will be randomly assigned to 1 of the 4 treatment arms and may receive 150 mg or 300 mg doses of TEV-45779 or XOLAIR. Thus, patients from a specific country will be randomized to all treatment arms.

Patients from South Korea will be part of the whole study population. Their data will be pooled and analyzed with the data from all study patients.

There will be 1 primary analysis according to FDA criteria and 1 according to EMA criteria. The results of both analyses will be completely reported in the Clinical Study Report.

As this is an investigational medicinal product, Teva has not determined at this time if a Marketing Authorization Application (MAA) will be submitted to the Ministry for Food and Drug Safety (MFDS). In the event that an MAA is submitted to the MFSD, Teva will determine the successfulness of this study result in South Korea by using EMA criteria as specific criteria for South Korea.

APPENDIX T. ADDITIONAL INFORMATION TO THE PROTOCOL FOR INDIA

For India, Cetirizine is to be used as the single H1 antihistamine at stable and fixed doses, not exceeding label recommendations, as a uniform standard treatment regimen, throughout the entire study according to Section 3.1.