MATRIKS BIOTEK
innovation for health & wellness

"trace & catch"

Instructions for Use

Omalizumab (Xolair®) ELISA

SHIKARI®

Q-OMA

Enzyme immunoassay for the quantitative determination of Omalizumab (Xolair®) in serum and plasma

REF **TR-OMAv1** Σ 12 x 8 2-8°C

Revision # 1.1 December 2016

CE IVD

Matriks Biotek® Laboratories
www.matriksbiotek.com

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	Omalizumab (Xolair®) monoclonal based quantitative analyses
Required Volume (µl)	5
Total Time (min)	70
Sample	Serum, plasma
Sample Number	96
Detection Limit (µg/mL)	0,010
Spike Recovery (%)	97
Shelf Life (year)	1

Intended Use

Enzyme immunoassay for the quantitative determination of omalizumab (Xolair®) in serum and plasma. *Matriks Biotek omalizumab ELISA* has been especially developed for the quantitative analysis omalizumab in serum and plasma samples between the Cmin and Cmax range of concentrations indicated in the pharmacokinetics section of prospectus.

Summary and Explanation

According to the prospectus; Xolair is approved by the U.S. Food and Drug Administration (FDA) for use in adults and adolescents 12 years of age and older, who have moderate to severe persistent asthma and a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Xolair is not indicated for acute bronchospasm or status asthmaticus. Xolair is also approved for chronic idiopathic urticaria in adults and adolescents (12 years of age and above) who remain symptomatic despite H1 antihistamine treatment. It is not indicated for other allergic conditions or other forms of urticaria. Because of the risk of anaphylaxis, healthcare providers administering Xolair should observe patients closely for an appropriate period of time and be prepared to manage anaphylaxis that can be life-threatening.3

On September 26, 2014, the U.S. FDA released a drug safety alert entitled: FDA approves label changes for asthma drug Xolair (omalizumab), including describing slightly higher risk of heart and brain adverse events. An FDA review of safety studies suggests a slightly increased risk of problems involving the heart and blood vessels supplying the brain among patients being treated with the asthma drug Xolair (omalizumab) than in those who were not treated with Xolair. As a result, FDA has added information about these potential risks to the drug label. Additionally, reviewers found no difference in the rates of cancer between those patients being treated with Xolair and those who were not being treated with Xolair. However, due to limitations in the 5-year study, FDA cannot rule out a potential risk of cancer with Xolair, so this information was added to the Warnings and Precautions section of the drug label.

Allergic Asthma

Omalizumab is indicated for treatment of adults and adolescents 12 years of age and older, who have moderate to severe persistent asthma and a positive skin test or in vitro reactivity to aperennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.

Chronic Urticaria

Omalizumab is indicated for treatment of chronic idiopathic urticaria in adults and adolescents (12 years of age and above) who remain symptomatic despite H1 antihistamine treatment.

Saini et al conducted a 40-week, randomized, double-blind, placebo-controlled trial (ASTERIA I) to evaluate the efficacy and safety of subcutaneous omalizumab as add-on therapy for 24 weeks in patients (n=319) with chronic idiopathic urticaria/spontaneous urticaria (CIU/CSU) who remained symptomatic despite H1 antihistamine treatment.1 Eligible patients aged 12–75 years with CIU/CSU who remained symptomatic despite treatment with approved doses of H1 antihistamines were randomized (1:1:1:1) in a double-blind manner to subcutaneous omalizumab 75 mg (n=78), 150 mg (n=80), or 300 mg (n=81) or placebo (n=80) every 4 weeks for 24 weeks followed by 16 weeks of follow-up. The primary outcome measured was change from baseline in weekly itch severity score (ISS) at week 12. Secondary outcomes evaluated at week 12, included changes from baseline in UAS7 and weekly number of hives score; time to MID response (≥5point decrease) in weekly ISS; the proportion of patients with UAS7≤6; the proportion of weekly ISS MID responders; changes from baseline in weekly size of largest hive score and overall DLQI score; the proportion of angioedema-free days during weeks 4 to 12; and the proportion of patients with complete response (UAS7=0). Compared with placebo mean weekly ISS was reduced from baseline to week 12 by an additional 2.96 points (95% confidence interval (CI): −4.71 to −1.21; p=0.0010), 2.95 points (95% CI: −4.72 to −1.18; p=0.0012), and 5.80 points (95% CI: −7.49 to −4.10; p<0.0001) in the omalizumab 75-mg, 150-mg, and 300-mg groups, respectively. The omalizumab 300-mg group met all nine secondary end points, including a significant decrease in the duration of time to reach minimally important difference response (≥5point decrease) in weekly ISS (p<0.0001) and higher percentages of patients with well-controlled symptoms (urticaria activity score over 7 days (UAS7) ≤6: 51.9% vs. 11.3% p<0.0001) and complete response (UAS7=0: 35.8% vs. 8.8% p<0.0001) versus placebo. During the 24-week treatment period, the proportions of patients who experienced one or more treatment-emergent adverse events (AEs) ranged from 57 to 69% in the omalizumab groups versus 51% in the placebo group. Additionally, 2 (2.9%), 3 (3.4%), 0, and 4 (5.0%) patients in the omalizumab 75mg, 150-mg, 300-mg, and placebo groups, respectively, experienced a serious adverse event. Omalizumab 300 mg administered every 4 weeks reduced weekly ISS and other symptom scores versus placebo in CIU/CSU patients who remained symptomatic despite treatment with approved doses of H1 antihistamines. Additionally, the results of this study showed a

sustained treatment effect of omalizumab 300 mg for up to 24 weeks on CIU/CSU symptom scores in patients with H1 antihistamine–refractory CIU/CSU. The safety profile for omalizumab over 24 weeks of treatment in patients with CIU/CSU receiving approved doses of H1 antihistamines was consistent with the established safety profile in allergic asthma and with previous observations in CIU/CSU.

Allergic Asthma in Children < 12 Years of Age

Deschildre et al evaluated omalizumab efficacy and safety in a real-life setting in children aged 6 to 18 years (n=104) with severe asthmas followed up in pediatric pulmonary tertiary care centers.37 Asthma control levels, exacerbations, inhaled corticosteroid dose, lung function and adverse events were evaluated over 1 year. Children were characterized by allergic sensitization to three or more allergens (66%), high IgE levels (mean 1125 kU · L(-1)), high rate of exacerbations (4.4 per year) and healthcare use during the previous year, and high inhaled corticosteroid dose (mean 703 µg equivalent fluticasone per day). Asthma control levels defined as good, partial or poor, improved from 0%, 18% and 82% at entry to 53%, 30% and 17% at week 20, and to 67%, 25% and 8% at week 52, respectively ($p<0.0001$). Reported exacerbation and hospitalization rates decreased by 72% and 88.5%, respectively. At 12 months, forced The safety of Xolair in the treatment of postmenopausal osteoporosis was assessed in a 3-year, randomized, double-blind, placebo-controlled, multinational study of 7808 postmenopausal women aged 60 to 91 years. A total of 3876 women were exposed to placebo and 3886 women were exposed to Xolair administered subcutaneously once every 6 months as a single 60 mg dose. All women were instructed to take at least 1000 mg of calcium and 400 IU of vitamin D supplementation per day.

Expiratory volume in 1 s (FEV1) improved by 4.9% ($p=0.023$), and inhaled corticosteroid dose decreased by 30% ($p<0.001$). Six patients stopped omalizumab for related significant adverse events. Omalizumab improved asthma control in children with severe allergic asthma and was generally well tolerated. Authors concluded that he observed benefit was greater than that reported in clinical trials.

Sorkness et al conducted a post-hoc analyses which examined patient characteristics of those eligible and ineligible for omalizumab; described onset of effect after initiation of omalizumab and offset of treatment effect after stopping therapy; and determined whether the efficacy differs by age, asthma severity, dosing regimen, and pre-specified biomarkers.36 Inner-city children and adolescents with persistent allergic asthma enrolled in the Inner-City Anti-IgE Therapy for Asthma (ICATA) trial that compared omalizumab with placebo added to guidelines-based therapy for 60 weeks were eligible for the evaluation (a significant portion of children and adolescents particularly suited for omalizumab because of asthma severity status were ineligible due to IgE >1300 IU/mL).

Two hundred ninety-three of 889 participants (33%) clinically suitable for omalizumab were ineligible for dosing according to a modified dosing table specifying IgE level and body weight criteria. Baseline symptoms were comparable among those eligible and ineligible to receive omalizumab, but other characteristics (rate of health care utilization and skin test results) differed. Patients receiving biweekly injections experienced a greater reduction in both exacerbations (OR = 2.54) and inhaled corticosteroids (ICS) usage (−204.8 µg/day) compared to patients receiving monthly injections (1.42 and −50.2 µg/day; p=0.08 and p=0.02, respectively). Omalizumab efficacy for symptom days per 2 weeks did not differ by dosing regimen (p=0.62). Patients with total IgE ≥700 IU/mL had the greatest reduction in ICS usage (−504.6 µg/day) because of treatment with omalizumab. The time of onset of omalizumab effect was <30 days and time of offset was between 30 and 120 days. No difference in efficacy was noted by age or asthma severity, but high exhaled nitric oxide, blood eosinophils, and body mass index predicted efficacy. Researchers concluded that results of this analysis showed that efficacy for exacerbations and ICS treatment was comparable in children 6 to 12 years of age compared with older children (>12 years). Additionally, the data suggested that omalizumab may be efficacious in both severe disease (steps 5-6 treatments) and more moderate disease (steps 1-4). Certain subgroups of persons, for example, those with higher exhaled nitric oxide, blood eosinophils, and BMI were more likely to benefit from omalizumab according to the secondary analysis.

The Inner-City Anti-IgE Therapy for Asthma (ICATA) Study was a 60-week, randomized, doubleblind, placebo-controlled, parallel-group trial (n=419) which evaluated the effectiveness of omalizumab (75-375 mg subcutaneously every 2-4 weeks), as compared with placebo, when added to guidelines-based therapy.25 The primary outcome was reduction in symptoms and exacerbations of asthma. Inner-city patients 6 to 20 years of age with persistent asthma (receiving long-term therapy for disease control and having symptoms of persistent asthma or evidence of uncontrolled disease as indicated by hospitalization or unscheduled urgent care in the 6 to 12 months preceding study entry), at least one positive skin test for a perennial allergen, weight between 20 and 150 kg, and having total serum levels of IgE between 30 and 1300 IU per milliliter were eligible for enrollment. Additionally, patients not receiving long-term control therapy were eligible for enrollment only if they had both persistent symptoms and uncontrolled asthma. The primary outcome defined as reduction in symptoms (number of days with symptoms during the previous two weeks) and exacerbations of asthma was evaluated every 4 weeks. Omalizumab as compared with placebo significantly reduced the number of days with asthma symptoms, from 1.96 to 1.48 days per 2-week interval, a 24.5% decrease (p<0.001). Similarly, the percentage of participants with exacerbations (one or more) during the study was 48.8% in the placebo group as compared with 30.3% in the omalizumab group (p<0.001), and the percentage who were hospitalized because of asthma was 6.3% as compared with 1.5%,.

Test Principle

Solid phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle. Standards and samples (serum or plasma) are incubated in the microtitre plate coated with the reactant specific for omalizumab (Xolair®). Following incubation wells are washed and then horse radish peroxidase (HRP) conjugate is added and binds to omalizumab. After incubation, the wells are washed and the bound enzymatic activity is detected by addition of chromogen-substrate. The color developed is proportional to the amount of omalizumab (Xolair®) in the sample or standard. Results of samples can be determined directly using the standard curve.

Warnings and Precautions

1. For professional use only.
2. Before starting the assay, read the instructions completely and carefully. Use the valid version of the package insert provided with the kit. Be sure that everything is understood. For further information please refer to the local distributor.
3. In case of severe damage of the kit package please contact Matriks biotek or your supplier in written form, latest one week after receiving the kit. Do not use damaged components in test runs, but keep safe for complaint related issues.
4. Obey lot number and expiry date. Do not mix reagents of different lots. Do not use expired reagents.
5. Follow good laboratory practice and safety guidelines. Wear lab coats, disposable latex gloves and protective glasses where necessary.
6. Reagents of this kit containing hazardous material may cause eye and skin irritations. See MATERIALS SUPPLIED and labels for details.
7. Chemicals and prepared or used reagents have to be treated as hazardous waste according the national biohazard safety guidelines or regulations.
8. Avoid contact with Stop solution. It may cause skin irritations and burns.

9. All reagents of this kit containing human serum (i.e. standards) have been tested and were found negative for HIV I/II, HBsAg and HCV. However, a presence of these or other infectious agents cannot be excluded absolutely and therefore reagents should be treated as potential biohazards in use and for disposal.

10. Some reagents contain sodium azide (NaN_3) as preservatives. In case of contact with eyes or skin, flush immediately with water. NaN_3 may react with lead and copper plumbing to form explosive metal azides. When disposing reagents, flush with large volume of water to avoid azide build-up.

Storage and Stability

The kit is shipped at ambient temperature and should be stored at 2-8°C. Keep away from heat or direct sun light. The strips of microtiter plate is stable up to the expiry date of the kit in the broken, but tightly closed bag when stored at 2–8°C.

Specimen Collection and Storage

Serum, Plasma (EDTA, Heparin)*

The usual precautions for venipuncture should be observed. It is important to preserve the chemical integrity of a blood specimen from the moment it is collected until it is assayed. Do not use grossly hemolytic, icteric or grossly lipemic specimens. Samples appearing turbid should be centrifuged before testing to remove any particulate material.

Storage:	2-8°C	-20°C	Keep away from heat or direct sun light Avoid repeated freeze-thaw cycles
Stability:	2 d	6 mon	

*. Omalizumab (Xolair®) infusion camouflages/masks the presence of antibody to Omalizumab in serum/plasma samples. Therefore, blood sampling time is critical for detection of Omalizumab. Matriks Biotek Laboratories propose to obtain blood sample just before the infusion of Omalizumab (Xolair®) or at least 2 weeks after the infusion of Omalizumab (Xolair®).

Materials Supplied

1 x 12 x 8	MTP	**Microtiter Plate** Break apart strips. Microtiter plate with 12 rows each of 8 wells coated with reactant for detection of Omalizumab (Xolair®).
6 x 2 mL	STND A-F	**Omalizumab Standards A-F** 1; 0,3; 0,1; 0.03; 0,01 and 0 microgram/mL Ready to use. Used for construction of the standard curve. Contains omalizumab (Xolair®), human serum, stabilizer and <0.1% NaN_3.
1 x 50 mL	ASSAY BUF	**Assay Buffer** Blue colored. Ready to use. Contains proteins and <0.1% NaN_3.
1 x 12 mL	HRP CONJ	**Peroxidase Conjugate** Red colored. Ready to use. Contains horse radish peroxidase (HRP) and stabilizers.
1 x 12 mL	TMB SUBS	**TMB Substrate Solution** Ready to use. Contains TMB
1 x 12 mL	TMB STOP	**TMB Stop Solution** Ready to use. 1N HCl.
1 x 50 mL	WASHBUF CONC	**Wash Buffer**, Concentrate (20x) Contains Buffer with Tween 20.
2 x 1	ADH FILM	**Adhesive Film** For covering of Microtiter Plate during incubation.
2x1	SLGP	**Semi-Log Graph Paper** For constructing standard curve and calculation of results

Materials Required but not Supplied

1. Micropipettes (Multipette Eppendorf or similar devices, < 3% CV).
2. Calibrated measures.
3. Tubes for sample dilution.

4. Wash bottle, automated or semi-automated microtiter plate washing system
5. Microtiter plate reader capable of reading absorbance at 450 nm.
6. Bidistilled or deionised water, paper towels, pipette tips and timer.

Procedure Notes

1. Any improper handling of samples or modification of the test procedure may influence the results. The indicated pipetting volumes, incubation times, temperatures and pretreatment steps have to be performed strictly according to the instructions. Use calibrated pipettes and devices only.
2. Once the test has been started, all steps should be completed without interruption. Make sure that required reagents, materials and devices are prepared ready at the appropriate time. Allow all reagents and specimens to reach room temperature (18-25 °C) and gently swirl each vial of liquid reagent and sample before use. Mix reagents without foaming.
3. Avoid contamination of reagents, pipettes and wells/tubes. Use new disposable plastic pipette tips for each reagent, standard or specimen. Do not interchange caps. Always cap not used vials. Do not reuse wells/tubes or reagents.
4. Use a pipetting scheme to verify an appropriate plate layout.
5. Incubation time affects results. All wells should be handled in the same order and time sequences. It is recommended to use an 8-channel micropipette for pipetting of solutions in all wells.
6. Microplate washing is important. Improperly washed wells will give erroneous results. It is recommended to use a multichannel pipette or an automatic microplate washing system. Do not allow the wells to dry between incubations. Do not scratch coated wells during rinsing and aspiration. Rinse and fill all reagents with care. While rinsing, check that all wells are filled precisely with Wash Buffer, and that there are no residues in the wells.
7. Humidity affects the coated wells/tubes. Do not open the pouch until it reaches room temperature. Unused wells/tubes should be returned immediately to the resealed pouch including the desiccant.

Pre-Test Setup Instructions

1. Preparation of Components

Dilute/ disolve	Component	with	Diluent	Relation	Remarks	Storage	Stability
10 mL	Wash Buffer*	Up to 200 mL	bidist. Water	1:20	Warm up at 37°C to dissolve crystals. Mix vigorously.	2-8 °C	4 w

***.** Prepare Wash Buffer before starting assay procedure.

2. Dilution of Samples*

Sample	To be diluted	With	Relation	Remarks
Serum/ Plasma	Initially 1:200	Assay Buffer	1:200	For dilution at 1:200; 5µl Sample + 995µl Assay Buffer

*. Patient samples with a concentration of omalizumab (Xolair®) above the measuring range are to be rated as "> highest standard". The result must not be extrapolated. The patient sample in question ***should be diluted with assay buffer*** and retested.

Test Procedure

1	Pipette **100µl** of **Assay Buffer** non-exceptionally into each of the wells to be used.
2	Pipette **10 µL** of each ready-to use Standards or **1:200** Serum Samples into the respective wells of microtiter plate Wells A1: Standard A B1: Standard B C1: Standard C D1: Standard D E1: Standard E F1: Standard F G1 and on: Sample (Serum/Plasma)
3	Cover the plate with adhesive foil. Incubate 30 min at room temperature (18-25°C).
4	Remove adhesive foil. Discard incubation solution. Wash plate 3 times each with 300 µL of diluted Wash Buffer. Remove excess solution by tapping the inverted plate on a paper towel.
5	Pipette 100 µL of ready-to use Peroxidase into each well.
6	Cover the plate with adhesive foil. Incubate 30 min at room temperature (18-25°C).
7	Remove adhesive foil. Discard incubation solution. Wash plate 3 times each with 300 µL of diluted Wash Buffer. Remove excess solution by tapping the inverted plate on a paper towel.
8	Pipette 100 µL of TMB Substrate Solution into each well.
9	Incubate 10 min (without adhesive foil.) at room temperature (18-25°C) in the dark.
10	Stop the substrate reaction by adding 100 µL of Stop Solution into each well. Briefly mix contents by gently shaking the plate. Color changes from blue to yellow.
11	Measure optical density with a photometer at 450/650 nm and reference at 620 nm is within 30 min after pipetting of the Stop Solution.

Quality Control

The test results are only valid only if the test has been performed following the instructions. Moreover the user must strictly adhere to the rules of GLP (Good Laboratory Practice) or other applicable standards/laws. All standards must be found within the acceptable ranges as stated above and/or label. If the criteria are not met, the run is not valid and should be repeated. In case of any deviation the following technical issues should be proven: Expiration dates of (prepared) reagents, storage conditions, pipettes, devices, incubation conditions and washing methods.

Calculation & Interpretation of Results

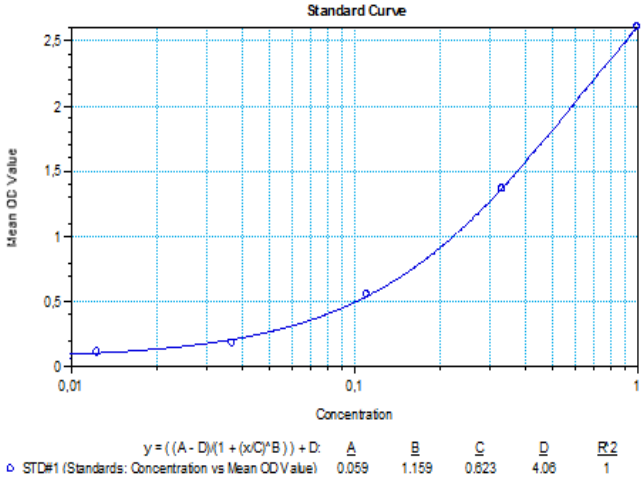
1. A standard curve should be calculated using the standard concentration (X-axis) versus the OD450 (we suggest that OD readings done at double wavelength at OD450/650 and OD value read at 650nm subtracted from 450nm OD VALUE) VALUES (Y-axis).
   In case of manual plot, we suggest semilog graph paper. If computer data regation is going to be used, we recommend primarily "4 Parameter Logistic (4PL)" or secondly the "point-to-point calculation".

2. The concentration of the samples can be read from this standard curve as follows. Using the absorbance value for each sample, determine the corresponding concentration of the drug from standard curve. This value always has to be multiplied by the dilution factor. If any diluted sample is reading greater than highest standard, it should be further diluted appropriately with Assay Buffer and retested. Also this second dilution has to be used for calculation the final results.

3. Any sample diluted at 1:10 and still reading greater than the highest standard should be further diluted appropriately with Assay Buffer and retested. Because the samples have been diluted, the concentration determined from the standard-curve must be multiplied by the dilution factor.

Typical Calibration Curve
(Example. Do not use for calculation!)

Sample	Mean OD 450/650	Concentration (ng/mL)
A	2.595	1000
B	1.361	300
C	0.550	100
D	0.182	30
E	0.115	10
F	0.054	0



Assay Characteristics

1. **Specificity:** There is no cross reaction with native serum immunoglobulins and tested monoclonal antibodies such as infliximab (Remicade®) and/or adalimumab (Humira®) , etanercept (Enbrel®), bevacizumab (Avastin®), trastuzumab (Herceptin®)

2. **Sensitivity:** The lowest detectable level that can be distinguished from the zero standard is 0,010 µg/mL.

3. **Precision Of Kit:**
   Intra-assay CV: <20% for omalizumab range 0.01-1 µg/mL.
   Inter-assay CV: <20% for omalizumab range 0.01-1 µg/mL.

4. **Recovery:** Recovery rate was found to be equal and higher than 90% with normal human serum samples supplemented with known concentrations of omalizumab.

Automation

Experiments have shown that the omalizumab ELISA is also suitable to run on an automated ELISA processor.

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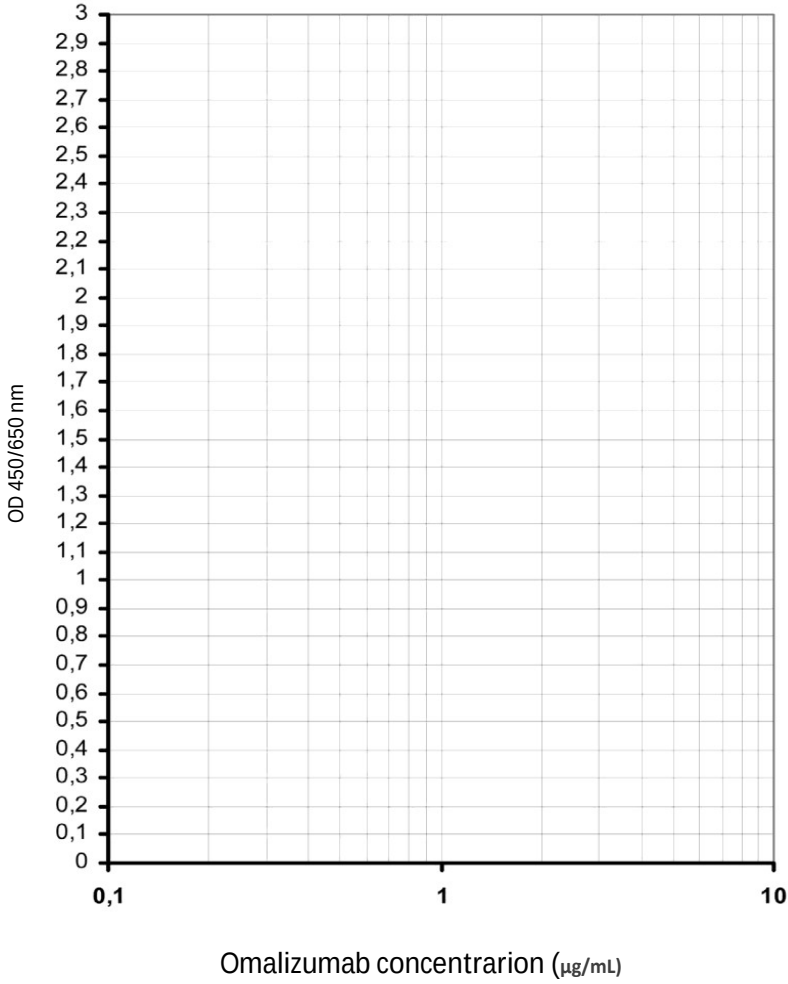
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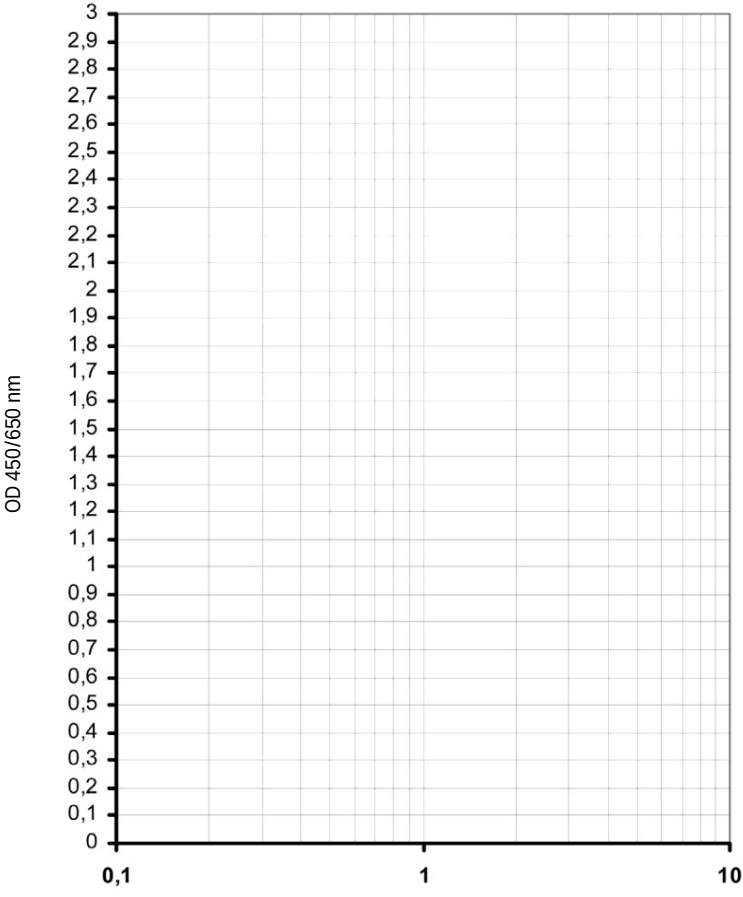
Omalizumab concentrarion (µg/mL)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