ATLANT CLINICAL

Protocol

A multicenter, double-blind, randomized, placebo-controlled comparison trial to evaluate safety, tolerability, and efficacy to choose the optimal dose of XC221 at daily doses of 100 and 200 mg in patients with uncomplicated influenza or other acute viral upper respiratory infections

Trial title	A multicenter, double-blind, randomized, placebo-controlled comparison trial to evaluate safety, tolerability, and efficacy to choose the optimal dose of XC221 at daily doses of 100 and 200 mg in patients with uncomplicated influenza or other acute viral upper respiratory infections
Sponsor	PHARMENTERPRISES LLC Bolshoy Blvd. 42, Building 1, offices 771, 772, Skolkovo Innovation Center, Moscow, 143026, Russia Tel.: +7 (985) 728-75-72
Manufacturer	ZAO Obninsk Chemical and Pharmaceutical Company, Russia
Investigational medicinal product	XC221, 100 mg tablets
Route of administration	Oral
Active ingredient	XC221GI
Phase of development	Phase II
Principal investigators and study centers	Study center 01 Principal Investigator – Sergey M. Noskov, Dr. Med. Sci., Professor; State Autonomous Budgetary Healthcare Institution of the Yaroslavl Region "Clinical Hospital no. 3"; ul. Mayakovskogo 61, Yaroslavl, 150007 Russia Tel.: +7 (4852) 24-23-32 Fax: +7 (4852) 24-23-32 E-mail: noskov03@gmail.ru Study center 02 Principal Investigator – Mikhail E. Statsenko, Dr. Med. Sci., Professor; Federal State Budgetary Institution of Higher Professional Education "Volgograd State Medical

	University", Ministry of Health of the Russian Federation; Ploshchad Pavshikh Bortsov 1, Volgograd, 400131, Russia Tel.: +7 (8442) 38-53-57 Fax: +7 (8442) 55-17-70 E-mail: mestatsenko@rambler.ru <u>Study center 03</u> Principal investigator – Vladimir A. Martynov, Dr. Med. Sci.; Federal State Budgetary Institution of Higher Professional Education "Ryazan State Medical University named after Academician I.P. Pavlov", Ministry of Health of the Russian Federation; ul. Vysokovoltnaya 9, Ryazan, 390026, Russia Tel.: +7 (4912) 76-55-03 E-mail: dr.martinov@mail.ru <u>Study center 04</u> Principal investigator – Yulia V. Drozdova; Federal State Budgetary Institution "Research Institute of Influenza", Ministry of Health of the Russian Federation; ul. Prof. Popova 15/17, St. Petersburg, 197376, Russia Tel.: +7 (812) 499-15-44 (45) Fax: +7 (812) 499-15-44 E-mail: drozdova-julia78@mail.ru <u>Study center 05</u> Principal investigator – Natal'ya V. Dunaeva, Cand. Med. Sci., Associate Professor; St. Petersburg State Budgetary Healthcare Institution "Center for Prevention and Control of AIDS and Infectious Diseases";

	nab. Obvodnogo kanala 179, St. Peterburg, 190103, Russia Tel.: +7 (812) 407-83-49, +7 (812) 251-08-53 Fax: +7 (812) 251-08-53 E-mail: nvch@mail.ru Study center 08 Principal investigator – Alina S. Agaf'ina, Cand. Med. Sci.; St. Petersburg State Budgetary Healthcare Institution "City Hospital no. 40 of the Kurortnyi District"; ul. Borisova 9, lit. B, Sestroretsk, 197706, Russia Tel.: +7 (812) 437-35-22 Fax: +7 (812) 437-31-38 E-mail: a.agafina@mail.ru Study center 09 Principal investigator – Andrey V. Ezhov, Dr. Med. Sci., Associate Professor, Professor; Budgetary Healthcare Institution of the Udmurt Republic "City Clinical Hospital no. 9 of the Ministry of Health of the Udmurt Republic"; ul. Promyshlennaya 52, Izhevsk, Udmurt Republic, 426063, Russia Tel.: +7 (3412) 66-11-33 Fax: +7 (3412) 66-11-33 E-mail: andigel2@rambler.ru Study center 10 Principal investigator – Natal'ya Yu. Pshenichnaya, Dr. Med. Sci., Professor; Municipal Budgetary Healthcare Institution "Rostov-on-Don City Hospital no. 1 named after N.A. Semashko";

	pr. Voroshilovskiy, 105/243/264, Rostov-on-Don, 344000, Russia Tel.: +7 (863) 232-08-17 Fax: +7 (863) 250-07-26 E-mail: natalia-pshenichnaya@yandex.ru Study center 11 Principal investigator – Marina G. Avdeeva, Dr. Med. Sci., Professor; Federal State Budgetary Institution of Higher Professional Education "Kuban State Medical University", Ministry of Health of the Russian Federation; ul. Mitrofana Sedina 4, Krasnodar, 350063, Russia Tel.: +7 (861) 255-44-23 E-mail: AvdeevaM@mail.ru Study center 12 Principal investigator – Natal'ya N. Burova, Dr. Med. Sci.; Federal State Budgetary Institution "Diagnostic Outpatient Center", Administrative Directorate of the President of the Russian Federation; Morskoy pr. 3, St. Petersburg, 197110, Russia Tel.: +7 (812) 670-09-62 Fax: +7 (812) 234-68-22 E-mail: nnburova@rambler.ru Study center 13 Principal investigator – Anna V. Snigireva, Cand. Med. Sci.; Federal State Budgetary Institution of Higher Education "Yaroslavl State Medical University", Ministry of Health of the Russian Federation; ul. Revolyutsionnaya 5, Yaroslavl, 150000, Russia

	Tel.: +7 (4852) 24-23-32 E-mail: n0613@yandex.ru
Study population	Male and female patients aged 18–45 years inclusive, diagnosed with uncomplicated influenza or other acute viral upper respiratory infections based on clinical symptoms only and meeting all the inclusion criteria, were enrolled in this trial.
First patient, first visit – Last patient, last visit	12-Feb-2018 – 28-Jun-2018
Aim and objectives of the study:	Study aim: The aim of this clinical trial was to evaluate safety, tolerability, and efficacy, as well as to determine the optimal dose of XC221 co-administered with the standard symptomatic therapy to treat influenza and acute viral URI. Study objectives: 1. To evaluate the safety of XC221 100 mg and 200 mg vs placebo, co-administered with the standard symptomatic therapy to treat influenza and acute viral URI by frequency of adverse events (AEs). 2. To evaluate the efficacy of XC221 100 mg and 200 mg vs placebo, co-administered with the standard symptomatic therapy to treat influenza and acute viral URI by its effect on main manifestations of the disease (symptom intensity and duration) using the modified Jackson scale. 3. To determine the optimal dose of XC221 among the suggested doses (100 and 200 mg per day) by analyzing efficacy, safety, and tolerability of IMP. 4. To evaluate the dynamics of MxA protein blood concentration during the administration of XC221 100 mg and 200 mg vs placebo. 5. To evaluate the dynamics of C-reactive protein (CRP) blood concentration during the administration of XC221 100 mg and 200 mg vs placebo. 6. To evaluate the dynamics of blood concentrations of 6Ckine, BCA-1, CTACK, ENA-78, Eotaxin, Eotaxin-2, Eotaxin-3, Fractalkine, GCP-2, GM-CSF, Gro-α, Gro-β, I-309, IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-16, IP-10, I-TAC, MCP-1, MCP-2,

	MCP-3, MCP-4, MDC, MIF, MIG, MIP-1α, MIP-1δ, MIP-3α, MIP-3β, MPIF-1, SCYB16, SDF-1α+β, TARC, TECK, and TNF-α cytokines during the administration of XC221 100 mg and 200 mg vs placebo.
Methodology (study design and procedures):	A multicenter, double-blind, randomized, placebo-controlled, comparison trial. The trial involved the following periods: screening (lasting no longer than 36 hrs after the onset of the earliest symptoms), treatment period (3 days), and follow-up period (11±1 days after the end of study treatment). Duration of participation in the trial for each patient was no longer than 16 days and 12 hrs. The following visits were performed during the trial: Visit 0 (Day 0) (screening); treatment period – Visit 1 (Day 1) (randomization), Visit 2 (Day 2), Visit 3 (Day 3), and the follow-up period – Visit 4 (Day 4), Visit 5 (Day 5), Visit 6 (Day 6), Visit 7 (Day 7), Visit 8 (Day 8), and the Study Termination Visit 9 (Day 14±1); Visit 4, Visit 6, and Visit 9 were performed by the patient to the study center in person, while Visit 5, Visit 7, and Visit 8 could be made either in person or as morning and evening telephone calls. Patients receiving both in- and outpatient treatment could be enrolled. The investigator made a decision regarding whether a patient will be followed up on an outpatient or inpatient basis, as well as regarding the length of hospital stay for inpatient subjects in compliance with the Methodological Guidelines for Diagnosis, Treatment, and Prevention of Influenza issued by the Ministry of Health of the Russian Federation (ed. by A.G. Chuchalin). During the trial, Visits 1–3 could be made both on an in- or outpatient basis (including at patient's home). If a patient underwent a domiciliary screening, samples for all laboratory tests could also be collected at home and were analyzed at the earliest possible time as the patient was supposed to administer the first dose of IMP no later than 36 hrs after the onset of the earliest disease symptoms. During the trial, at Visit 1 (Day 1) all patients meeting the inclusion criteria and not meeting any of the exclusion criteria were randomly assigned into three groups (groups A, B, and C) at a 1:1:1 allocation ratio to be treated with the investigational medicinal

	product/placebo co-administered with the standard symptomatic therapy: Group A – the IMP was XC221 at a daily dose of 100 mg, co-administered with the standard symptomatic therapy; Group B – the IMP was XC221 at a daily dose of 200 mg, co-administered with the standard symptomatic therapy; Group C – placebo, co-administered with the standard symptomatic therapy. During the trial, the randomized patients received the study therapy on an in- or outpatient basis during 3 days under control of an investigator at the following visits: Visit 1 (Day 1), Visit 2 (Day 2), and Visit 3 (Day 3). After the 3-day treatment period, the patients were followed up for the subsequent 11±1 days (the follow-up period). During the follow-up period, the following visits were performed: Visit 4 (Day 4), Visit 6 (Day 6), and Visit 9 (Day 14±1) – the patient visited the study center in person; Visit 5 (Day 5), Visit 7 (Day 7), and Visit 8 (Day 8) could be made either in person or on an in-patient/outpatient basis or as morning and evening telephone calls to assess patient's wellbeing. Visit 9 (Day 14±1) was made 14±1 days after treatment initiation. After completing Visit 9 (Day 14±1), patients' participation in the clinical trial was considered completed. At Visit 1 (Day 1), diaries were handed over to the patients so that they could write down the body temperature values. During the treatment period, the patient was supposed to measure his/her body temperature twice a day: in the morning (at 8–11 a.m.) and in the evening (8–11 p.m.). The temperature measurements results were written down in the patient's temperature diary. During the trial, starting with Visit 0 (screening visit) through Visit 8 (Day 8), the investigator evaluated the severity of the symptoms of influenza/acute viral URI daily (in the morning and in the evening) using the modified Jackson scale, either in person or in a telephone conversation. At Visits 1 (Day 1) through 4 (Day 4), the first measurement of body temperature and evaluation of symptom severity were carried out

	in person by the investigator, while the second assessment of symptom severity and obtaining the temperature measurement records the same day could be performed by the investigator in a telephone conversation. All the procedures at Visits 5 (Day 5), 7 (Day 7), and 8 (Day 8) could be performed either in person (on an inpatient/outpatient basis) or as telephone conversations, twice daily (in the morning and in the evening). Visit 6 (Day 6) was made only on an inpatient or outpatient basis (but the second assessment of the symptoms severity and obtaining the information about the body temperature measurements results on the same day could be performed by the investigator in a telephone conversation). At Visit 4 (Day 4), the patients brought their diaries filled out throughout the period between Visit 1 (Day 1) and Visit 4 (Day 4) to the investigator; the investigator checked whether all necessary records were made, discussed the reported complaints, and returned the diaries to patients so that they continued making records during the follow-up period, starting with Visit 5 (Day 5) through Visit 9 (Day 14±1). The patient was supposed to write down the body temperature values and all his/her complaints and symptoms twice daily, in the morning and in the evening. At Visit 0 (Day 0) (screening) or Visit 1 (Day 1), nasopharyngeal and oropharyngeal swabs were taken to establish the viral etiology of the disease by PCR (a qualitative test to detect the following infectious agents: influenza A and B viruses, human respiratory syncytial virus, human metapneumovirus, human coronavirus, human rhinovirus, human adenovirus (subgroups B, C, and E), human bocavirus, human parainfluenza viruses 1, 2, 3, and 4) (the samples were sent to the central laboratory to be analyzed). The therapy prescribed to patients in this trial was not supposed to be modified according to the analysis results to detect the virus in the biological samples. No confirmation of viral nature of the disease was needed for patients to be enrolled in this trial. The diagnosis of influenza or acute viral URI was made only by evaluating the clinical symptoms to recruit the patients into the trial and prescribe therapy. The viral nature of the disease was taken into account when analyzing the data obtained in the trial.

	At Visit 1 (before the first dose of IMP/placebo was taken), Visit 4, and Visit 6, patients' blood samples were collected to analyze serum concentrations of MxA protein, C-reactive protein, and cytokines 6Ckine, BCA-1, CTACK, ENA-78, Eotaxin, Eotaxin-2, Eotaxin-3, Fractalkine, GCP-2, GM-CSF, Gro-α, Gro-β, I-309, IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-16, IP-10, I-TAC, MCP-1, MCP-2, MCP-3, MCP-4, MDC, MIF, MIG, MIP-1α, MIP-1δ, MIP-3α, MIP-3β, MPIF-1, SCYB16, SDF-1α+β, TARC, TECK, and TNF-α.
The number of patients screened/randomized, and patients who completed the study	Screened patients: 121 Randomized patients: 120 Patients who completed the study: 120
Inclusion criteria:	1. Men and women aged 18 to 45 years (inclusive). 2. Clinically diagnosed mild or moderate influenza or acute viral URI. 3. Patient's body temperature at screening ≥37.5°C and at least one intoxication or catarrhal symptom from the ones listed in the modified Jackson scale, with severity grade estimated as score ≥ 2. 4. Uncomplicated course of influenza or acute viral URI based on assessment of clinical symptoms. 5. The interval between the onset of the earliest symptoms of the disease and enrollment (administration of the first dose of IMP/placebo) is no longer than 36 hrs. 6. Women of reproductive age (who are not in menopause and who have not undergone surgical sterilization) and men who have sexual activity should use a reliable method of contraception (acceptable methods of contraception in this study are: intrauterine devices, oral contraceptives, contraceptive patch, long-acting injectable contraceptives, a double barrier method (condom with spermicide, diaphragm with spermicide)) throughout the study period and 30 days after the last dose administration of IMP/placebo. 7. A patient agrees to adhere to the treatment regimen, visits and laboratory examinations provided by the protocol.

	8. Signed Informed Consent Form.
Exclusion criteria:	Patients meeting at least one of these criteria were not eligible for the study: 1. Existence of complications of influenza or acute viral URI (including the presence/development of bacterial infection). 2. Hypersensitivity to the active ingredient and excipients of IMP or placebo. 3. Administration of antiviral medications (antiviral agents, interferons and interferon inducers, drugs that have immunomodulating action) or systemic or local anti-infective agents 7 days prior to screening. 4. Severe infection with signs of cardiovascular insufficiency development and other manifestations of infectious-toxic shock, as well as with the presence of neuroinfection syndrome (encephalic and meningo-encephalic reactions, polyradiculoneuritis, neuritis). 5. Signs of the pneumonia development (the presence of at least two of the following symptoms): dyspnea, chest pain when coughing, systemic cyanosis, dullness of percussion sound upon symmetrical evaluation of the upper and lower sections of the lungs). 6. Infectious diseases during the last week prior to the Screening visit. 7. History of bronchial asthma. 8. History of increased convulsive activity. 9. Severe, decompensated or unstable somatic diseases (any diseases or conditions that are life-threatening or may worsen the patient's prognosis, and make him/her ineligible for the clinical study). 10. History of cancer, HIV, tuberculosis. 11. Diabetes mellitus 12. Drug or alcohol abuse. 13. Participation in any other clinical trial in the last 90 days prior to the Screening visit. 14. Pregnancy or lactation. 15. Military or prison populations. 16. Impossibility or inability to comply with the study procedures.

	17. A member of the investigator's family or other person interested in the results of the study. 18. Abnormal laboratory values, which, according to the study doctor, interfere with the patient's inclusion in the study. 19. History of renal insufficiency.
Withdrawal criteria:	The Principal Investigator was to withdraw a patient from the study at any point in the following situations: 1. Adverse events requiring discontinuation of IMP. 2. Patient's enrollment turned out to be a protocol deviation. 3. Patient needed to take medications prohibited by this trial, including the situation when the study treatment proved ineffective. 4. Investigator believed that further participation in the trial contradicted the patient's best interest. 5. Patient would like to withdraw his/her informed consent. 6. Patient failed to adhere to the protocol. 7. Female patient was pregnant.
Investigational medicinal product, dosage schedule, route of administration, lot number	XC221, 100 mg tablets Active ingredient: XC221GI <u>Dosage schedule:</u> Group A – XC221 at a daily dose of 100 mg co-administered with the standard symptomatic therapy; Group B – XC221 at a daily dose of 200 mg co-administered with the standard symptomatic therapy; (40 patients). <u>Route of administration:</u> orally, once daily, one tablet from the respective two bottles (a total of 2 tablets per day) regardless of meals. <u>Lot number</u>: 21116
Duration of therapy with IMP:	3 days
Placebo, dosage schedule, route of administration, lot number	Placebo, 100 mg tablets

	Active ingredient: none Dosage schedule: Group C – placebo co-administered with the standard symptomatic therapy. Route of administration: orally, once daily, one tablet from the respective two bottles (a total of 2 tablets per day) regardless of meals. Lot number: 11116
Duration of placebo therapy:	3 days
Efficacy endpoints:	Efficacy of the investigational medicinal product will evaluated according to the primary and secondary endpoints. Primary endpoint: Time to sustained improvement of clinical symptoms based on the modified Jackson scale (score ≤ 1 for each symptom) measured in hours after administration of the first dose of IMP. *Time to sustained improvement means the time of making the first evaluation out of three consecutive evaluations based on the modified Jackson scale at which all clinical symptoms of acute viral URI and influenza corresponded to score 1 or lower.* Secondary endpoints: 1. The area under the curve "modified Jackson scale score" during 3-day therapy; 2. Time to body temperature normalization since treatment initiation, measured in hours (normalization is regarded as setting of body temperature below 37°C without elevation above these values during the follow-up until Day 14 visit); 3. Time to normalization of body temperature since the onset of the earliest symptoms of the disease, measured in hours (normalization is regarded as setting of body temperature below 37°C without elevation above these values during the follow-up until Day 14 visit); 4. The mean modified Jackson scale score on days 1, 2, 3, 4, 5, 6, 7, and 8 after treatment initiation;

	5. The mean modified Jackson scale score on days 1, 2, 3, 4, 5, 6, 7, and 8 after the onset of the earliest symptoms of the disease; 6. The percentage of patients in whom the sum of modified Jackson scale scores is ≤ 3 (the score for each symptom is to be ≤ 1) on days 1, 2, 3, 4, 5, 6, 7, and 8 after treatment initiation; 7. The percentage of patients in whom the sum of modified Jackson scale scores is ≤ 3 (the score for each symptom is to be ≤ 1) on days 1, 2, 3, 4, 5, 6, 7, and 8 after the onset of the earliest symptoms of the disease; 8. The mean body temperature on days 1–14 after treatment initiation; 9. The mean body temperature on days 1–14 after the onset of the earliest symptoms of the disease; 10. The percentage of patients with normalized body temperature on days 1–14 after study initiation; 11. The percentage of patients with normalized body temperature on days 1–14 after the onset of the earliest symptoms of the disease; 12. The percentage of patients with complications of influenza/acute viral URI that developed during the period of days 1–4 and days 1–14 after treatment initiation; 13. The percentage of patients with complications of influenza/acute viral URI that developed during the period of days 1–4 and days 1–15 after the onset of the earliest symptoms of the disease; 14. The percentage of patients with severe complications of influenza/acute viral URI that developed during the period of days 1–4 and days 1–14 after treatment initiation; 15. The percentage of patients with severe complications of influenza/acute viral URI that developed during the period of days 1–4 and days 1–15 after the onset of the earliest symptoms of the disease; 16. Timeframe of developing complications of influenza/acute viral URI after treatment initiation; 17. Timeframe of developing complications of influenza/acute viral URI after the onset of the earliest symptoms of the disease;

	18. Time to resolution (score 0) of each symptom in the modified Jackson scale (sneezing, rhinorrhea, nasal congestion, cough, fever, malaise, chills, headache, myalgia, sore throat, itchy throat, and hoarseness) since treatment initiation in the population of patients in whom the respective symptom was evaluated as score 2 or 3 at Visit 0 (Day 0); 19. Time to resolution (score 0) of each symptom in the modified Jackson scale (sneezing, rhinorrhea, nasal congestion, cough, fever, malaise, chills, headache, myalgia, sore throat, itchy throat, and hoarseness) since the onset of the earliest symptoms of the disease in the population of patients in whom the respective symptom was assessed as score 2 or 3 at Visit 0 (Day 0); 20. The percentage of patients having score 0 for each symptom in the modified Jackson scale (sneezing, rhinorrhea, nasal congestion, cough, fever, malaise, chills, headache, myalgia, sore throat, itchy throat, and hoarseness) on days 2, 3, 4, 5, 6, 7, and 8 after treatment initiation in the population of patients in whom the respective symptom was evaluated as score 2 or 3 at Visit 0 (Day 0); 21. The percentage of patients having score 0 for each symptom in the modified Jackson scale (sneezing, rhinorrhea, nasal congestion, cough, fever, malaise, chills, headache, myalgia, sore throat, itchy throat, and hoarseness) on days 2, 3, 4, 5, 6, 7, and 8 after the onset of the earliest symptoms in the population of patients in whom the respective symptom was evaluated as score 2 or 3 at Visit 0 (Day 0).
Safety endpoints:	<u>Secondary endpoint</u>: frequency of adverse events (AEs) and serious adverse events (SAEs) in the XC221 group and in the placebo group. Tolerability was evaluated as good, fair, and poor based on the presence/absence of adverse drug reactions causing treatment suspension or discontinuation.

Exploratory endpoints	1. Mean blood concentration of MxA protein in patient groups treated with XC221 100 mg and 200 mg XC221 as compared to the placebo group at Visit 4 and Visit 6; 2. Changes in blood concentrations of MxA protein in patients at Visit 4 and Visit 6 as compared to Visit 1 in treatment groups; 3. Mean blood concentration of C-reactive protein in patient groups treated with XC221 100 mg and 200 mg as compared to the placebo group at Visit 4 and Visit 6; 4. Changes in blood concentrations of C-reactive protein in patients at Visit 4 and Visit 6 as compared to Visit 1 in treatment groups; 5. Mean serum concentrations of 6Ckine, BCA-1, CTACK, ENA-78, Eotaxin, Eotaxin-2, Eotaxin-3, Fractalkine, GCP-2, GM-CSF, Gro-α, Gro-β, I-309, IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-16, IP-10, I-TAC, MCP-1, MCP-2, MCP-3, MCP-4, MDC, MIF, MIG, MIP-1α, MIP-1δ, MIP-3α, MIP-3β, MPIF-1, SCYB16, SDF-1α+β, TARC, TECK, TNF-α in patient groups treated with XC221 100 mg and 200 mg as compared to the placebo group at Visit 4 and Visit 6; 6. Changes in serum concentrations of 6Ckine, BCA-1, CTACK, ENA-78, Eotaxin, Eotaxin-2, Eotaxin-3, Fractalkine, GCP-2, GM-CSF, Gro-α, Gro-β, I-309, IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-16, IP-10, I-TAC, MCP-1, MCP-2, MCP-3, MCP-4, MDC, MIF, MIG, MIP-1α, MIP-1δ, MIP-3α, MIP-3β, MPIF-1, SCYB16, SDF-1α+β, TARC, TECK, TNF-α in patients at Visit 4 and Visit 6 as compared to Visit 1 in treatment groups; 7. Evaluation of the relationship between cytokine concentration and the modified Jackson scale score.
Statistical methods	<u>Hypothesis testing</u> In accordance with the aim and objectives of the trial, a hypothesis that time to sustained improvement of clinical symptoms based on the modified Jackson scale differs between the groups was formulated for the primary endpoint.

	The groups were compared for the parameter "time to sustained improvement of clinical symptoms" using the generalized Wilcoxon test (the Gehan–Wilcoxon test). The null hypothesis stated that there were no differences between two groups for the hazard function assessed for the primary endpoint in each IMP group as compared to the placebo group. It was assumed that if the Z-score is higher than the selected α-quantile of the standard normal distribution, the null hypothesis will be rejected in favor of the alternative hypothesis stating that there is difference between the two groups. Sample size justification It was expected that the optimal dose of the investigational medicinal product (XC221 100 mg or XC221 200 mg) would be selected in this trial by exploratory data analysis. The optimal IMP dose was supposed to be selected by the Sponsor according to the treatment group that would have the minimum median time to reach the effect for the primary endpoint but a similar or superior safety profile compared to that in the remaining groups. It was assumed that if the median time to reach the effect for the primary endpoint in two dose groups was equal, the smaller dose would be selected. The sample size was calculated using the PASS 14 software according to the data obtained in the previous trial of the same Sponsor (FLU-XC8-01). In it, the hazard rates for a similar endpoint were found to be 0.83 and 1.23 for the placebo and treatment groups, respectively. The sample size for the present trial was estimated so that the width of 95% two-sided confidence interval of hazard rate was no greater than the twofold difference in hazard rates between the treatment and placebo groups in a similar study (0.8); the percentage of censored observations was ≤ 5%. Hence, it was found that the sample size required per group was 39 subjects. The selected significance level $\alpha = 0.05$; the pre-set power was 80%. Having assumed that the percentage of patients withdrawn throughout the study was 2.5%, 40 patients needed to be screened for each group. Size of the placebo group was equal to that of the treatment groups. Hence, a total of 120 patients were planned to be randomly assigned into three groups at a 1:1:1 allocation ratio (40 subjects into each group: the placebo group and the groups treated with XC221 100 mg or XC221 200 mg). Assuming

	that the probability of subject withdrawal at screening was ~15%, up to 140 patients were to be screened. This was a multicenter trial, with patients recruited on a competitive basis. In order to minimize the bias, each study center could randomize no more than 30% (36 patients) of the total sample size. Statistical methodology All variables for analysis were presented using the descriptive statistical methods. An analysis was conducted to compare groups at primary and secondary endpoints. Categorical variables were analyzed using the χ^2 test; the two-tailed Fisher's exact test was used if more than 20% of expected frequencies were < 5. The areas under "variable versus time" curves were calculated using the trapezoidal rule. Groups were compared in terms of quantitative variables using ANOVA/ANCOVA; the non-parametric alternative was employed if the assumptions underlying the method were not met. Survival analysis (plotting the Kaplan–Meier curves, comparing the hazard functions using the Gehan–Wilcoxon test) and the stratified Cox regression model were used for the censored Time-to-Event data. The secondary endpoint data for patients prematurely withdrawn from the study were substituted using the LOCF algorithm. Interim analysis Interim analysis was not involved in this study. Analysis groups Three equal-sized groups, with 40 subjects per group (2 groups receiving different doses of IMP and the placebo group) were planned for this study. The groups treated with IMP were supposed to be compared in a pairwise manner to the placebo group; it was also planned that the treatment groups would be compared to each other. Baseline comparability The baseline data (demographic and anthropometric characteristics, as well as disease duration documented prior to treatment initiation) were compared between the groups in the Full Analysis Set population. If significant differences between treatment groups were revealed for any baseline parameter, sensitivity analysis was performed to test

	whether the conclusions about the efficacy remained unchanged after applying a correction for different baseline parameters in groups. Safety analysis The safety population consisted of all the patients treated with any dose of IMP/placebo. Safety parameters (vital signs, laboratory data, and AEs) were descriptively analyzed for each group. The numbers of AEs and patients with AEs were summarized according to their treatment group and categorized according to the system organ classes and preferred terms. Additional summarizing was performed for severity of AEs and their relationship to IMP. SAE narratives were additionally made in a separate analysis. Patients withdrawn prematurely from the trial can be found in the list of patients and were categorized according to the main reason for withdrawal (in each treatment group). Tolerability analysis Frequency tables were plotted to analyze the tolerability data (in the safety population); a conclusion regarding the potential differences in tolerability between the analyzed samples was drawn according to these tables. Efficacy analysis The main efficacy analysis for the primary endpoint was carried out using the Full Analysis Set population. Sensitivity analysis in the population of patients with verified viral infection and the Per Protocol population was conducted. Sensitivity analysis using the stratified Cox model was carried out separately for the Per Protocol population, with the following covariates: "study center", "presence of viral infection", and "concomitant treatment with NSAIDs". Secondary endpoint analysis was conducted in the Full Analysis Set population and the population of patients with verified viral infection. Concentrations of C-reactive protein and 6Ckine, BCA-1, CTACK, ENA-78, Eotaxin, Eotaxin-2, Eotaxin-3, Fractalkine, GCP-2, GM-CSF, Gro-α, Gro-β, I-309, IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-16, IP-10, I-TAC, MCP-1, MCP-2, MCP-3, MCP-4, MDC, MIF, MIG, MIP-1α, MIP-1δ, MIP-3α, MIP-3β, MPIF-1, SCYB16, SDF-1α+β, TARC, TECK, and TNF-α cytokines were analyzed in the Full Analysis Set population.

	Software Specialized SAS software (version 9.4) was used for statistical analysis.