Clinical Study Report

An Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of Reslizumab (3.0 mg/kg) as Treatment for Patients With Eosinophilic Asthma Who Completed a Prior Teva-Sponsored Study in Eosinophilic Asthma

Phase 3

Study C38072/3085

IND 101,399

EudraCT Number: 2010-024540-15

Sponsor
Teva Global Branded Products R&D, Inc.
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Study Initiation Date (first patient enrolled):	09 June 2011
Study Early Termination Date:	09 January 2014
Last Patient Last Visit:	16 January 2015
Report Approval Date:	22 June 2015

The conduct of this study with regard to Good Clinical Practice is addressed in Section 16.1.8.

Confidentiality Statement

2. SYNOPSIS

Name of Sponsor/Company: Teva Global Branded Products R&D, Inc.	**Individual study table referring to part of dossier in which the individual study or study table is presented**	(For National Authority Use Only)
Name of Finished Product: Reslizumab sterile solution for intravenous infusion	**Volume:**	
Name of Active Ingredient: Reslizumab (CEP-38072)	**Reference:**	

Note: This protocol underwent 4 global amendments. The final entry criteria and study methodology after these 4 amendments are presented in this clinical study report (CSR) synopsis and in the main text of the CSR. Changes to entry criteria and/or study methodology with each protocol amendment are summarized in the CSR section called "Changes in the Conduct of the Study" and described in detail in each protocol.

Teva communicated its intent to terminate Study C38072/3085 to all investigators involved in the trial on 09 January 2014. The rationale for the termination was that the primary study objective, in terms of open-label events for patient exposure to study drug without confirmed benefit/risk, had been sufficiently met. This was primarily based on substantial over-enrollment from the originally planned sample size (approximately 740 patients) and is consistent with the Stopping Rules and Discontinuation Criteria in Section 3.6 of the original protocol. The decision to terminate the study was not due to any new or emerging safety concerns at that time. Following study termination, protocol amendment 5 was developed and issued on 14 April 2014 in countries within the European Union (EU) to comply with applicable EU legislation in this particular circumstance. This revised protocol was submitted and approved in all EU countries.

Title of Study: An Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of Reslizumab (3.0 mg/kg) as Treatment for Patients with Eosinophilic Asthma who Completed a Prior Teva-Sponsored Study in Eosinophilic Asthma

Investigators and Study Centers: The study was conducted at 201 centers in 30 countries. A complete list of investigators and their affiliations is included in the CSR.

Publication (reference): Results from this study have not been published at the time of approval of this report.

Study Period: 09 June 2011 to 09 January 2014 (study termination date) Phase of Development: 3

Primary Objective: The primary objective of the study was to obtain additional safety data for reslizumab at a dosage of 3.0 mg/kg every 4 weeks, relative to baseline, for up to 24 months in adolescent and adult patients with moderate to severe eosinophilic asthma. Safety was assessed by the following:

- adverse events throughout the study
- clinical laboratory test (serum chemistry, hematology, and urinalysis) results at weeks 4, 8, and 24 and every 24 weeks thereafter throughout the study
- brief physical examination findings at all visits (every 4 weeks) throughout the study

- vital signs measurements every 4 weeks throughout the study
- concomitant medication usage every 4 weeks throughout the study

Secondary Objectives: The secondary objectives of the study were to evaluate the long-term efficacy of reslizumab as assessed by the following:

- Pulmonary function test (PFT) results, as measured by forced expiratory volume in 1 second (FEV_1), percent-predicted forced expiratory volume in 1 second (% predicted FEV_1), forced vital capacity (FVC), and forced expiratory flow at 25% to 75% of the forced vital capacity ($FEF_{25\%-75\%}$) every 4 weeks for 16 weeks, at 24 weeks, and every 12 weeks thereafter throughout the study
- short-acting beta-agonist (SABA) use every 4 weeks for 16 weeks, at 24 weeks, and every 12 weeks thereafter throughout the study
- asthma symptom score (Asthma Symptom Utility Index [ASUI]) every 4 weeks for 16 weeks, at 24 weeks, and every 12 weeks thereafter throughout the study
- Asthma Control Questionnaire (ACQ) every 4 weeks for 16 weeks, at 24 weeks, and every 12 weeks thereafter throughout the study
- Asthma Quality of Life Questionnaire (AQLQ) every 24 weeks throughout the study

Immunogenicity was assessed by testing for the presence of anti-reslizumab antibodies every 24 weeks throughout the study and at the end of treatment (4 weeks after the last infusion of reslizumab 3.0 mg/kg) or early withdrawal.

Number of Patients (Planned and Analyzed): For this study, 740 to ≤1000 patients were planned to be enrolled; a total of 1052 patients were enrolled. One patient was enrolled, but did not receive study drug. Thus, there were 1051 patients analyzed for safety and efficacy.

Diagnosis and Main Criteria for Inclusion: Patients were included in the study if all of the following main criteria were met (not all inclusive):

a. The patient was male or female, 12 through 75 years of age, with a previous diagnosis of asthma. Patients 12 through 17 years of age were excluded from participating in Korea, India, and Argentina; patients 66 through 75 years of age were excluded from participating in Korea and India.

b. Written informed consent was obtained. Patients 12 through 17 years old, where participating, needed to provide assent in accordance with local standards.

c. Patient must have completed treatment in a previous double-blind asthma exacerbation study or received at least 2 doses of study drug treatment in a pulmonary function study. (Note: Patients in Studies C38072/3082 and C38072/3083 were to have completed treatment in their respective studies to enter Study C38072/3085. Only patients in Study C38072/3081 were allowed to enter Study C38072/3085 after having received at least 2 doses of study drug treatment.)

d. The patient must have been willing and able to comply with study restrictions and to remain in the clinic for the required duration during the study period, and willing to return to the clinic for the follow-up evaluation as specified in this protocol.

Main Criteria for Exclusion: Patients were excluded from participating in this study if 1 or more of the following main criteria were met (not all inclusive):

a. The patient had a clinically meaningful comorbidity that would have interfered with the study schedule or procedures or compromised the patient's safety.

b. The patient had another confounding underlying lung disorder (eg, chronic obstructive pulmonary disease, pulmonary fibrosis, or lung cancer).

c. The patient was a current smoker.

d. The patient was expected to be poorly compliant with study drug administration, study procedures, or visits.

e. The patient had any aggravating factors that were inadequately controlled (eg, gastroesophageal reflux disease).

f. Female patients of childbearing potential (not surgically sterile or 2 years postmenopausal) must have used a medically accepted method of contraception and must have agreed to continue use of this method for the duration of the study and for 30 days after the end-of-treatment (EOT) visit. Acceptable methods of contraception included barrier method with spermicide, abstinence, intrauterine device, or steroidal contraceptive (oral, transdermal, implanted, and injected).

g. The patient had a current infection or disease that might have precluded assessment of asthma.

h. Any change in concomitant medications from baseline of the double-blind study was to be evaluated at screening/baseline visit for exclusion from the open-label study.

Study Drug Dose, Mode of Administration, Administration Rate, and Batch Number:

Investigational Product: Reslizumab (3.0 mg/kg) was administered as an intravenous (iv) infusion every 28 days (±7 days) for up to 24 months. Reslizumab was provided as a sterile solution for infusion presented as 100 mg (10 mL) or 35 mg (3.5 mL) per vial, formulated at 10 mg/mL in 20-mM sodium acetate, 7% sucrose, and pH 5.5 buffer. Study drug was added to and mixed with saline diluent. More information regarding study drug administration can be found in the Pharmacy Manual.
The reslizumab lot numbers used during the study are available upon request.

Reference Therapy Dose, Mode of Administration, and Administration Rate: Not applicable

Method of Blinding: Not applicable

Duration of Treatment: The study consisted of a screening/baseline visit followed by an open-label treatment period, an EOT visit conducted 4 weeks after the last dose of reslizumab, and a 90-day (±7 days) follow-up evaluation. Patients were expected to participate in this study for up to 27 months.

General Design and Methodology: This was a multicenter, open-label study to obtain additional safety data for reslizumab treatment at a dosage of 3.0 mg/kg in patients (12 through 75 years of age) with moderate to severe eosinophilic asthma. Study patients were deemed eligible based on activities from the preceding Teva-sponsored, double-blind study of reslizumab in eosinophilic asthma.

A signed and dated informed consent form was obtained during screening/baseline (conducted at the EOT visit in the previous Teva-sponsored study of reslizumab). To be eligible for this study, patients must have either completed treatment in a previous Teva-sponsored study (Study C38072/3081, C38072/3082, or C38072/3083) or have received at least 2 doses of study drug treatment in a pulmonary function study (Study C38072/3081).

Patients received reslizumab by iv infusion at a dosage of 3.0 mg/kg after baseline procedures were completed and every 4 weeks (28 days ±7 days) for up to 24 months. Patients returned to the study center every 4 weeks relative to baseline during the open-label treatment and 4 weeks after the last reslizumab infusion or early termination. All patients were required to return for a follow-up evaluation 90 days (±7 days) after the EOT visit, which included an adverse event assessment, a blood draw for measurement of eosinophil levels, and vital signs measurement. Safety evaluations performed at every visit when study drug was administered included adverse event inquiry, vital signs measurement, concomitant medication use inquiry, brief physical examination, and urine pregnancy test. All the other safety evaluations were performed throughout the study according to the schedule of procedures and assessments. Body weight was measured every 16 weeks. Patients were also monitored for asthma exacerbations at every visit throughout the study. The number of courses of oral corticosteroids or an increase in their use for at least 3 days was collected. In addition to standard safety monitoring by the Sponsor, an independent Data and Safety Monitoring Board oversaw the safety of the patients throughout the study.

Efficacy evaluations included PFTs, AQLQ, ASUI, ACQ, and SABA use. The PFTs, ASUI, and ACQ evaluations and the SABA use inquiry were performed every 4 weeks for 16 weeks, at 24 weeks, and every 12 weeks thereafter until EOT visit or early termination. The AQLQ was performed at 24 weeks and every 24 weeks thereafter until EOT visit or early termination. Patients had final procedures and assessments performed at the EOT visit, 4 weeks after the final infusion. Patients who were withdrawn from the study before the completion of the open-label treatment period had EOT procedures and assessments performed at their final visit.

Blood samples for the analysis of serum reslizumab concentrations, blood eosinophil determination, and anti-reslizumab antibody assessment were obtained from all patients (inside and outside of the United States [US]) who experienced a serious adverse event, an adverse event leading to withdrawal, or an exacerbation of asthma symptoms. Blood samples were drawn for blood eosinophil count as part of the clinical laboratory tests. The blood eosinophil counts were measured using a standard complete blood count (CBC) with differential blood test. Blood samples for blood eosinophil determination were obtained at weeks 4, 8, and 24 and every 24 weeks thereafter until the EOT (4 weeks after the last infusion) or early withdrawal; blood samples for eosinophil count were obtained at the end of the study (90±7 days after the EOT visit or early withdrawal). Blood samples for anti-reslizumab antibody assessment were obtained for the evaluation of immunogenicity every 24 weeks and at the EOT visit (4 weeks after the last infusion) or early withdrawal.

Safety Measures and Endpoint(s): Safety measures/variables and endpoints included the following:

- adverse events evaluated throughout the study
- serum chemistry, hematology, and urinalysis tests (except for urine beta-human chorionic gonadotropin [test conducted predose every 4 weeks for women who were not 2 years postmenopausal

or surgically sterile) performed at baseline (EOT visit of the previous Teva-sponsored double-blind study of reslizumab in eosinophilic asthma [Study C38072/3081, C38072/3082, or C38072/3083]); at weeks 4, 8, and 24; and every 24 weeks thereafter until EOT visit/early termination (and 90 days [±7 days] after the EOT visit for blood eosinophils)

- vital sign measurements assessed every 4 weeks throughout the study and 90 days (±7 days) after the EOT visit

Efficacy Measures and Endpoints: This study was primarily a safety study; however, the long-term efficacy of reslizumab treatment was evaluated during the study with the following efficacy variables:

- change from baseline in PFT results as measured by FEV_1, % predicted FEV_1, FVC, and $FEF_{25\%-75\%}$ every 4 weeks for 16 weeks, at 24 weeks, and every 12 weeks thereafter until EOT visit or early termination
- change from baseline in SABA use every 4 weeks for 16 weeks, at 24 weeks, and every 12 weeks thereafter until EOT visit or early termination
- change from baseline in ASUI every 4 weeks for 16 weeks, at 24 weeks, and every 12 weeks thereafter until EOT visit or early termination
- change from baseline in ACQ score every 4 weeks for 16 weeks, at 24 weeks, and every 12 weeks thereafter until EOT visit or early termination
- change from baseline in AQLQ score every 24 weeks until EOT visit or early termination

Pharmacodynamics: Blood samples were drawn for blood eosinophil count as part of the clinical laboratory tests. The blood eosinophil counts were measured using a standard CBC with differential blood test. Blood samples for blood eosinophil determination were obtained at baseline; at weeks 4, 8, and 24; and every 24 weeks thereafter until the EOT visit (4 weeks after the last infusion) or early withdrawal; blood samples for eosinophil count were obtained at the end of the study (90±7 days after the EOT visit or early withdrawal). In addition, blood samples for blood eosinophil determination were obtained from all patients (inside and outside of the US) experiencing a serious adverse event, an adverse event leading to withdrawal, or an exacerbation of asthma symptoms.

Immunogenicity: Blood samples for anti-reslizumab antibody assessment were obtained for the evaluation of immunogenicity every 24 weeks and at the EOT visit (4 weeks after the last infusion) or early withdrawal. In addition, a blood sample for anti-reslizumab antibody assessment was obtained from all patients (inside and outside of the US) experiencing a serious adverse event, an adverse event leading to withdrawal, or an exacerbation of asthma symptoms.

Statistical Considerations: All patients in this study were enrolled from previous Teva-sponsored, double-blind studies for reslizumab in patients with eosinophilic asthma. Randomization was not applicable to this study. The sample size for this open-label extension study was not based on power considerations. The sample size was determined by the number of patients rolled over from 3 double-blind, placebo-controlled, Phase 3 studies of reslizumab in eosinophilic asthma. The set of enrolled patients included all patients who were enrolled, regardless of whether or not a patient took any study drug. The safety analysis set included all patients who received at least

1 dose of reslizumab in this study. All efficacy summaries were performed on the safety analysis set. All analyses were descriptive. No inferential statistics were planned or conducted.

Summary of Results

Patient Disposition and Demography: A total of 1052 patients with eosinophilic asthma at 201 centers in 30 countries were enrolled in this study. Of the 1052 patients enrolled, 1051 (>99%) patients received at least 1 dose of reslizumab in Study C38072/3085 and were evaluated for safety. One (<1%) patient withdrew before taking any study drug. Four hundred-eighty (46%) patients received reslizumab for the first time in Study C38072/3085, having previously received placebo in Study C38072/3081, C38072/3082, or C38072/3083. A total of 50 (5%) patients completed the 104-week treatment period and follow-up. A total of 1002 (95%) patients in this open-label study discontinued the study prior to completion, and 896 of these (85% of enrolled patients) did not complete the study due to early termination of the open-label study by the Sponsor. The median (minimum, maximum) duration of treatment during the open-label study was 343.0 (36.0, 863.0) days and 319.0 (36.0, 840.0) days in the reslizumab-experienced and reslizumab-naïve patients, respectively. Considering the predecessor studies, 277 patients (49%) had ≥24 months of treatment with reslizumab. Overall, the mean age of patients in the study was 47.2 years. Sixty-one percent of patients in the study were female, 77% were white, and 19% were Hispanic or Latino. The mean values for weight, height, and BMI were 76.0 kg, 165.7 cm, and 27.7 kg/m^2, respectively.

Demographic characteristics at entry into the open-label study were analyzed by previous double-blind treatment group and total enrolled population. There were no clear differences in demographic characteristics between the reslizumab-naïve and reslizumab-experienced groups, with the exception of a greater number of female patients included in the reslizumab-experienced group. All patients enrolled in the open-label study, from previous Teva-sponsored, double-blind studies for reslizumab (Studies C38072/3081, C38072/3082, and C38072/3083), had a diagnosis of eosinophilic asthma based on blood eosinophil inclusion of ≥400/µL during screening in the double-blind studies. Study-specific baseline characteristics, including spirometry parameters, asthma questionnaires, SABA usage, and eosinophil levels, were collected at entry into the open-label study. As expected, baseline lung function and patient-reported measures of asthma control (ACQ, AQLQ, ASUI, and SABA use) were better on average in reslizumab-experienced patients compared to reslizumab-naïve patients. Baseline mean FEV_1 values were lower in the reslizumab-naïve group versus the reslizumab-experienced group (2.096 and 2.285 L, respectively). Mean blood eosinophil counts were higher in patients in the reslizumab-naïve group (0.528×10^9/L) compared to patients in the reslizumab-experienced group (0.078×10^9/L).

Efficacy Results: A trend for improvement in lung function based on FEV_1, % predicted FEV_1, FVC (volume response), and $FEF_{25\%-75\%}$ (small airways response) was observed in reslizumab-naïve patients. These improvements were evident as early as 4 weeks after the first reslizumab dose and were sustained through endpoint. The median change from baseline in FEV_1 in the reslizumab-naïve group at weeks 4 and 48 was 0.060 and 0.095 L, respectively. For the reslizumab-experienced group, there was no change from baseline at week 4 and a change of 0.010 L at week 48. Reslizumab-experienced patients had better spirometry characteristics compared to reslizumab-naïve patients at baseline, indicative of already improved asthma and consistent with their prior reslizumab exposure. In general, these improved spirometry results were sustained throughout the study without tachyphylaxis.

Patient-reported measures of asthma control and quality of life (AQLQ, ACQ, and ASUI) were better at baseline in the reslizumab-experienced group; the reslizumab-naïve group improved to similar levels by the first on-treatment assessment at 4 weeks. Improved levels were sustained in both groups throughout the EOT. Both groups had small changes in SABA use throughout the study that are of unclear clinical significance.

As expected, mean eosinophil levels were higher at baseline for reslizumab-naïve patients than for reslizumab-experienced patients. Reslizumab treatment produced a decrease in blood eosinophil levels in reslizumab-naïve patients, similar to the levels in reslizumab-experienced patients after the first dose. The mean (0.25×10^9/L) and median (0.10×10^9/L) blood eosinophil values for the overall Study 3085 population at the follow-up visit (90 days after end of treatment or approximately 4 months after the last dose of reslizumab) were substantially lower than the mean and median baseline values reported in the individual placebo-controlled feeder studies (Studies C38072/3081, 3082, and 3083), indicative of general lack of rebound effect.

Safety Results: The safety data in this study indicate that treatment with reslizumab at an iv dose of 3.0 mg/kg every 4 weeks for up to 24 months was generally safe and well tolerated in patients with eosinophilic asthma.

Three deaths occurred during the study; none of which were assessed as related to reslizumab. The overall proportion of patients with serious adverse events (7%) was low and similar between the reslizumab-naïve and reslizumab-experienced groups, whether assessed at the preferred term level or system organ class (SOC) level. The overall rate of withdrawals from the study due to adverse events in each treatment group was low (6 [1%] patients in the reslizumab-naïve group and 12 [2%] patients in the reslizumab-experienced group) and not predominated by a particular SOC. There were 15 patients who were diagnosed with malignancies during the study, including 3 patients with nonserious events of basal cell carcinomas. The types and frequencies of the malignancies are considered to be reflective of what would be observed over time in a primarily adult study population, and therefore do not support a causal role for reslizumab.

The pattern of all adverse events by SOC is what would be expected for a population of patients with moderate to severe asthma. The overall incidence of treatment-related adverse events was similar between groups, and there were no differences in rate between groups at the SOC level that were of concern.

Adverse events assessed as related to the study drug infusion were most commonly reported in the nervous system disorders (<1%) and general disorders and administrative site conditions (1%) SOCs. As expected, the nature and frequency of these events were similar in the reslizumab-naïve and reslizumab-experienced groups. There were no helminthic parasitic infections reported. Hypersensitivity reactions to reslizumab were assessed by reviewing high-level terms within the immune system disorders and skin and subcutaneous tissue disorders SOCs. There was no evidence of an increased risk of immune disorders, including hypersensitivity reactions, in reslizumab-naïve patients compared to reslizumab-experienced patients. There were no cases of anaphylaxis reactions related to reslizumab. Seven patients reported events in the skin and subcutaneous tissue disorders SOC that were assessed as treatment related by the investigator; however, all of these events were mild to moderate in severity, and none of these events resulted in study discontinuation.

Per serum chemistry parameters, mean changes to endpoint were generally small and not clinically relevant. Per hematology parameters, with the exception of eosinophils and the effect on the total white blood cell (WBC) count, mean values were similar between reslizumab-naïve and reslizumab-experienced groups and did not show any meaningful changes with treatment. Other than the expected changes in eosinophil count and total WBC, there were no obvious differences between the reslizumab-naïve and reslizumab-experienced groups in shifts from baseline or frequency of potentially clinically significant values for any hematology parameter during the 24-month treatment period. There were no meaningful trends in mean changes in urinalysis values. There were no clinically meaningful trends in vital sign values or physical examination findings.

There were no clinically meaningful differences between the reslizumab-naïve and reslizumab-experienced groups in ADA response; the proportion of patients having at least 1 positive test result over the treatment period was similar and low in each group.

Conclusions: The results of this open-label extension study showed that continuous iv treatment with reslizumab 3.0 mg/kg every 4 weeks for up to 24 months was well tolerated in patients with moderate to severe asthma and elevated eosinophil counts, who were previously enrolled in 1 of the reslizumab safety and efficacy studies in patients with eosinophilic asthma.

The positive treatment effects produced by reslizumab in the placebo-controlled feeder studies were evident at baseline in this open-label extension study, and were maintained through up to an additional 24 months of treatment with reslizumab 3 mg/kg without diminution. Consistent with the published results of the precedent safety and efficacy studies, trends for improvement in pulmonary function, asthma symptoms, and overall quality of life scores were observed in reslizumab-naïve patients who were new to therapy.

16.1.4 List and Description of Investigators and Other Important Participants in the Study

Table 1: List of Investigators

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
1	[redacted] Clinical Research Institute of Southern Oregon, PC 3860 Crater Lake Avenue Suite B Medford, OR 97504 UNITED STATES OF AMERICA	[redacted]
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3	[redacted] Aeroallergy Research Labs of Savannah 505 Eisenhower Drive Savannah, GA 31406 UNITED STATES OF AMERICA	
4	[redacted] Choc Pediatric Subspecialty Faculty 725 West La Veta, Suite 100 Orange, CA 92868 UNITED STATES OF AMERICA	

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
5	[redacted] Community Research Foundation 6700 Southwest 21st Street Miami, FL 33155 UNITED STATES OF AMERICA	[redacted]
8	[redacted] Midwest Allergy and Asthma Clinic 16945 Frances Street Omaha, NE 68130 UNITED STATES OF AMERICA	[redacted]
9	[redacted] Asthma, Nasal Disease & Allergy Research Center 95 Pitman Street Providence, RI 02906 UNITED STATES OF AMERICA	
11	[redacted] Allianz Medical and Research Center 10900 Warner Avenue Suite 101B Fountain Valley, CA 92708 UNITED STATES OF AMERICA	
12	[redacted] Convergys Clinical Research, Inc. 8245 East Monte Vista Road Suite 200 Anaheim Hills, CA 92808 UNITED STATES OF AMERICA	
14	[redacted] Southwest Allergy and Asthma Research Center, P. A. 7711 Louis Pasteur Suite 901 and 905 San Antonio, TX 78229 UNITED STATES OF AMERICA	[redacted]
15	[redacted] Allergy & Asthma Clinical Research, Inc. 130 La Casa Via, Clinical Research Division, Building 2, Suite 110 Walnut Creek, CA 94598 UNITED STATES OF AMERICA	[redacted]

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
16	[redacted] North Texas Institute for Clinical Trials 6310 Southwest Boulevard Suite 200 Fort Worth, TX 76109 UNITED STATES OF AMERICA	[redacted]
17	[redacted] Advanced Research Institute, Inc. 7114 Congress Street New Port Richey, FL 34653 UNITED STATES OF AMERICA	[redacted]
19	[redacted] Allergy And Asthma Dtc 2300 Centerville Road Tallahassee, FL 32308 UNITED STATES OF AMERICA	
20	[redacted] New Horizons Clinical Research 4260 Glendale Milford Road Suite 201 Cincinnati, OH 45242 UNITED STATES OF AMERICA	
21	[redacted] Asthma & Allergy Consultants, LLP 102 Morgan Place Summerville, SC 29485 UNITED STATES OF AMERICA	
24	[redacted] Innovative Research of West Florida Innovative Research of West Florida 1573 South Fort Harrison Avenue Clearwater, FL 33756 UNITED STATES OF AMERICA	
25	[redacted] DataQuest Medical Research 565 Old Norcross Road Suite 102 Lawrenceville, GA 30046 UNITED STATES OF AMERICA	

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
27	[redacted] Kendall South Medical Center, Inc. 2433 Southwest 147th Avenue Miami, FL 33185 UNITED STATES OF AMERICA	[redacted]
30	[redacted] Wake Forest University Health Sciences Medical Center Boulevard Winston-Salem, NC 27157 UNITED STATES OF AMERICA	[redacted]
31	[redacted] Bernstein Clinical Research Center, Inc. 8444 Winton Road Cincinnati, OH 45231 UNITED STATES OF AMERICA	
32	[redacted] Vanderbilt University ASAP Research 2611 West End Avenue Suite 120 Nashville, TN 37203 UNITED STATES OF AMERICA	
33	[redacted] University of Wisconsin Medical School 600 Highland Avenue, Box 5669 Madison, WI 53792 UNITED STATES OF AMERICA	

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
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41	[redacted] Research Center of Fresno, Inc. 3636 North First Street Suite 141 Fresno, CA 93726 UNITED STATES OF AMERICA	
43	[redacted] California Allergy & Asthma Medical Group, Inc. 11645 Wilshire Boulevard Suite 1155 Los Angeles, CA 90025 UNITED STATES OF AMERICA	[redacted]
44	[redacted] Dallas Allergy Immunology Research 7777 Forest Lane, Suite B-332 Dallas, TX 75230 UNITED STATES OF AMERICA	[redacted]

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
45	[redacted] Alamo Clinical Research Associates 910 San Pedro San Antonio, TX 78212 UNITED STATES OF AMERICA	[redacted]
46	[redacted] Private Practice Bangor, ME 04401 UNITED STATES OF AMERICA	
47	[redacted] National Jewish Health 1400 Jackson Street, K-333 Denver, CO 80206 UNITED STATES OF AMERICA	
49	[redacted] University of Kentucky 135 East Maxwell Street Suite 250 Lexington, KY 40508 UNITED STATES OF AMERICA	
50	[redacted] Allergy, Asthma & Clinical Research Center 4200 West Memorial Road Suite 206 Oklahoma City, OK 73120 UNITED STATES OF AMERICA	
53	[redacted] Saint Francis Sleep Allergy and Lung Institute 802 North Belcher Road Clearwater, FL 33765 UNITED STATES OF AMERICA	
55	[redacted] Florida Center for Allergy and Asthma Research 9035 Sunset Drive, Suite 202 Miami, FL 33173 UNITED STATES OF AMERICA	

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
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59	[redacted] West Coast Clinical Trials 3545 Howard Way, Suite 100 Costa Mesa, CA 92626 UNITED STATES OF AMERICA	
63	[redacted] Allergy and Asthma Center of Boerne 114 Trade Avenue TTS Research Boerne, TX 78006 UNITED STATES OF AMERICA	
64	[redacted] Boys Town National Research Hospital 14080 Boys Town Hospital Road, Boys Town Medical Campus - Pacific Street Boys Town, NE 68010 UNITED STATES OF AMERICA	
66	[redacted] Central PA Asthma and Allergy Care, LLC 501 Howard Avenue, Suite 201A Altoona, PA 16601 UNITED STATES OF AMERICA	

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
69	[redacted] Western Sky Medical Research 2121 Wyoming Avenue El Paso, TX 79903 UNITED STATES OF AMERICA	[redacted]
73	[redacted] Asthma & Allergy Physicians of Rhode Island Clinical Research Institute (AAPRI CRI) 470 Toll Gate Road, Suite 203 Warwick, RI 02886 UNITED STATES OF AMERICA	
74	[redacted] Washington University School of Medicine 660 South Euclid Avenue Campus Box 8127 Saint Louis, MO 63110 UNITED STATES OF AMERICA	
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103	[redacted] University of Calgary Calgary, Quebec, H4J 1C5, Alberta T2N 4Z6 CANADA	
104	[redacted] SKDS Research Inc. Newmarket, Ontario L3Y5G8 CANADA	
105	[redacted] Professional Medicine Corporation Windsor, Ontario N8X-5A6 CANADA	
120	[redacted] Centro Médico Dra De Salvo - Avenida Cabildo 1548 - Piso 6°B - Ciudad Autonoma de Buenos Aires - C1426ABP – Argentina	

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
121	[redacted] Fundacion CIDEA, Sanatorio San Jose - Billinghurst 1677 - 3er Piso - Ciudad Autonoma de Buenos Aires - C1425DTG – Argentina	[redacted]
122	[redacted] Centro Modelo de Cardiologia - Laprida 554 - San Miguel de Tucuman - T4000IFL – Argentina	
123	[redacted] Sanatorio Parque - Cordoba 2392 - 1ª Planta - Rosario-Santa Fe - S2000KZD – Argentina	
125	[redacted] Centro Respiratorio Infantil - Montevideo 370 - Rosario - S2000BRH – Argentina	
126	[redacted] Organización Médica de Investigación - Uruguay 725 - PB - Ciudad Autónoma de Buenos Aires - C1015ABO – Argentina	
128	[redacted] Centro Respiratorio Quilmes - Hipolito Yrigoyen 856 - Quilmes-Buenos Aires - B1878FNR – Argentina	
140	[redacted] Hospital São Lucas da PUC - RS - Av. Ipiranga, 6690 - Departamento de Pneumonologia - Porto Alegre - 90610-000 – Brazil	
142	[redacted] Centro de Estudos de Pneumologia da Faculdade de Medicina ABC - Av. Príncipe de Gales, 821 - Santo André, São Paulo - 09060-650 – Brazil	

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
143	[redacted] Santa Casa de Porto Alegre - Rua Professor Anne Dias, 295 – Pavimento Pereira Filho – 1º andar – Sala 7 - 90020-090 – Porto Alegre – Brazil	[redacted]
144	[redacted] Hospital Nossa Senhora da Conceição - Avenida Francisco Trein 596 - Ambulatorio de Pneumologia - sala 4014-B - Porto Alegre - 91350-200 – Brazil	
146	[redacted] Santa Casa de Misericórdia de Belo Horizonte - Avenida Francisco Sales, 1111 - Departamento de Pneumologia - Belo Horizonte - 30150-221 – Brazil	
147	[redacted] Hospital Moinhos de Vento - Rua Ramiro Barcelos 910 - Instituto de Educação e Pesquisa - Porto Alegre - 90035-001 - Brazil	
150	[redacted] Universidade Federal de Santa Catarina Campus Universitário – Trindade – 3º andar – NU Paiva CEP 88040-970 – Florianópolis – Brazil	
160	[redacted] Hospital Regional de Rancagua, Unidad de Respiratorio Avenida Libertador Bernardo O´Higgins N°611, Piso 1, Sector B, Rancagua – Chile	
161	[redacted] Centro de Investigaciones Clínicas del Sur (CICS), Portales N°287, Temuco – Chile	

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
162	[redacted] Hospital Base Valdivia, Bueras 1003, Policlínico Respiratorio, piso 1 oficina 5, o Simpson 850 Valdivia – Chile	[redacted]
164	[redacted] Investigaciones Médicas TASOL, Avenida Salvador N°95, Oficina 908, Providencia, Santiago – Chile	
166	[redacted] Hospital Carlos Van Buren, Consultorio de Especialidades, San Ignacio 725, Piso 1, Sector D, Valparaíso – Chile	
180	[redacted] Fundacion Oftalmologica de Santander Foscal - Calle 155A Numero 23-09 - Urbanización El Bosque - Floridablanca – Colombia	
181	[redacted] Fundacion Neumologica Colombiana - Carrera 13B 161-85 - Segundo Piso - Bogotá – Colombia	
182	[redacted] Fundación Valle del Lili - Carrera 98 Numero 18-49 - Cali – Colombia	
185	[redacted] Centro Especializado en Enfermedades Pulmonares Sociedad Por Acciones Simplificada - Calle 134 Numero 7 - 83 - CS 333 - Bogotá – Colombia	

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
202	[redacted] Clínica de Sueño del Noroeste (ubicada en Hospital Angeles de Tijuana)- Av. Paseo de los Heroes No. 10999 - Consultorio 701- Zona Rio - Suite 701 – CP 22010 – Tijuana, Baja California– Mexico	[redacted]
204	[redacted] Instituto Jalisciense de Investigacion Clinica S.A. de C.V. (IJICSA) - Calle Penitenciaria Numero 20 - Colonia Centro – CP 44100 Guadalajara, Jalisco– Mexico	[redacted]
205	[redacted] Instituto Nacional de Pediatría (Servicio de Alergia) - Insurgentes Sur 3700C - Colonia Insurgentes Cuicuilco, Delegación Coyoacan – CP 04530, Mexico, Distrito - Federal– Mexico	[redacted]
220	[redacted] Complejo Hospitalario San Pablo - Avenida El Polo 789, Santiago de Surco - Lima 33 – Peru	[redacted]
221	[redacted] Hospital Nacional "Luis N. Saenz" de la Policia Nacional del Peru - Avenida Brasil cuadra 26 s/n, Jesus Maria - Lima 11 – Peru	[redacted]
222	[redacted] Hospital Nacional Cayetano Heredia - Avenida Honorio Delgado 262, San Martin de Porres - Lima 31 – Peru	[redacted]

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
223	[redacted] Clinica Internacional - Avenida Garcilazo de la Vega 1420, Cercado de Lima - Lima 01 – Peru	[redacted]
225	[redacted] Clinica San Borja - Avenida Guardia Civil 337, San Borja - Lima 41 – Peru	
226	[redacted] ABK Reuma SRL - Avenida Sucre 134, Pueblo Libre - Lima 21 – Peru	
227	[redacted] Centro de Investigaciones Ricardo Palma - Calle Ricardo Angulo 130, San Isidro - Lima 27 – Peru	
229	[redacted] Hospital Nacional Edgardo Rebagliati Martins 490 EsSalud - Avenida Edgardo Rebagliati Martins 490, Jesus Maria - Lima 11 – Peru	

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
260	[redacted] Pintelaan 185, Pneumologie, Gent, 9000, Belgium	[redacted]
261	[redacted] Route de Lennik 808, Pneumologie, Bruxelles, 1070, Belgium	
262	[redacted] Medical Pegase, Rue des Fabriques 6, Pneumologie, Gembloux, 5030, Belgium	
263	[redacted] Domaine Universitaire du Sart Tilman, Pneumologie, Liège, 4000, Belgium	

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
264	[redacted] Universitaires Saint-Luc, Avenue Hippocrate 10, Pneumologie, Bruxelles, 1200, Belgium	[redacted]
280	[redacted] Pavlova 6, Oddeleni alergologie a klinicke imunologie, Olomouc , 77520, Czech Republic	[redacted]
281	[redacted] Fakultni nemocnice Brno, Jihlavska 20, Klinika Nemoci plicnich a tuberkulozy, Brno, 62500, Czech Republic	[redacted]
283	[redacted] KASMED s.r.o., Klokotska 106, Alergologicka ambulance, Tabor, 39001, Czech Republic	[redacted]
284	[redacted] Alergologicka ambulance, Bratri Mrstiku 38, Poliklinika Breclav, Breclav, 69074, Czech Republic	[redacted]
285	[redacted] Fakultni nemocnice Hradec Kralove, Sokolska 581, Plicni klinika, Hradec Kralove, 50005, Czech Republic	[redacted]
286	[redacted] Krajska nemocnice Liberec, a.s., Husova 10, Oddeleni tuber a resp nemoci (TRN), Liberec, 46063, Czech Republic	[redacted]
287	[redacted] / HORNMED s.r.o., Charbulova 296/8, Brno, 61800, Czech Republic	[redacted]

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300	[redacted] Ojenlaser-Klinik, Sdr. Boulevard 29, Odense, Odense, DK5000, Denmark	[redacted]
342	[redacted] Nord, Chemin des Bourrely, Service de Pneumologie, Pavillon Mistral 4ème étage, Marseille, 13015, France	[redacted]
361	[redacted] Praxis Dr. Anneliese Linnhoff, Hohenzollerndamm 2, Research Center for Medical Studies (RCMS), Lungen-und Bronchialheilkunde, Berlin, 10717, Germany	[redacted]
363	[redacted] Universitätsmedizin der Johannes Gutenberg-Universität Mainz, Langenbeckstraße 1, Schwerpunktpraxis Pneumologie, III. Medizinische Klinik, Gebäude 406, II.OG, Mainz, 55131, Germany	[redacted]
366	[redacted] Charité - Universitätsmedizin Berlin, Augustenburger Platz 1, Klinik für Pädiatrie M.S. Pneumologie und Immunologie, Berlin, 13353, Germany	[redacted]
367	[redacted] Synexus Clinical Research GmbH, Johannisplatz 1, Studienzentrum Leipzig - Zentrale, Leipzig, 04103, Germany	[redacted]
369	[redacted] IKF Pneumologie, Stresemannallee 3, Institut für klinische Forschung, Frankfurt, 60596, Germany	[redacted]

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370	[redacted] Hamburger Institut für Therapieforschung GmbH, Colonnaden 72, Hamburg, 20354, Germany	[redacted]
371	[redacted] Berufsgenossenschaftliches Universitätsklinikum Bergmannsheil GmbH, Bürkle-de-la-Camp-Platz 1, Medizinische Klinik III für Pneumologie, Allergologie, Schlaf- und Beatmungsmedizin, Bochum, 44789, Germany	[redacted]
372	[redacted] Studienzentrum KPPK Gmbh, Koblenz, 56068, Germany	[redacted]
380	[redacted] Sotiria Chest hospital of Athens, Mesogion 152, 7th Pulmonary Department, Athens, 11527, Greece	[redacted]
401	[redacted] Kórház-Rendelőintézet, Rákóczi fejedelem út 125-127. 2660 Balassagyarmat Hungary	[redacted]
402	[redacted] Szent Borbála Kórház, Szanatórium út 1-3., 2800 Tatabánya Hungary	[redacted]
403	[redacted] Soproni Erzsébet Oktató Kórház és Rehabilitációs Intézet, Győri út 15., 9400 Sopron Hungary	[redacted]

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
404	[redacted] Karolina Kórház Rendelőintézet, Tüdőgyógyászat, Régi Vámház tér 2-4., 9200 Mosonmagyaróvár Hungary	[redacted]
405	[redacted] Tüdőgyógyintézet Törökbálint III. Osztály, Munkácsy M. utca 70. 2045 Törökbálint Hungary	[redacted]
406	[redacted] Koch Róbert Kórház és Rendelőintézet, 1. Tüdőosztály, Dankó Pista u. 80. 3780 Edelény Hungary	[redacted]
407	[redacted] Farmakontroll Egészségügyi Szolgáltató BT., Gesztenyés u. 10. 2440 Százhalombatta Hungary	[redacted]
420	[redacted] Tel Aviv Sourasky Medical Center, 6 Weitzman Street, Allergy and Asthma Clinic, Tel-Aviv, 6423906, Israel	[redacted]
421	[redacted] Kaplan Medical Center, Pasternak Street , Pulmonary Unit, Rehovot, 76100, Israel	[redacted]

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
422	[redacted] Rabin Medical Center, 59 Jabotinsky Street, Pulm Institute, Beilinson Campus, OP clinic building, 1st floor, Petach Tikva, 49100, Israel	[redacted]
423	[redacted] Barzilai Medical Center, 2 Hahistadrout Street, Pulmonary Unit, outpatient clinics, 5th floor, Ashkelon, 7830604, Israel	
425	[redacted] Shaare Zedek Medical Center, 12 Shmuel Biet Street, Pulmonary Unit, Shaare Zedek MC, Jerlem, 91031, Israel	
426	[redacted]. Meir Medical Center 59 Tchernichovsky Street, Dept of Pulm Med, Kfar Saba, 44281, Israel	
428	[redacted]. Hadassah University Hospital Ein Kerem, Zahra Street , Institute of Pulmonary Medicine ,Kiryat Hadassah, Jerlem, 9112001, Israel	
432	[redacted] The Lady Davis Carmel Medical Center, 7 Michal Street, Dept of Resp Physio and Chest Dz, Haifa, 34362, Israel	
433	[redacted] The Chaim Sheba MC, Tel Hashomer, Dept Allergy, Immun and Angio, Ramat Gan, 5266202, Israel	

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
500	[redacted] Specjalistyczna Poradnia Pulmonologiczna, Limanowskiego 20/22, 63-400 Ostrow Mazowiecki, Ostrow Wielkopolski, 63400, Poland	[redacted]
501	[redacted] Specjalistyczny Zespol Chorob Pluc i Gruzlicy, J.Falata 2, Oddzial Pulmonologiczno - Alergiczny, Bystra, 43360, Poland	[redacted]
504	[redacted] ALERGO -MED. , PCK 26, 33-100 Tarnow Specjal. Przchodnia Lekarska Sp. z o.o., Tarnow, 33100, Poland	[redacted]
507	[redacted] Prywatny Gabinet Internistyczno - Alergologiczny, Ogrodowa 5, Bialystok, 15010, Poland	[redacted]
509	[redacted] Kliniczny Oddzial Pulmonologiczny, Skawinska 8, Powstancow warszawy 5, Bydgoszcz, 85681, Poland	[redacted]
511	[redacted] Samodzielny Niepubliczny Zaklad Opieki Zdrowotnej ALERGOLOGIA PLUS, Drobnika 49, Osrodek Diagnostyki i Terapii Uczulen, Poznan, 60693, Poland	[redacted]
512	[redacted] SPZOZ Uniwersytecki Szpital Kliniczny nr 1 im. Norberta Barlickiego Uniwersytetu Medycznego w Lodzi, Oddzial Kliniczny Pulmunologii i Alergologii, Kopcinskiego 22,Lodz, 90153, Poland	[redacted]

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
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520	[redacted] Pneumophtysiology Clinical Hospital 6 B.P. Hasdeu Street Pneumology Department Cluj-Napoca, 400371, Romania	[redacted]
522	[redacted] Targu Mures Emergency County Clinical Hospital, 50 Gheorghe Marinescu Street, IInd medical Department, Targu Mures, 540136, Romania	[redacted]
523	[redacted] Novo Medica, 6A Costache Negri Entrance, Bucharest, 050554, Romania	[redacted]
524	[redacted] National Institute of Pneumology, 90 Viilor Road, Sector 5, Bucharest, 050159, Romania	[redacted]
540	[redacted] City Hospital # 26, Ulitsa Kostyushko, 2, Floor 8, room 31, St.Petersburg, 196247, Russia	[redacted]
541	[redacted] First Pavlov State Medical University of St. Petersburg, Ulitsa Lva Tolstogo, 6/8, Chair of Faculty Therapy, St. Petersburg, 197022, Russia	[redacted]
542	[redacted] First Pavlov State Med Univ of St. Petersb , Ulitsa Roentgena, 12, Pulmonology Research Department, St. Petersburg, 197022, Russia	[redacted]

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
543	[redacted] Research Pulmonology Institute of Roszdrav, Odinnadtsataya Parkovaya Ulitsa, 32/61, Pulmonology Department, Moscow, 105077, Russia	[redacted]
544	[redacted] City Clinical Hospital n.a. S.P. Botkin, Vtoroy Botkinskiy Proezd, 5, Moscow, 125284, Russia	[redacted]
545	[redacted] City Hospital 5, Zmeinogorskiy Trakt, 75, Pulmonology Department, Barnaul, 656045, Russia	[redacted]
546	[redacted] Clinical Emergency Hospital n.a.N.V. Soloviev, Ulitsa Zagorodniy Sad, 11, Yaroslavl, 150003, Russia	[redacted]
549	[redacted] Rsch Institute of Complex Cardio Patho , Sosnovyy Bulvar, 6, Kemerovo, 650002, Russia	[redacted]
552	[redacted] Tomsk Regional Clinical Hospital Ulitsa Ivana Chernykh, 96 Tomsk 634063, Russia	[redacted]
554	[redacted] City Clinical Hospital #7, Kolomenskiy Proezd, 4, Allergology Department, Moscow, 115446, Russia	[redacted]
555	[redacted] Novosibirsk State Medical University Krasniy Prospect, 52 Novosibirsk 630091, Russia	[redacted]

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
556	[redacted] PhD Outpatient Clinic #3 of Russian President Administration, Grokholskiy Pereulok, 31, Moscow, 129090, Russia	[redacted]
557	[redacted] Novosibirsk Municipal Clinical Hospital for Emergency Medicine #2, 41, Yakusheva Street, Pulmonology Department, Novosibirsk, 630102, Russia	[redacted]
558	[redacted] Russian Medical Academy Of Postgraduate Education, Principal Investigator, Ulitsa Pekhotnaya, 3, Allergology Department, Moscow, 123182, Russia	[redacted]
559	[redacted] Central Clinical Hospital #1 OAO “RZhD”, Volokolamskoe Shosse, 84, Pulmonology Department, Moscow, 125367, Russia	[redacted]
560	[redacted] Plucna ambulancia Hrebenar, s.r.o., Fabiniho 15, Spisska Nova Ves, 052 01, Slovak Republic	[redacted]
561	[redacted] ZAPA JJ s.r.o., SNP 19, Levice, 934 01, Slovak Republic	[redacted]
562	[redacted] ANA JJ s.r.o., 17. Novembra 1300, Ambulancia alergologie a imunologie, Topolcany, 955 01, Slovak Republic	[redacted]
563	[redacted] NsP Sv. Jakuba, n.o., Bardejov, Sv. Jakuba 21, Ambulancia pneumologie a ftizeologie, Bardejov, 085 01, Slovak Republic	[redacted]

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580	[redacted] Private Practice, [redacted] Newgate Centre, Johannesburg, Gauteng, 2113, South Africa	[redacted]
582	[redacted] Westville Hospital, Spine Road, 218 Highway Medical Centre, Durban, Kwazulu-Natal, 3630, South Africa	[redacted]
583	[redacted] Global Clinical Trials (Pty) Ltd, 132 Celliers Street, Shop 29, Nedbank Plaza, Pretoria, 1, South Africa	[redacted]
584	[redacted] Private Practice, [redacted] Dept of Internal Med ,Tygerberg Hospital, Cape Town, Western Cape, 7505, South Africa	[redacted]
585	[redacted] Vawda Z Private Practice, 343 Randles Road, Durban, Kwazulu-Natal, 4091, South Africa	[redacted]
586	[redacted] University of Cape Town Lung Institute, George Street, Mowbray , Cape Town, Western Cape, 7700, South Africa	[redacted]
587	[redacted] Dr. I Engelbrecht, 174 Cradock Avenue, Lyttleton, Pretoria 0157, Centurion, Gauteng, 140, South Africa	[redacted]

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
588	[redacted] Emmed Research, 213 Middelberg Street, Jacaranda Hospital, Suite 2 Muckleneuk, Pretoria, Gauteng, 84, South Africa	[redacted]
589	[redacted] Soweto Clinical Trials Centre CC, 1900 Sycamore Street, Ext 2, Soweto Clinical Trials Centre, Dlamini, Soweto 1818, Johannesburg, Gauteng, 1818, South Africa	[redacted]
600	[redacted] Skånes universitetssjukhus, Ögon Klinik B, Lund, Lunginstitutionen, 3rd floor, Klinikgatan 18, SE-221 85 Lund, Sweden	[redacted]
602	[redacted] Universitetssjukhuset, Clinical Trial Center, Gröna stråket 12 plan 2, SE-413 45 Göteborg, Sweden	[redacted]
603	[redacted] Universitetssjukhuset i Linköping, Allergicentrum ing. 49, SE-581 85 Linköping, Sweden	[redacted]
604	[redacted] Kreftig Research Centre, Medicinaregatan 1F, SE-405 30 Göteborg, Sweden	[redacted]
620	[redacted] Healthcare Municipal Institution "Kharkiv City Clinical Hospital #13", Prospekt Gagarina, 137, Kharkiv, 61124, Ukraine	[redacted]

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
621	[redacted] State Institution "Dnipropetrovsk Medical Academy of the Ministry of Health of Ukraine", Vulytsya Batumska, 13, Chair of Faculty Surgery and Internship Surgery, Clinical Hospital #6, Dnipropetrovsk, 49074, Ukraine	[redacted]
622	[redacted] MD SI "National Institute of Phthisiology and Pulmonology n.a. F.G.Yanovsky" under NAMS of Ukraine, Vulytsya Amosova, 10, Clinical and Functional Department, Kyiv, 03680, Ukraine	[redacted]
623	[redacted] SI "National Institute of Phthisiology and Pulmonology n.a. F.G.Yanovsky" under NAMS of Ukraine, Vulytsya Amosova, 10, Clinical and Functional Department, Kyiv, 03680, Ukraine	[redacted]
624	[redacted] SI "National Institute of Phthisiology and Pulmonology n.a. F.G.Yanovsky" under NAMS of Ukraine, Vulytsya Amosova, 10, Clinical and Functional Department, Kyiv, 03680, Ukraine	[redacted]
625	[redacted] SI "National Institute of Phthisiology and Pulmonology n.a. F.G.Yanovsky" under NAMS of Ukraine, Vulytsya Amosova, 10, Clinical and Functional Department, Kyiv, 03680, Ukraine	[redacted]

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
626	[redacted] City Clinical Hospital #1, Khmelnytske Shose, 96, Department of Pulmonology, Chair of Propedeutics of Internal Medicine, Vinnytsya National Medical University n.a. M.I. Pyrohov, Vinnytsya National Medical University n.a. M.I. Pyrohov, Vinnytsya, 21029, Ukraine	[redacted]
629	[redacted] MD ME MMPI Donetsk Regional Clinical Territorial Medical Association, Prospekt Illicha, 14, Chair of Internal Diseases #1, Department of Pulmonology, Donetsk Regional Clinical Territorial Medical Association, Donetsk, 83099, Ukraine	[redacted]
630	[redacted] Regional Centre of Phthisiology and Pulmonology, Vulytsya I.Franka, 17, Ivano-Frankivsk, 76018, Ukraine	[redacted]
631	[redacted] Municipal Institution “Zaporizhzhia Regional Clinical Hospital" of Zaporizhzhia Regional Council, Orekhivske Shose, 10, Regional Centre of Allergology and Clinical Immunology, Zaporizhzhia, 69600, Ukraine	[redacted]
632	[redacted] MD Municipal Institution "City Clinical Hospital #6", Vulytsya Stalevariv, 34, Zaporizhzhya, 69035, Ukraine	[redacted]

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641	[redacted] Monash Medical Centre, 246 Clayton Road, Clayton, Victoria, 3168, Australia	[redacted]
642	[redacted] Frankston Hospital, Hastings Road, Frankston, Victoria, 3199, Australia	
643	[redacted] Lung Institute of Western Australia, Ground Floor, E Block, Sir Charles Gairdner Hospital, Hospital Avenue, Nedlands, Western Australia, 6009, Australia [redacted]	
645	[redacted] Liverpool Hospital, Department of Respiratory Medicine, Elizabeth Street, Liverpool, New South Wales, 2170, Australia	
680	[redacted] Kangdong Sacred Heart Hospital, 150 Sungahn-ro, Gangdong-gu, Seoul, 134-701, Korea [redacted]	

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
681	[redacted] Korea University Guro Hospital, 148 Gurodong-ro, Guro-gu, Seoul, 152-703, Korea	[redacted]
682	[redacted] Chonnam National University Hospital, 42 Jebongro, Dong-gu Gwangju, 501-757, Korea	
683	[redacted] Severance Hospital, 50 Yonsei-ro, Seodaemun-gu, Seoul, 120-752, Korea	
685	[redacted] Ajou University Hospital, San 5, Woncheon-dong, Yeongtong-gu Gyeonggi-do, Suwon-si, 443-721, Korea	

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686	[redacted] Seoul National University Hospital 101 Daehang-ro, Jongno-gu Department of Internal Medicine Seoul, 110-744, Korea	[redacted]
700	[redacted] Jalan Yaacob Latif, Bandar Tun Razak, 56000 Kuala Lumpur, Malaysia	
701	[redacted] Hospital Pulau Pinang, 10990 Pulau Pinang, Malaysia	
702	[redacted] University Malaya Medical Centre, Lembah Pantai 59100 Kuala Lumpur, Malaysia	
704	[redacted] Hospital Taiping, Jalan Tamingsari, 34000 Taiping, Perak, Malaysia	
705	[redacted] MBBS and Obstetrics, Level 4, Bangunan Klinik Pakar, Jalan Prima Selayang 7, 68100 Batu Caves, Selangor, Malaysia	

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721	[redacted] Medical Research Institute of New Zealand, Level 7, CSB Building, Wellington Hospital, Riddiford Street, Newtown, Wellington, 6021, New Zealand	[redacted]
723	[redacted] Respiratory Department Middlemore Hospital, Hospital Road, Private Bag 93311, Otahuhu, Auckland, 1640, New Zealand	
724	[redacted] RMC Medical Research Ltd, 285 South Road, Dunedin, 9012, New Zealand	
740	[redacted] 2F, Clinical Trial Unit (CTU), Quirino Memorial Medical Center JP Rizal cor Katipunan Ave., Project 4, Quezon City 1109 Philippines	
741	[redacted] Rm 211, Marian Bldg. FEU-NRMF, Dahlia Ave., West Fairview, Quezon City 1118 Philippines	[redacted]
742	[redacted] Rm 304 (3/F) Asthma Comprehensive Care Unit, Out Patient Dept. Philippine General Hospital Taft Ave., Manila 1000 Philippines	[redacted]
743	[redacted] G/F Pulmonary Division Philippine Heart Center East Ave., Quezon City 1100 Philippines	[redacted]
745	[redacted] Rm 1214, Research Rm, G/F (near OPD), Lung Center of the Philippines, Quezon Ave., Quezon City 1104 Philippines	[redacted]

Investigational center number	Investigator and affiliation	Sub-investigator(s) name
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780	[redacted] Chulalongkorn University Hospital, Division of Allergy/Immunology, Department of Medicine, Bangkok 10330, Thailand	
782	[redacted] Central Chest Institute of Thailand, Division of Respiratory Medicine, 39 Tiwanon Road, Muang, Nonthaburi 11000, Thailand	
784	[redacted] Maharaj Nakhonratchasima Hospital, Pulmonary Unit, Department of Internal Medicine, Muang, Nakhonratchasima 30000, Thailand	

9.8. Changes in the Conduct of the Study or Planned Analyses

9.8.1. Changes in the Conduct of the Study

There were 4 global amendments to the protocol for this study. Changes relative to all amendments are reflected in the methods described in this report. The amended protocol, dated 14 April 2014, with a summary of all revisions and their rationale, including the EU-specific amendment (Amendment 5), is provided in Section 16.1.1.

9.8.1.1. Amendment 1 (Dated 04 February 2011)

Amendment 1 (dated 04 February 2011) to the protocol was issued before any patients were enrolled into the study.

The following major changes (not all-inclusive) were made to the protocol:

- the original title of the protocol "A 24-Month Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of Reslizumab (3.0 mg/kg) as Treatment for Patients (12 Through 75 Years of Age) With Eosinophilic Asthma Who Completed a Prior Cephalon-Sponsored Study in Eosinophilic Asthma" was changed, because study treatment could be as long as 104 weeks (26 months) and the age range was already specified in the protocol
- clinical laboratory tests were added at weeks 4 and 8, and all objectives and endpoints relative to these measures were revised to include the data collected
- text was revised to clarify that the reslizumab dose is based on baseline body weight
- footnote "o" was added for vital signs measurements at visit 1
- text regarding informed consent for minors was revised to reflect that only 1 parent was required to sign the informed consent form
- the word "rescue" was deleted when used regarding SABA use review
- the administration rate for reslizumab was corrected from 2 mg/min to 2 mL/min text was revised to clarify that the investigator may adjust the dose for concomitant medications taken for asthma based on best clinical practices
- the time for refraining from SABA use before study visits was changed from 4 to 6 hours
- text regarding monitoring of adverse events during any washout phase of the study was deleted since this open-label study did not have a washout phase
- text regarding safety variables and analysis was revised to reflect additional analysis of clinical laboratory test results at weeks 4 and 8

9.8.1.2. Amendment 2 (Dated 14 April 2011)

Amendment 2 (dated 14 April 2011) to the protocol was issued before any patients were enrolled into the study.

The following major changes (not all-inclusive) were made to the protocol:

- administrative changes were documented
- a 90-day follow-up evaluation was added for the assessment of adverse events, blood eosinophils, and vital signs to allow for additional safety monitoring

- in addition to standard safety monitoring by the sponsor, an independent DSMB was implemented to oversee the safety of the patients

9.8.1.3. Amendment 3 (Dated 19 April 2011)

Amendment 3 (dated 19 April 2011) to the protocol was issued before any patients were enrolled into the study.

The following major changes (not all-inclusive) were made to the protocol:

- a change was made to stipulate that blood samples were to be collected for pharmacokinetic evaluation, blood eosinophil determination, and anti-reslizumab antibody assessment each time a patient experienced a serious adverse event, an adverse event leading to withdrawal, or an exacerbation of asthma symptoms
- inclusion criteria (a) and (b) were changed for clarification of country-specific age requirements
- exclusion criterion (f) was revised to clarify acceptable contraceptive methods to be used during the study

9.8.1.4. Amendment 4 (Dated 19 April 2013)

Amendment 4 (dated 19 April 2013) to the protocol was issued after 627 patients were enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study.

The following major changes (not all-inclusive) were made to the protocol:

- Cephalon was acquired and became an affiliate of Teva Branded Pharmaceutical Products R&D, Inc; administrative changes due to the acquisition were reflected, where appropriate, in the study protocol
- clinical laboratory information was revised to encompass appropriate countries
- background information was clarified/restated and a table with completed clinical studies of reslizumab was added for harmonization with other reslizumab study protocols
- pharmacokinetic, pharmacodynamic, and immunogenicity content was added for clarification
- patient population with eosinophilic asthma qualified as “moderate to severe”
- added to 90-day follow-up evaluation: (±7 days)
- immunogenicity (from anti-reslizumab antibody assessment) was removed as a safety evaluation in the study
- text for emergency treatment was added to include: unscheduled visits to the physician’s office for nebulizer treatment or other urgent treatment to prevent worsening of asthma symptoms, or a visit to the emergency room for treatment, regardless of subsequent admission
- beta-agonist use was qualified as “short-acting” and % FEV_1 as % “predicted”
- text was added to specify who was required to have a urine β-HCG test
- IRT registration was added to the procedure and assessment schedule
- baseline body weight was specified to be used throughout the study to determine dose

9.8.1.5. Country-Specific Amendment Korea 01 (Dated 21 November 2013)

The Country-Specific Amendment for Korea 01 (dated 21 November 2013) was issued after

983 patients were enrolled into the study.

The primary reason for this country-specific amendment was to change the age inclusion criteria for study centers in Korea to match those in India.

9.8.1.6. Amendment 5 (Dated 14 April 2014)

Teva communicated its intent to terminate Study C38072/3085 to all investigators involved with the trial on 09 January 2014. The rationale for the termination was that the primary study objective, in terms of open-label events for patient exposure to an investigational product without confirmed benefit/risk, had been sufficiently met. This was primarily based on substantial overenrollment from the originally planned sample size (approximately 740 patients) and is consistent with the Stopping Rules and Discontinuation Criteria in Section 3.6 of the original protocol. The decision to terminate the study was not due to any new or emerging safety concerns at that time. Following study termination, protocol amendment 5 was developed and issued on 14 April 2014 in countries within the European Union to comply with applicable EU legislation in this particular circumstance. This revised protocol was submitted and approved in all EU countries.

The following major procedural changes (not all-inclusive) were made to the protocol:

- change in signatory and administration of the study
- purpose of the study was redefined to align with changes to the primary objective, ie, obtaining additional safety data for reslizumab
- planned enrollment increased from 740 to 1000 patients, as actual enrollment exceeded initial predictions
- decision to terminate the study early (duration “up to 24 months”) as exposure to study drug had been met with no new or emerging safety or efficacy concerns
- duration of patient participation was corrected to include 90-day follow-up visit
- study was defined as being complete when the last patient completed his/her last study visit

List of Batch Numbers of Study Medication

Investigational Product: reslizumab 3 mg/kg

Protocol No.: C38072/3085

Investigational Product:	**Batch Number**
reslizumab 10mg/ml	10GG003A503 (10-001036)
reslizumab 10mg/ml	10-000862
reslizumab 10mg/ml	11-000701
reslizumab 10mg/ml	11-002802
reslizumab 10mg/ml	11-002803
reslizumab 10mg/ml	11-002804
reslizumab 10mg/ml	12-000792