

Accepted Manuscript

Cardiovascular and cerebrovascular events among patients receiving omalizumab:
Pooled analysis of patient-level data from 25 randomized, double-blind, placebo-
controlled clinical trials

Carlos Iribarren, MD, MPH, PhD, Kenneth J. Rothman, DrPH, Mary S. Bradley, MS,
Gillis Carrigan, PhD, Mark D. Eisner, MD, Hubert Chen, MD, MPH

PII: S0091-6749(17)30040-4

DOI: [10.1016/j.jaci.2016.12.953](https://doi.org/10.1016/j.jaci.2016.12.953)

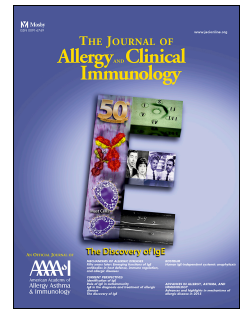
Reference: YMAI 12582

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 17 February 2016

Revised Date: 10 November 2016

Accepted Date: 7 December 2016



Please cite this article as: Iribarren C, Rothman KJ, Bradley MS, Carrigan G, Eisner MD, Chen H, Cardiovascular and cerebrovascular events among patients receiving omalizumab: Pooled analysis of patient-level data from 25 randomized, double-blind, placebo-controlled clinical trials, *Journal of Allergy and Clinical Immunology* (2017), doi: 10.1016/j.jaci.2016.12.953.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

**Cardiovascular and cerebrovascular events among patients receiving
omalizumab: Pooled analysis of patient-level data from 25 randomized, double-
blind, placebo-controlled clinical trials**

**Carlos Iribarren, MD, MPH, PhD,^a Kenneth J. Rothman, DrPH,^b Mary S. Bradley,
MS,^{c*} Gillis Carrigan, PhD,^c Mark D. Eisner, MD,^c Hubert Chen, MD, MPH^c**

^a*Division of Research, Kaiser Permanente Medical Care Program, Oakland, Calif,*
carlos.iribarren@kp.org; ^b*RTI Health Solutions, Research Triangle Park, NC,*
krothman@rti.org; ^c*Genentech, Inc., South San Francisco, Calif,*
bradley.mary@gene.com, carrigan.gillis@gene.com, eisner.mark@gene.com,
chen.hubert@gene.com

^{*}Employee at the time of study

Correspondence to: Hubert Chen, MD, MPH, 1 DNA Way, MS #453A, South San
Francisco, CA 94080. E-mail: chenh37@gene.com. Tel: 650-225-4619. Fax: 650-467-
2322.

Role of the funding source

This analysis was funded by Genentech, Inc., South San Francisco, Calif, and
Novartis Pharma AG, Basel, Switzerland. Medical writing support for this manuscript
was provided by Linda Goldstein, PhD, and Charlotte Kenreigh, PharmD, of Excel
Scientific Solutions, Southport, Conn, and funded by Genentech, Inc. and Novartis
Pharmaceuticals Corporation.

24

25 References: 2/9

26 Tables/figures: 2/2

27 Supplemental material: (text, 4 tables and 1 figure)

28

29 **Capsule summary:** Among patients who participated in randomized clinical trials of
30 omalizumab, no substantial overall increase in the risk of cardiovascular events was
31 observed in the treatment arms compared with placebo. <<29/35 words>>

32

33 **Key words:** *Adverse event, arterial thromboembolic event, cardiovascular,*
34 *cerebrovascular, clinical trials, moderate-to-severe asthma, omalizumab, safety, serious*
35 *adverse event*

36

37

To the editor:

Omalizumab is an anti-IgE antibody used in the treatment of moderate to severe persistent asthma. EXCELS (An Epidemiologic Study of Xolair [omalizumab]: Evaluating Clinical Effectiveness and Long-term Safety in Patients With Moderate-to-Severe Asthma; NCT00252135) was a prospective observational cohort study conducted as a postmarketing commitment to the US Food and Drug Administration to better understand the long-term safety of omalizumab in clinical practice. Results from EXCELS suggest that omalizumab is not associated with increased risk of malignancy.¹ In a subsequent analysis, however, we reported an imbalance in cardiovascular and cerebrovascular events.² The observational design of EXCELS precluded randomization and blinding to treatment, and thus differences in asthma severity between cohorts at baseline may have contributed to this imbalance, but some increase in risk could not be excluded. Here we report results from a separate analysis of cardiovascular events using pooled data from randomized controlled trials (RCTs) of omalizumab.

Twenty-five core trials and two extension studies met the inclusion criteria for this pooled analysis (Table E1); data included patients recruited from 26 countries. Common reasons for exclusion included open-label or single-arm (uncontrolled) design, limited drug exposure (eg, single dose), and pediatric-only studies.

All potential events of interest were identified from the Adverse Event Report Form or Discontinuation Case Report Form using a pre-specified search strategy (Figure E1). External adjudication was then performed by 5 cardiologists and 3

neurologists. Additional methodologic information and statistical analysis can be found in the online repository (text and Table E2).

The pooled population of RCTs included 3342 omalizumab-treated patients and 2895 placebo-treated patients, of whom 72% ($n = 2409$) and 80% ($n = 2320$), respectively, were treated for allergic asthma. Total observation time was 1857 person-years (PY) for omalizumab and 1681 PY for placebo; median duration of treatment was 154 days (omalizumab) and 161 days (placebo). Baseline demographic and clinical characteristics were generally comparable between the treatment groups (Table E3). Using the broad search strategy, 351 potential events of interest occurring in 249 patients were identified for external adjudication (Fig E1).

The pre-specified primary analysis included all deaths and serious arterial thrombotic events (ATEs) (Table 1). The results are shown in Fig 1. The Mantel-Haenszel rate difference per 1000 PY, stratified by clinical trial, for ATEs overall (rate difference, 0.30; 95% confidence interval [CI], -1.6 to 2.2) was consistent with the primary analysis (rate difference, 0.30; 95% CI, -4.2 to 4.6). The largest difference observed was for arrhythmia, which was higher in the placebo versus omalizumab groups. Results were similar in the main subgroup treated for allergic asthma (data not shown), where the rate difference was 0.48 events per 1000 PY (95% CI, -4.7 to 5.6) and the rate ratio (RR) was 1.2 (95% CI, 0.25-5.9).

The secondary analysis included all deaths and all ATEs, serious and non-serious (Table 1). The rate difference was 0.85 events per 1000 PY (95% CI, -3.7 to 5.3), with a RR of 1.4 (95% CI, 0.32-6.6). Results were similar in the main subgroup treated for allergic asthma (data not shown), where the rate difference was 1.1 events

per 1000 PY (95% CI, -4.2 to 6.4) and the RR was 1.4 (95% CI, 0.33-6.8). Further subgroup analyses were not generally informative owing to the small number of overall ATEs (Table E4).

Taken together, this analysis of pooled safety data from >6200 participants in 25 RCTs (>3500 PY of observation) revealed few CV events in either the omalizumab (n=5) or placebo groups (n=4). Rates for ATE, as well as for individual events, were similar between the 2 groups; however, the CIs were wide, reflecting statistical uncertainty of these estimates. The secondary analysis, which included nonserious events, showed higher rates in both the omalizumab and placebo groups, but the rate differences were also small and the CIs were wide and included the null hypothesis.

Findings from this analysis should be interpreted in the context of its own limitations. First, owing to the duration of clinical trials, the results are relevant only as they relate to shorter-term exposure to omalizumab. Second, patients participating in clinical trials often are different than those treated in actual practice. Third, while randomization is intended to balance unmeasured confounders in any given individual trial, it does not guarantee balanced groups when the data are pooled. To address this concern, a sensitivity analysis stratified by clinical trial also was performed and yielded similar results. Finally, although every attempt was made to keep adjudicators blinded to treatment status, the blinded case narratives were written by a third party (ie, neither sponsor nor adjudicator), who was unblinded to treatment allocation.

In conclusion, in this analysis of pooled RCT data, the rates of observed ATEs were similar between the omalizumab and placebo groups. However, the low number of events and wide CIs limit the ability to exclude small differences in risk.

107

108

109 Carlos Iribarren, MD, MPH, PhD^a110 Kenneth J. Rothman, DrPH^b111 Mary S. Bradley, MS^c112 Gillis Carrigan, PhD^c113 Mark D. Eisner, MD^c114 Hubert Chen, MD, MPH^c

115

116 ^a*Division of Research, Kaiser Permanente Medical Care Program, Oakland, Calif;* ^b*RTI*117 *Health Solutions, Research Triangle Park, NC;* ^c*Genentech, Inc., South San Francisco,*118 *Calif*

119

ACKNOWLEDGMENTS

The authors would like to acknowledge former Novartis employees Janice Canvin, Martin Blogg, John Powell, and Guy Peachey, for their invaluable contributions to the study design, data collection and analysis, and interpretation of the results. The study was funded by Genentech, Inc., South San Francisco, Calif, and Novartis Pharma AG, Basel, Switzerland. Medical writing support for this manuscript was provided by Linda Goldstein, PhD, and Charlotte Kenreigh, PharmD, of Excel Scientific Solutions, Southport, Conn, and funded by Genentech, Inc. and Novartis Pharmaceuticals Corporation.

REFERENCES

1. Long A, Rahmaoui A, Rothman KJ, Guinan E, Eisner M, Bradley MS, et al. Incidence of malignancy in patients with moderate-to-severe asthma treated with or without omalizumab. *J Allergy Clin Immunol* 2014;134:560-567 e4.
2. Iribarren C, Rahmaoui A, Long AA, Szeffler SJ, Bradley MS, Carrigan G, et al. Cardiovascular and cerebrovascular events among patients receiving omalizumab: Results from EXCELS, a prospective cohort study of moderate-to-severe asthma. *J Allergy Clin Immunol* 2016.

140 **TABLE I.** Primary and Secondary Analyses: Rates of AEs, ATEs and other CV

141 SAEs

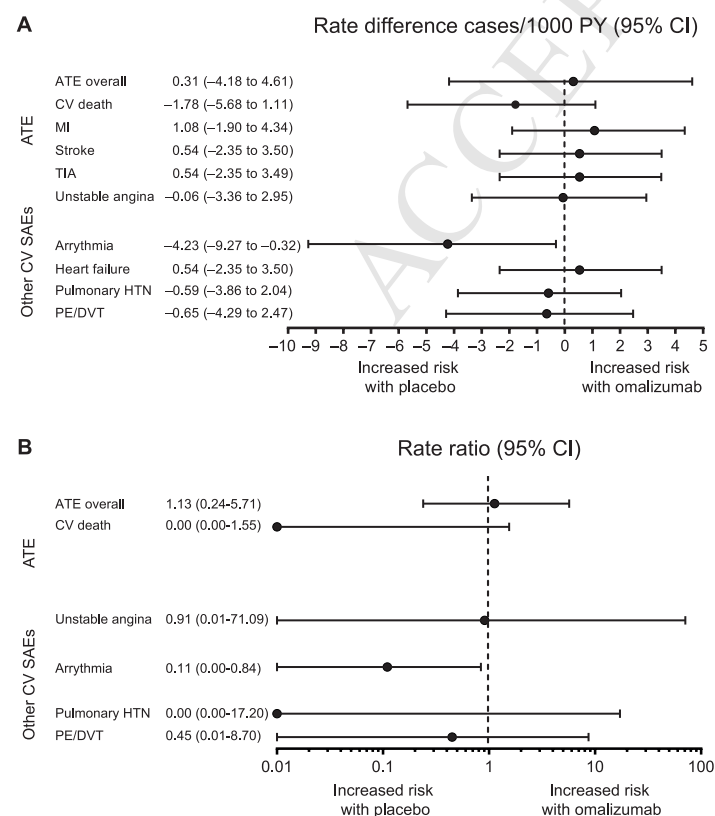
Primary Analysis		
	Omalizumab	Placebo
All ATEs: Deaths and SAEs	(n = 3342)	(n = 2895)
Events, no.	5	4
PY, no.	1856	1681
ATE rate per 1000 PY (95% CI)	2.7 (0.88-6.3)	2.4 (0.65-6.1)
Event rate per 1000 PY (95% CI)		
CV death	0.00 (0.00-2.0)	1.8 (0.37-5.2)
MI	1.1 (0.13-3.9)	0.00 (0.00-2.2)
Stroke	0.54 (0.01-3.0)	0.00 (0.00-2.2)
TIA	0.54 (0.01-3.0)	0.00 (0.00-2.2)
Unstable angina	0.54 (0.01-3.0)	0.60 (0.02-3.3)
Other CV SAEs		
Events, no.	3	11
PY, range	1852-1857	1674-1681
Event rate per 1000 PY (95% CI)		
Arrhythmia	0.54 (0.01-3.0)	4.8 (2.1-9.4)
Heart failure	0.54 (0.01-3.0)	0.0 (0.0-2.2)
Pulmonary HTN	0.00 (0.00-1.2)	0.59 (0.02-3.3)
PE/DVT	0.54 (0.01-3.0)	1.2 (0.14-4.3)
Secondary analysis		

	Omalizumab	Placebo
All AEs	(n = 3342)	(n = 2895)
ATEs, no.	6	4
PY, no.	1855	1680
Rate per 1000 PY (95% CI)	3.2 (1.2-7.0)	2.4 (0.65-6.1)
Stroke, no.	2	0
PY, no.	1856	1681
Rate per 1000 PY (95% CI)	1.08 (0.13-3.9)	0.00 (0.00-2.2)
Arrhythmia, no.	13	24
PY, no.	1852	1674
Rate per 1000 PY (95% CI)	7.0 (3.7-12)	14 (9.2-21)
PE/DVT, no.	3	3
PY, no.	1855	1681
Rate per 1000 PY (95% CI)	1.6 (0.33-4.7)	1.8 (0.37-5.2)

AE, adverse event; ATE, arterial thromboembolic event; CV, cardiovascular; DVT, deep
 vein thrombosis; HTN, hypertension; MI, myocardial infarction; PE, pulmonary embolism;
 PY, person-years; SAE, serious adverse event; TIA, transient ischemic attack.

FIGURE LEGEND

FIG 1. Primary analysis: ATEs and other CV SAEs. Rate difference (**A**), and rate ratio (**B**). *ATE*, arterial thromboembolic event; *CV*, cardiovascular; *DVT*, deep vein thrombosis; *HTN*, hypertension; *MI*, myocardial infarction; *PE*, pulmonary embolism; *SAE*, serious adverse event; *TIA*, transient ischemic attack.



Supplementary information

Cardiovascular and cerebrovascular events among patients receiving omalizumab: Pooled analysis of patient-level data from 25 randomized, double-blind, placebo-controlled clinical trials

Carlos Iribarren, MD, MPH, PhD,^a Kenneth J. Rothman, DrPH,^b Mary S. Bradley, MS,^c Gillis Carrigan, PhD,^c Mark D. Eisner, MD,^c Hubert Chen, MD, MPH,^c

^a*Division of Research, Kaiser Permanente Medical Care Program, Oakland, Calif, carlos.iribarren@kp.org; ^bRTI Health Solutions, Research Triangle Park, NC, krothman@rti.org; ^cGenentech, Inc., South San Francisco, Calif, bradley.mary@gene.com, carrigan.gillis@gene.com, eisner.mark@gene.com, chen.hubert@gene.com*

Correspondence to: Hubert Chen, MD, MPH, 1 DNA Way, MS #453A, South San Francisco, CA 94080. E-mail: chenh37@gene.com. Tel: 650-225-4619. Fax: 650-467-2322.

Supplementary Methods

Eligibility for inclusion of studies in the pooled database analysis included the following: (1) designed as a randomized, double-blind, placebo-controlled, parallel-group study and conducted by Genentech, Inc. or Novartis Pharma AG for the treatment of asthma or other conditions; (2) omalizumab was used at approved dosages and administered subcutaneously using a lyophilized or liquid formulation; (3) included patients ≥ 12 years of age; and (4) treatment period ≥ 8 weeks. Selection criteria for clinical trials were developed with input from the Division of Pulmonary, Allergy, and Rheumatology Products at the Food and Drug Administration (FDA). The pooled analysis was initiated in 2011, and thus only trials completed by December 31, 2010 and those with access to locked datasets were eligible for inclusion.

The date of first study drug administration was used for both the start of treatment exposure and start of observation. The end of exposure was the last on-study treatment date. Duration of exposure was calculated as the end of exposure date – treatment start date + 1 (in days). For all patients, the end of observation was the earlier of (1) the last treatment date + 30 days or (2) the day before the date of first treatment in the next trial of a series (where applicable). In the event of death, the date of death was used as the end of observation if it occurred earlier than the derived value described above. The duration of observation was calculated as the end of observation time – treatment start date + 1 (in days).

All potential events of interest (EOIs) were identified from the Adverse Event (AE) Report Form or from the Discontinuation Case Report Form using a prespecified search strategy (Figure E1). All verbatim AE terms were coded using the Medical Dictionary for

Regulatory Activities (MedDRA) System. Standardized MedDRA Queries (SMQs) used to identify potential EOs included myocardial infarction (MI), arrhythmia, heart failure, stroke, pulmonary hypertension, pulmonary embolus/deep vein thrombosis, and other ischemic heart disease. More broadly, MedDRA System Organ Classes (SOCs) for cardiac disorders and vascular disorders also were searched to capture EOs. The MedDRA High-Level Term transient cerebrovascular events (capsular warning syndrome, reversible ischemic neurological deficit, transient ischemic attack [TIA]) also was searched to supplement the SOC search. Finally, the MedDRA Preferred Terms death, sudden death, sudden cardiac death, hemiparesis, amaurosis fugax, and hemiplegia were searched to identify potential EOs not identified by the SMQ, SOC, and High-Level Term searches.

Adjudicators were not told which organization was sponsoring the review process to minimize bias. Adjudicators assigned each EO to 1 of the 9 following CV event categories: CV death, MI, arrhythmia, heart failure, stroke, TIA, pulmonary hypertension, pulmonary embolism/deep vein thrombosis, and unstable angina. Category definitions are provided in Table E1. Given the rare nature of these events, it was anticipated that it would be necessary to combine events with a shared pathophysiology to detect a true difference in rates. Therefore, before conducting the analyses, a combined category representing major arterial thromboembolic events (ATEs) was defined based on an approach utilized by the Antiplatelet Trialists' Collaboration.¹ Specifically, this prespecified endpoint included the following 5 events: CV death, MI, stroke, TIA, and unstable angina.

Statistical analysis

A total of 25 core trials and 2 extension studies met the inclusion criteria; 16 randomized controlled trials enrolled patients with allergic asthma and 9 randomized controlled trials enrolled patients with other conditions. Data from extension studies were included if there were no gaps in treatment and group assignment remained blinded. The population for analysis included all patients who received any study medication and provided any post-treatment data on or after their first treatment date. The indication for treatment with omalizumab (allergic asthma or other indications) was captured.

The prespecified primary analyses were based on deaths and SAEs in the pooled population (ie, all indications). The number of patients with ≥ 1 CV event was summarized by treatment group. Overall incidence was calculated as events per 1000 person-years (PY) with exact 95% CIs. Rate ratios (RR) and rate differences between the treatment groups were computed with corresponding 95% CIs. Recognizing differences in trial design, a Mantel-Haenszel rate difference, stratified by clinical trial, was calculated for the overall ATE rate as a sensitivity analysis.² The secondary analyses were based on all AEs, both serious and nonserious; incidence per 1000 PY, RRs, and rate differences with corresponding 95% CIs were calculated. A Cox proportional hazards model for ATEs was prespecified in the analysis plan only if there were ≥ 10 ATEs in $\geq 50\%$ of the trials.

Subgroup analyses were performed on data combined from all 25 studies. The prespecified categories were age (<65 vs ≥ 65 years), sex (male vs female), race

(white vs other), baseline body mass index (BMI; <30 vs ≥ 30 kg/m²), history of CV disease (yes vs no), and baseline total IgE ($\leq$ median vs $>$ median).

References

1. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86.
2. Rothman KJ. Controlling confounding by stratifying data. Chapter 10. In *Epidemiology. An introduction*. New York: Oxford University Press, 2nd edition; 2012. p. 176-197.
3. Hicks K, Hung H, Mahaffey K, Mehran R, Nissen S, Stockbridge N, et al. Standardized definitions for end point events in cardiovascular trials. 2010.
4. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al; American College of Cardiology Foundation Task Force on Expert Consensus Documents; American Heart Association; American College of Chest Physicians; American Thoracic Society Inc; Pulmonary Hypertension Association. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association. Developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol* 2009;53:1573-619.

FIG E1. Selection process and disposition of events. *AE*, adverse event; *EOI*, event of interest; *HLT*, High-Level Term; *PT*, Preferred Term; *SAE*, serious adverse event; *SMQ*, Standardized Medical Dictionary for Regulatory Activities Query; *SOC*, System Organ Class.

TABLE E1. Patients with an ATE, stratified by study

Study	Omalizumab	Placebo
Pooled population, no.	3342	2895
Patients with an ATE, no.	5	4
Observation time (y)	1855.81	1680.46
006, no.	400	136
Patients with an ATE, no.	0	0
Observation time (y)	96.09	32.26
007, no.	164	86
Patients with an ATE, no.	0	0
Observation time (y)	28.47	14.56
008 and 008 extension, no.	268	257
Patients with an ATE, no.	1	1
Observation time (y)	258.26	234.95
009 and 009 extension, no.	274	272
Patients with an ATE, no.	1	1
Observation time (y)	268.08	243.55
011, no.	174	165
Patients with an ATE, no.	0	0
Observation time (y)	109.29	105.11
012, no.	22	23
Patients with an ATE, no.	0	0
Observation time (y)	6.72	7.15

0113, no.	7	2
Patients with an ATE, no.	0	0
Observation time (y)	3.39	0.96
0114, no.	144	145
Patients with an ATE, no.	0	0
Observation time (y)	45.46	46.09
2210, no.	34	16
Patients with an ATE, no.	0	0
Observation time (y)	11.00	5.19
2304, no.	209	196
Patients with an ATE, no.	0	0
Observation time (y)	118.22	107.35
2306, no.	245	237
Patients with an ATE, no.	1	0
Observation time (y)	131.75	128.72
A1303, no.	48	50
Patients with an ATE, no.	0	0
Observation time (y)	11.50	12.03
A1304, no.	151	164
Patients with an ATE, no.	0	0
Observation time (y)	48.26	50.29
A2303, no.	68	69
Patients with an ATE, no.	0	0

Observation time (y)	65.10	68.81
D01, no.	66	56
Patients with an ATE, no.	0	0
Observation time (y)	32.21	27.34
DE03, no.	69	70
Patients with an ATE, no.	0	0
Observation time (y)	25.90	26.74
DE05, no.	27	22
Patients with an ATE, no.	0	0
Observation time (y)	13.68	9.97
FR01, no.	9	9
Patients with an ATE, no.	0	0
Observation time (y)	4.81	5.65
FR02, no.	20	11
Patients with an ATE, no.	0	0
Observation time (y)	6.60	3.42
Q2982g, no.	157	171
Patients with an ATE, no.	0	0
Observation time (y)	70.06	77.85
Q3662g, no.	428	420
Patients with an ATE, no.	2	2
Observation time (y)	358.71	342.80
Q4160g, no.	47	14

Patients with an ATE, no.	0	0
Observation time (y)	15.50	4.59
Q229N, no.	36	33
Patients with an ATE, no.	0	0
Observation time (y)	11.84	11.66
US23, no.	139	136
Patients with an ATE, no.	0	0
Observation time (y)	51.97	50.18
US33, no.	136	135
Patients with an ATE, no.	0	0
Observation time (y)	62.96	63.22

ATE, arterial thromboembolic event.

TABLE E2. EOI definitions derived from CDISC 2010^{3*}

Event	Definition
Death	All were considered CV unless an unequivocal and documented non-CV cause could be established
MI	Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia; stipulated that timing and trends in cardiac biomarkers and ECG information required careful analysis
Unstable angina requiring hospitalization	Symptoms of myocardial ischemia at rest or accelerating pattern of angina; and symptoms prompting an unscheduled visit to a health care facility and hospitalization within 24 h of most recent symptoms; and specific ECG changes (recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings); or definite evidence of myocardial ischemia on myocardial scintigraphy, stress echocardiography, or MRI believed to be responsible for myocardial ischemic symptoms/signs; or angiographic evidence of $\geq 70\%$ of lesion and/or thrombus in an epicardial coronary artery believed to be responsible for the myocardial ischemic symptoms/signs; or need for coronary revascularization during same hospital stay (criterion fulfilled if admission for myocardial ischemia led to transfer to another institution for the procedure without interceding home

	discharge); and no evidence of acute MI
Stroke	Acute symptomatic episode of neurological dysfunction attributed to a vascular cause
TIA	Transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction
HF requiring hospitalization	Clinical symptoms of HF; and hospitalization; and physical signs of HF; and need for additional/increased therapy directed at HF; and no other noncardiac etiology for signs or symptoms; it was recognized that some patients may have had coexisting diseases; thus, CHF would need to be the primary disease process accounting for signs and symptoms
Pulmonary hypertension†	Required confirmation by a complete right heart catheterization; hemodynamic definition: mean pulmonary artery pressure >25 mmHg; pulmonary capillary wedge pressure, left atrial pressure, or left ventricular end diastolic pressure ≤15 mmHg; and pulmonary vascular resistance >3 Wood units
Arrhythmia‡	Arrhythmias classified as abnormal and confirmed by ECG
PE and DVT‡	Required ≥1 of the following: • Demonstration of DVT by venography • Demonstration of DVT by duplex ultrasonography • High probability ventilation/perfusion lung scan combined with a high clinical probability of PE based on symptoms, signs, and diagnostic testing (including chest X-ray, ECG,

blood D-dimer)

- Documentation of PE by helical computed tomography of the chest with intravenous contrast; scan had to be acquired by a multidetector row helical (spiral) scanner with adequate technical resolution
- Demonstration of PE by pulmonary angiogram

*Unless otherwise specified.

†American College of Cardiology Foundation/American Heart Association 2009 expert consensus document on pulmonary hypertension.⁴

‡CDISC did not provide a definition; obtained from other sources.

CDISC, Clinical Data Interchange Standards Consortium; *CHF*, congestive heart failure; *CV*, cardiovascular; *DVT*, deep vein thrombosis; *ECG*, electrocardiogram; *EOI*, event of interest; *HF*, heart failure; *MI*, myocardial infarction; *MRI*, magnetic resonance imaging; *PE*, pulmonary embolus; *TIA*, transient ischemic attack.

TABLE E3. Baseline demographics and clinical characteristics

Characteristic	Omalizumab (n = 3342)	Placebo (n = 2895)
Age (y)		
Mean (SD)	38 (15)	39 (15)
Median (range)	38 (12-82)	39 (12-75)
Female, no. (%)	1934 (58)	1774 (61)
Race, no. (%)	n = 3322	n = 2884
White	2640 (79)	2198 (76)
Black	241 (7)	207 (7)
Asian	216 (7)	234 (8)
Other	225 (7)	245 (9)
BMI ≥ 30 kg/m ² , no. (%)	865 (26)	820 (28)
Serum total IgE (IU/mL)		
Mean (SD)	207 (184)	206 (173)
Median (range)	149 (16-1940)	153 (15-1755)
Mean (SD) % predicted FEV1	70 (17)	71 (17)
Ever smoked, no. (%)	500 (15)	497 (17)
History of cardiac disorder, no. (%)	94 (3)	79 (3)
Long-acting β -agonist use, no. (%)	1283 (38)	1235 (43)
Systemic corticosteroid use, no. (%)	190 (6)	159 (6)

BMI, body mass index; FEV1, forced expiratory volume in 1 second; IgE, immunoglobulin E.

TABLE E4. Subgroup analyses: Rates of ATEs

	Omalizumab	Placebo
All ATEs: Deaths and SAEs	(n = 3342)	(n = 2895)
Age <65 y, no.	3198	2765
Events, no.	4	4
PY, no.	1765	1609
ATE rate per 1000 PY (95% CI)	2.3 (0.62-5.8)	2.5 (0.68-6.4)
Age ≥ 65 y, no.	144	130
Events, no.	2	0
PY, no.	90	71
ATE rate per 1000 PY (95% CI)	22 (2.7-78)	0.00 (0.00-51)
Male, no.	1408	1121
Events, no.	3	2
PY, no.	777	659
ATE rate per 1000 PY (95% CI)	3.9 (0.80-11)	3.0 (0.37-11)
Female, no.	1934	1774
Events, no.	3	2
PY, no.	1078	1021
ATE rate per 1000 PY (95% CI)	2.8 (0.57-8.1)	2.0 (0.24-7.1)
White, no.	2640	2198
Events, no.	5	3
PY, no.	1478	1300
ATE rate per 1000 PY (95% CI)	3.4 (1.1-8.0)	2.3 (0.48-6.7)

BMI <30 kg/m ² , no.	2477	2074
Events, no.	4	1
PY, range	1311	1170
Event rate per 1000 PY (95% CI)	3.0 (0.83-7.8)	0.85 (0.02-4.8)
BMI ≥30 kg/m ² , no.	865	820
Events, no.	2	3
PY, range	544	510
Event rate per 1000 PY (95% CI)	3.7 (0.45-13)	5.9 (1.2-17)
Total IgE ≤ median, no.	1685	1433
Events, no.	2	2
PY, range	892	810
Event rate per 1000 PY (95% CI)	2.2 (0.27-8.1)	2.5 (0.30-8.9)
Total IgE > median, no.	1655	1460
Events, no.	4	2
PY, range	962	870
Event rate per 1000 PY (95% CI)	4.2 (1.1-11)	2.3 (0.28-8.3)
History of CV disease, no.	161	133
Events, no.	2	0
PY, range	93	79
Event rate per 1000 PY (95% CI)	22 (2.6-76)	0.00 (0.00-46)
No history of CV disease, no.	3181	2762
Events, no.	4	4
PY, range	1762	1602

Event rate per 1000 PY (95% CI)	2.3 (0.62-5.8)	2.5 (0.68-6.4)
---------------------------------	----------------	----------------

ATE, arterial thromboembolic event; *BMI*, body mass index; *CV*, cardiovascular; *IgE*,

immunoglobulin E; *PY*, person-years; *SAE*, serious adverse event.

