Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Rothenberg ME, Klion AD, Roufosse FE, et al. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. N Engl J Med 2008;358:1215-28. DOI: 10.1056/NEJMoa070812.

SUPPLEMENTARY INFORMATION

Supplement Appendix 1. Sponsor and Author Responsibilities, Exclusion Criteria, Description of Blinding Methods, Additional Statistical Methods, EDN Assay, and Steroid Conversion Table.

Statement of Responsibilities

The study was jointly designed by members of an expert HES investigator advisory board (composed of the authors and other experts) and the sponsor, with scientific guidance regarding study design received from the FDA in the US and CPMP in Europe. The primary author participated in the initial presentation of the study to the FDA. The sponsor had responsibility for data collection and quality control, and all authors were involved in data analysis and interpretation. The data was made available to authors via hard copies and a web-based portal access system. Per the protocol, a sponsor committee consisting of a physician and statistician, who were not directly involved with the study, conducted an Interim Review of Safety Data at two time points during the conduct of the study. The findings from this review committee were transmitted to Investigators and IRB/ethics committees. The authors decided to publish the paper, all contributed to the writing of the manuscript via a series of email exchanges and teleconferences, and approval from all authors was required. The EDN analysis was performed by Dr Gerald Gleich's laboratory. Editorial assistance was provided by two professional medical writers who are listed in the acknowledgments.

Exclusion criteria

Exclusion criteria were life-threatening HES or other serious illness; eosinophilia owing to drug eruption or parasitic infection in the previous year, graft-versus-host disease, bullous pemphigoid, cystic fibrosis, rheumatoid arthritis, or HIV infection; Churg-Strauss syndrome; Wegener's granulomatosis; malignancy; severely abnormal laboratory tests; severe cardiac dysfunction; or drug or alcohol abuse in the preceding 6 months. Known hypersensitivity to antibody therapy, prior anti-human IL-5 monoclonal antibody therapy, treatment with an investigational drug in the previous 30 days, and pregnancy were additional exclusion criteria. The Institutional Review Board or Independent Ethics Committee of each site approved the protocol, and all patients provided written informed consent. The study adhered to Good Clinical Practice and the principles of the Declaration of Helsinki.

Methods for Randomization

Study subjects were randomized centrally through an Interactive Voice Response System. A randomization schedule, within the two strata based upon subjects' entry prednisone (or equivalent) daily dose of ≤30mg or >30mg, was generated by GlaxoSmithKline Biomedical Data Sciences using randomly permuted blocks. Subjects in each stratum were randomized in a 1:1 ratio to receive either 750 mg mepolizumab intravenous (IV) infusion or saline (as placebo) IV infusion, every 4 weeks beginning from Day 1 until the last infusion at Week 32.

Because mepolizumab for injection is provided as open-label vials to the study sites, third party blinding was employed to ensure the subjects, investigators, and all who were involved in the evaluation of the study subjects were blinded to a subject's treatment assignment until the closure of the database after study completion.

Statistical Methods

A sample size of 84 evaluable patients (42 per treatment group) was estimated to provide 90% power at a 5% two-sided significance level to detect a difference of 33% between treatment groups in the primary end point (assuming the proportion achieving a prednisone dose of ≤10 mg per day for ≥8 weeks was 80% and 47% in the mepolizumab and placebo groups, respectively). Differences in response rates between mepolizumab and placebo in the primary end point were tested using a Cochran Mantel-Haenszel test, stratifying by baseline prednisone (or equivalent) dose level (≤30 mg or >30 mg), at a 5% two-sided significance level in the ITT population. Odds ratios (OR; primary pre-specified analysis), relative risks (not stratified by baseline prednisone dose level), and hazard ratios of the time-to-achieving the end point (stratified by baseline prednisone dose level) were also calculated.

Adverse events were summarized. A log-rank test was used to compare the time taken to experience an adverse event between treatments, which takes into account patients who withdrew from the study.

Secondary end points were analyzed as follows: binary responder/nonresponder end points were analyzed in the same way as the primary end point, time-to-treatment failure was analyzed using the stratified log-rank test (adjusted for baseline prednisone dose level) to test for differences between treatments, and the prednisone dose at Week 36 was analyzed using an analysis of covariance (adjusted for baseline prednisone dose level). The last available on-treatment prednisone dose was carried forward for patients missing Week 36 data.

The differences in response rates between mepolizumab and placebo for the primary endpoint and the eosinophil secondary endpoint in each of the baseline prednisone dose subgroups (≤30 mg and >30 mg) were tested using a Chi-squared test.

An exploratory sensitivity analysis of the primary endpoint using logistic regression was pre-planned. The statistical model on which inference was based included terms for baseline prednisone (or equivalent) dose level category (≤30 mg, >30 mg) and treatment group, regardless of their significance. Additionally, other terms were tested in a model-building approach and included if statistically significant ($P<0.05$). The model building utilized a forward selection method, i.e. each term was added in turn and the term that gave the greatest significant reduction in deviance was included in the model. This continued until all terms giving a significant reduction in deviance were in the model. No interaction terms were included in this model.

Measurement of Eosinophil-derived Neurotoxin (EDN)

Sera were collected from study patients at four different time points, baseline, 12 weeks, 24 weeks and 36 weeks, respectively. EDN was assayed using chemiluminescence immunoassay technology and two monoclonal antibodies. Briefly, sera were incubated in plates coated with J167-6C5 capture antibody, washed and incubated with acridinium labeled J167-2G4 anti-EDN detection antibody. After a final wash, EDN was measured using a LMAX II384 luminometer (Molecular Devices) and the SOFTmax® PRO (ver.4.6) Software (Molecular Devices, Sunnyvale, CA). The authors are grateful to Ann Georgelas and Saritha Tunuguntla (University of Utah) for expeditious completion of the EDN assays. The differences in the EDN data between mepolizumab and placebo were tested using the Kruskal Wallis test.

Steroid Conversion Table:

Alternate Corticosteroid	**Equivalent Dose to Prednisone 1 mg (Multiplier)**
Methylprednisolone	0.8 mg (1.25)
Prednisolone	1 mg (1)
Triamcinolone	0.8 mg (1.25)

Supplement Appendix 2. Serious Adverse Events From the Mepolizumab in HES Trial (Study MHE100185).

Listing of Serious Adverse Events

Pt	Patient age, y & gender (M/F)	Study drug	Serious adverse event	Intensity	Day of onset*	Outcome	Duration	Relationship to study drug†	Action taken
A	36 (F)	Placebo	HES relapse	Severe	59	Recovered/resolved	17 days	Unrelated	No action
B	43 (F)	Placebo	Pneumonia	Moderate	30	Recovered/resolved	9 days	Unrelated	No action
C	62 (F)	Placebo	Dysaesthesia	Mild	9	Recovering/resolving	Ongoing	Unrelated	No action
			Eosinophilia	Moderate	163	Recovered/resolved	14 days	Unrelated	Study drug withdrawn
			Polyneuropathy	Moderate	163	Recovered/resolved	14 days	Unrelated	Study drug withdrawn
D	46 (M)	Mepolizumab 750 mg	Hepatitis	Severe	94	Recovered/resolved	7 days	Unrelated	No action
			Rhinitis	Mild	258	Recovered/resolved	12 days	Unrelated	No action
E	52 (F)	Mepolizumab 750 mg	Asthma exacerbation	Moderate	135	Recovered/resolved	45 days	Unrelated	No action
			Bronchitis	Moderate	135	Recovered/resolved	45 days	Unrelated	No action
			Dehydration	Moderate	144	Recovered/resolved	4 days	Unrelated	No action
F	18 (M)	Mepolizumab 750 mg	Asthma exacerbation	Moderate	107	Recovered/resolved	28 days	Unrelated	No action
			HES relapse (GI)	Severe	111	Recovered/resolved	24 days	Unrelated	No action
G	19 (M)	Mepolizumab 750 mg	Renal failure	Severe	1	Recovered/resolved	4 days	Unrelated	No action
H	18 (M)	Mepolizumab 750 mg	Pyrexia	Mild	76	Recovered/resolved	5 days	Unrelated	No action
			Renal failure	Severe	98	Ongoing until death‡	—	Unrelated	No action
			Cardiac arrest	Severe	109	Fatal	2 days	Unrelated	Study drug withdrawn
I	50 (M)	Placebo	Osteonecrosis (hip)	Severe	98	Not recovered/not resolved	Ongoing	Unrelated	No action
J	44 (M)	Mepolizumab 750 mg	Pancreatitis	Severe	74	Recovered/resolved	42 days	Unrelated	No action
			Pancreatitis	Severe	237	Recovered/resolved	93 days	Unrelated	No action
K	72 (F)	Mepolizumab 750 mg	Pneumonia	Moderate	161	Recovered/resolved	35 days	Unrelated	No action
			Spinal compression fracture (T12)	Severe	202	Recovering/resolving	Ongoing	Unrelated	No action
L	33 (M)	Placebo	Nephrotic syndrome	Moderate	129	Recovering/resolving	Ongoing	Unrelated	Study drug withdrawn

*Days since first infusion of investigational product; †Relationship to study drug was assessed by the investigator; ‡Subject died due to a cardiac arrest on Day 111

Safety Narratives for All Serious Adverse Events Reported During Study MHE100185

Patient A

Suspect Drugs: **Placebo**

Serious Events: **Hypereosinophilic syndrome**

This 36-year-old female subject was enrolled in a blinded study for the treatment of hypereosinophilic syndrome, receiving intravenous investigational product every 4 weeks.

The subject developed abdominal pain with symptoms of itching, urticaria, and vomiting 59 days after the start of investigational product, and developed asthma 2 weeks later. The subject was hospitalized and diagnosed with severe relapse of hypereosinophilic syndrome. Relevant test results included an elevated eosinophil count of 1000/mm^3 (normal <500/mm^3) and an elevated C-reactive protein level of 24.2 mg/L (normal <6 mg/L). The subject was treated with prednisone, oxygen therapy, amoxicillin trihydrate, and salbutamol sulphate. Concomitant medications included levocetirizine hydrochloride (Xyzal).

Treatment with investigational product was not stopped because of these events. The relapse of hypereosinophilic syndrome resolved after 17 days, and the subject was discharged the following day. The investigator considered there was no reasonable possibility that the relapse of hypereosinophilic syndrome may have been caused by the investigational product. The investigator also considered the relapse of hypereosinophilic syndrome to be possibly associated with the disease under study.

Patient B

Suspect Drugs: **Placebo**

Serious Events: **Pneumonia**

This 43-year-old female subject was enrolled in a blinded study for the treatment of hypereosinophilic syndrome. The subject received intravenous investigational product for 1 month.

Thirty days after the start of investigational product and 2 days after the most recent dose, the subject developed confusion, loss of bladder control, and diarrhea. A chest x-ray showed dense infiltrates in the right lung and laboratory results showed a high white blood cell count and hypoxia. A neurologic exam showed that the subject was disoriented to time and had decreased word-finding ability. She was hospitalized and diagnosed with pneumonia. The subject began treatment with levofloxacin. Concomitant medications included amitriptyline, prednisone, temazepam, and cyclobenzaprine. The event resolved after 9 days, and the subject was discharged. The investigator considered there was no reasonable possibility that the pneumonia may have been caused by the investigational product. The disease under study and the subject's concurrent medical conditions of asthma and shortness of breath were cited as possible causes.

Patient C

Suspect Drugs: **Placebo**

Serious Events: **Dysaesthesia, Eosinophilia, Polyneuropathy**

This 62-year-old female subject was enrolled in a blinded study for the treatment of hypereosinophilic syndrome, and received blinded investigational product.

Nine days after the start of investigational product, the subject developed increased dysaesthesia and hypoesthesia in both feet, and was hospitalized as a result of the dysaesthesia. The subject had a slight increase in dyspnea and cough. Treatment with investigational product was continued. A neurologic examination (electroneurography and myography) 5 days later showed no signs of increased disease activity, and the dysaesthesia was unresolved at this time. Concomitant medications included prednisone (Prednison), alendronate sodium (Fosamax), and ossofortin forte. The investigator considered there was no reasonable possibility that the dysaesthesia may have been caused by investigational product. The investigator also considered the event to be possibly associated with the disease under study.

Approximately 5 months (163 days) after the start of investigational product, the subject developed grade 2 (or moderate) dysaesthesia in both legs with an increase of inflammation markers and eosinophils. The subject was hospitalized. Relevant test results included eosinophils 1185 cells/µL and C-reactive protein 11.0 mg/L (normal ranges not provided). The subject recovered 14 days after event onset. The investigator considered that there was no reasonable possibility that the events may have been caused by investigational product and that the events were possibly due to lack of efficacy and disease

under study. Treatment with investigational product was discontinued after the sixth infusion, the subject was withdrawn from the study, and was enrolled into the open-label study.

The final diagnosis was considered to be polyneuropathy and eosinophilia. The events were considered unrelated to investigational product.

Patient D

Suspect Drugs: **Mepolizumab**

Serious Events: **Hepatitis, Rhinitis**

This 46-year-old male subject was enrolled in a blinded study for the treatment of hypereosinophilic syndrome. The subject received intravenous investigational product every 4 weeks.

Ninety-four days after the start of investigational product, and 9 days after the most recent dose, the subject developed fever with a body temperature of 39°C. The subject was hospitalized 4 days later. Blood cultures were negative. Liver function tests showed that aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were elevated. Results for AST were 81 U/L at admission, 150 U/L and 205 U/L at 1 day post-admission, 139 U/L at 2 days post-admission, and 46 U/L at 3 days post-admission (normal range 17–59 U/L). Results for ALT were 107 U/L at admission, 180 U/L and 249 U/L at 1 day post-admission, 273 U/L at 2 days post-admission, and 165 U/L at 3 days post-admission (normal range 21–72 U/L). The subject was diagnosed with hepatitis. Results of bone marrow analysis were normal. Tests for Hepatitis A, B, and C, CMV, and EBV were all negative. The subject was treated with corticosteroids (Medrol), cefepime (Maxipime), paracetamol (Perfusalgan), and amoxicillin trihydrate plus potassium clavulanate (Augmentin).

Treatment with investigational product was not stopped because of this event. The event resolved after 7 days. The investigator considered there was no reasonable possibility that the hepatitis may have been caused by the

investigational product. The investigator also considered the hepatitis to be possibly associated with the disease under study.

Approximately 8 months after the start of investigational product, the subject developed mild rhinitis and a fever. He was hospitalized and was treated with amoxicillin trihydrate + potassium clavulanate (Augmentin) and amoxicillin trihydrate + potassium clavulanate (Amoxiclav).

Treatment with investigational product was not stopped because of this event. The subject was discharged and the event resolved after 12 days' duration. The investigator considered there was no reasonable possibility that the rhinitis may have been caused by the investigational product. The cause of the rhinitis was cited as unknown.

Patient E

Suspect Drugs: **Mepolizumab**

Serious Events: **Asthma, Bronchitis, Dehydration**

This 52-year-old female subject was enrolled in a blinded study for the treatment of hypereosinophilic syndrome. The subject began to experience flu-like symptoms 135 days after the start of treatment with intravenous investigational product and 23 days after receiving her last dose. She was hospitalized with an exacerbation of asthma and bronchitis. The subject was treated with levofloxacin (Levaquin), Combivent, and prednisone and the events improved. The symptoms resolved after 45 days.

Nine days later, the subject experienced dehydration. A chest x-ray was normal but her white blood cell count and neutrophil count were both elevated. She was treated with intravenous fluids and the dehydration resolved after 4 days.

The investigator considered there was no reasonable possibility that the asthma exacerbation, bronchitis, and dehydration may have been caused by investigational product. Medical conditions at the time of the event included asthma, fibromyalgia, and smoking. Concurrently, she received fluticasone.

Patient F

Suspect Drugs: **Mepolizumab**

Serious Events: **Asthma, Hypereosinophilic syndrome**

This 18-year-old male subject was enrolled in a blinded study for the treatment of hypereosinophilic syndrome. Medical conditions included asthma and acne. Concomitant medications included erythromycin (Eryfluid), fluticasone propionate + salmeterol xinafoate (Seretide), and montelukast sodium (Singulair). Treatment with concurrent montelukast sodium was stopped 4 months after study entry.

During the run-in period, the subject received treatment with prednisolone, which was tapered from 50 mg/day to 2.5 mg/day over 13 weeks. The subject received intravenous investigational product every 4 weeks. The subject experienced non-serious abdominal pain and vomiting 107 days after the start of treatment with investigational product, and 26 days after administration of the previous (fourth) dose. Additionally, the subject developed a moderately severe exacerbation of asthma. Four days later, the subject developed a severe gastrointestinal relapse of underlying hypereosinophilic syndrome.

On the day of the fifth infusion of the investigational product, the subject had an eosinophil count of 0.2×10^9/L (normal range: 0–0.8×10^9/L), monocyte count of 1.0×10^9/L (normal range: 0.2–1.0×10^9/L), platelet count of 322×10^9/L (normal range: 150–400×10^9/L), and white blood cell count of 9.53×10^9/L (normal range: 4–10×10^9/L). Three days later, the subject was hospitalized due to eating difficulties with vomiting and abdominal pain with complete food intolerance. At this time, the subject's eosinophil count was 0.2×10^9/L. Other laboratory results showed a platelet count of 318×10^9/L, elevated monocyte count of 1.4×10^9/L,

and white blood cell count of 8.22×10^9/L. The subject received treatment with methylprednisolone 250 mg/day and the symptoms disappeared; the subject then started treatment with prednisolone 10 mg/day. An abdominal plain x-ray showed few median air-fluid levels and no pneumoperitoneum.

One week after hospitalization, the eosinophil count had increased to 0.63×10^9/L, monocyte count and white blood cell count were elevated at 1.4×10^9/L and 13.2×10^9/L, respectively, and platelet count was normal at 368×10^9/L. The subject relapsed the next day and, 3 days later, received an increased dose of background prednisone up to 20 mg/day. The gastrointestinal symptoms resolved after 24 days, when the eosinophil count was 0.6×10^9/L; the subject also had an elevated white blood cell count of 13.3×10^9/L and a platelet count of 314×10^9/L. The subject was treated with fluticasone propionate, salmeterol and montelukast sodium, which was later stopped. The exacerbation of asthma was also considered resolved after 28 days. Treatment with the investigational product was continued.

The investigator considered that there was not a reasonable possibility the asthma exacerbation and digestive relapse of hypereosinophilic syndrome were related to treatment with the investigational product. The investigator reported that the relapse of hypereosinophilic syndrome was related to the subject's participation in the study, since it did not allow him to maintain background corticosteroid therapy. The disease under study and its treatment failure were cited as possible causes of the event.

Patient G

Suspect Drugs: **Mepolizumab**

Serious Events: **Renal failure**

This 19-year-old male subject was enrolled in a blinded study for the treatment of hypereosinophilic syndrome. The subject was known to have eosinophilic renal infiltration and episodes of acute renal failure.

On the day of commencing the investigational product, the subject was hospitalized with a diagnosis of severe renal failure. The subject was treated with intravenous and oral prednisolone. Treatment with investigational product was continued. The renal failure resolved after 4 days, and the subject was discharged from hospital. The investigator considered there was no reasonable possibility that the renal failure may have been caused by investigational product. The investigator also considered the event to be possibly associated with the disease under study. The renal failure was considered to be related to the subject's history of renal failure.

Follow up information revealed that the subject experienced hematuria without pain. The subject underwent an examination, which consisted of a cytoscopy and an intravenous urography.

Follow-up laboratory information also revealed that the subject had a low creatinine level 1 week prior to administration of the first dose of investigational drug at 58 µmol/L and creatinine clearance of 2.75 mL/sec. Furthermore, laboratory studies obtained on the day of the first infusion included total protein of 37 g/L (normal range 60–83 g/dL), albumin 12 g/L (35–48 g/L), urea 14.8 mmol/L (1.8–6.4 mmol/L), sodium 133 mmol/L (136–146 mmol/L), and C-reactive protein

9.1 mg/L (normal range not provided). Additionally, the subject had a history of renal failure for 2–5 years, which usually correlated with rise in eosinophil count and reduction in prednisolone.

Patient H

Suspect Drugs: **Mepolizumab, Mepolizumab, Warfarin sodium**

Serious Events: **Fatal cardiac arrest, Pyrexia, Renal failure**

This 18-year-old male subject was enrolled in an open-label study for the treatment of hypereosinophilic syndrome. The subject's past medical history included amputation of digits of hands (due to vasculitis) and of left foot, asthma, atrioventricular block, deep vein thrombosis, defibrillator insertion, gastrointestinal infection, myocarditis, pulmonary embolism, renal calculus, retroperitoneal hemorrhage, seizures, and vena cava filter insertion. The subject received four doses of intravenous mepolizumab.

The subject developed bloody stools 76 days after the start of investigational product and 20 days after the most recent dose. He also presented with shortness of breath, fever, wheezing, anemia, renal insufficiency, and hyperuricemia. The subject was hospitalized at that time, because of a fever of 101.7°F, which was considered severe. Fever was treated with intravenous vancomycin and imipenem/cilastatin (Primaxin). The subject remained afebrile during the remainder of hospitalization. Both the bloody stools and fever resolved after a total duration of 5 days. Chest x-ray on admission showed pleural effusion. The subject’s creatinine on admission was 2 mg/dL and the subject was treated with intravenous fluids. Creatinine on discharge was 1.5 mg/dL. While hospitalized, his hematocrit dropped from 35.7% to 31.8% and remained stable with a discharge value of 31.2%. Treatment with investigational product was continued. The investigator considered there was no reasonable possibility that the fever may have been caused by investigational product. The investigator also

considered the bloody stools, shortness of breath, and fever to be possibly associated with medical conditions of fluid overload and coagulopathy and concomitant medication, coumadin.

On follow-up, the investigator reported that a discharge note indicated the subject had a proctoscopy, which revealed external and internal hemorrhoids. The subject was treated with hemorrhoidal cream.

Subsequently, 98 days after the start of investigational product, the subject developed renal failure, was hospitalized, and treated with fluids. At time of reporting, the subject was improving. In the investigator's opinion, the renal failure was unrelated to treatment with investigational product. Upon follow-up, the investigator reported the subject's fractional extraction of sodium was less than 1%. A renal sonogram was performed to rule out obstructive causes of renal failure. The subject was initially treated with intravenous normal saline and the acute renal failure progressively improved during the hospital stay. The subject's creatinine value at discharge was 1.3 mg/dL.

Medical conditions at the time of the event included allergy to angiotensin-converting enzyme (ACE) inhibitors, allergy to heparin and penicillin, colitis, dilated cardiomyopathy, gangrene of toe, hypereosinophilic syndrome, Loeffler's endocarditis, three myocardial infarctions, Raynaud’s phenomenon, renal insufficiency, and systemic hypertension. Concomitant medications included prednisone, Lexapro, warfarin sodium, losartan, allopurinol, pantoprazole, furosemide, and carvedilol.

The subject experienced cardiac arrest 109 days after the start of mepolizumab treatment. He had passed out at home and his body felt cold. No

immediate cardiopulmonary resuscitation (CPR) was performed and an ambulance was requested. Paramedics performed CPR, intubated, and transported him to the emergency department where he received CPR, defibrillations, and amiodarone, and was then stabilized. Troponin level in emergency department was 7.07 ng/mL (normal: <0.10). The subject was also treated with atropine. The emergency department was unable to review systems owing to the critical nature of the subject's condition. The subject was placed on dopamine HCL and transferred to intensive care. Vital signs showed temperature of 92°F and pulse 94. The maximum dose of dopamine was administered and the subject was treated with Levophed. The subject became unresponsive with dilated and fixed pupils. The subject was also in acute respiratory failure. Advanced cardiac life support followed—CPR was performed for 30 minutes, but the subject died of cardiac arrest the following day. The investigator considered that there was no reasonable possibility that the cardiac arrest may have been caused by mepolizumab and that the events were possibly due to acute respiratory failure, gangrene, acute and chronic renal insufficiency, and hypereosinophilic syndrome with end-stage multiorgan involvement.

Follow-up received from medical records included the following: prednisone was tapered from 50 mg/day at baseline to a dose of 2.5 mg/day after 11 weeks. The total dose was subsequently increased to 15 mg/day, which was continued until the subject's death. Eosinophil counts were controlled from baseline for approximately 3 months, when the final dose of investigational product was administered. However, 3 days prior to the cardiac arrest, eosinophil counts increased above the pre-dose levels to 2840 cells/μL. Two

echocardiograms were reported pretreatment. Approximately 5 weeks prior to administration of the first dose of mepolizumab, left ventricular ejection fraction was estimated at 35–40%. Repeat echocardiogram on the day the first mepolizumab dose was administered showed that left ventricular function had deteriorated substantially, and the left ventricular ejection fraction was estimated at 25–30%.

Pre-dose electrocardiogram (ECG) results on the day of the first dose of mepolizumab showed a normal PR interval, normal sinus rhythm, rate 70 bpm, QRSD bifascicular block, right bundle branch block, and left posterior fascicular block, QT consider left atrial enlargement, QTc consider left ventricular hypertrophy with ST-T abnormalities, and late T wave abnormalities. ECG results remained unchanged through to the day of the last mepolizumab infusion.
Two months after the patient's death, a meeting was held between the investigator and GlaxoSmithKline, which provided additional information. A postmortem was not performed. The cause of death on the discharge summary was cardiac arrest. It was concluded that this was due to dysrhythmia which was similar to previous episodes and attributed to the failure of the internal pacemaker/defibrillator. It was confirmed that the echocardiograms on trial drug did not show evidence of deterioration, but there was deterioration between the screening and baseline echocardiograms. There was no clinical evidence of failure to control the hypereosinophilic syndrome during the first 3 months of the trial. Up to this time, the patient had been clinically stable with no clinical evidence of worsening cardiac disease. The hypereosinophilic syndrome was very severe, having only been present for slightly more than a year, but being

associated with finger amputations due to vasculitis, lung, gut, and cardiac organ damage.

Patient I

Suspect Drugs: **Placebo**

Serious Events: **Osteonecrosis**

This 50-year-old male subject was enrolled in a blinded study for the treatment of hypereosinophilic syndrome. The subject received intravenous investigational product for 85 days before being withdrawn and enrolled in the open label extension study. Ninety-eight days after the start of investigational product and 17 days after receiving the fourth dose of investigational product, the subject complained of left hip pain that necessitated the use of a cane. He underwent magnetic resonance imaging, which revealed bilateral avascular necrosis of the hip. The event was considered disabling and he was referred to an orthopedic surgeon for treatment. His pain was being controlled by ibuprofen (Motrin) and Tylenol #3. The subject underwent bilateral hip replacement and is doing well. Medical conditions at the time of the event included persistent eosinophilia. Concomitant medications included high-dose prednisone (>20 mg/day). The investigator considered there was no reasonable possibility that the avascular necrosis may have been caused by investigational product, but that it may possibly have been associated with prednisone therapy.

Patient J

Suspect Drugs: **Mepolizumab**

Serious Events: **Pancreatitis**

This 44-year-old male subject was enrolled in a blinded study for the treatment of hypereosinophilic syndrome. The subject's past medical history included kidney stone and pancreatitis possibly related to microlithiasis.

The subject developed severe left lower abdominal pain, flushing, sweating, nausea, and fever 74 days after the start of investigational product. The subject was hospitalized for further work-up and evaluation. Kidney stones were ruled out via computed tomography and the subject was diagnosed with pancreatitis. An abdominal ultrasound showed no evidence of gallbladder stones or signs of gall bladder wall thickening. Relevant laboratory tests showed an elevated lipase level of 1264 IU/L. The subject was treated with normal saline, potassium, hydromorphone (Dilaudid), morphine, and antibiotics (unspecified). Treatment with investigational product was continued. The subject's condition significantly improved and he was discharged home after a week. The pancreatitis subsequently resolved 42 days after initial onset. Medical conditions at the time of the event included gastroesophageal reflux disease and hypertension. Concomitant medications included cetirizine hydrochloride (Zyrtec), lisinopril (Zestril), omeprazole (Prilosec), atorvastatin calcium (Lipitor), methylphenidate hydrochloride (Concerta), and fluticasone propionate (Flovent). The investigator considered there was no reasonable possibility that the pancreatitis may have been caused by investigational product. The investigator

also considered the pancreatitis to be possibly associated with an infection or an unknown cause.

Subsequently, 237 days after the start of investigational product, the subject developed acute abdominal pain and fever. The subject was hospitalized and was again diagnosed with pancreatitis. The subject was treated with intravenous fluids, pain medication, and antibiotics, and was discharged from hospital after 4 days. Elective laparoscopic cholecystectomy was conducted 6 weeks later, at which time the subject had completed the blinded clinical study and had entered the open-label study. The event was considered resolved after a total duration of 93 days. Treatment with investigational product was continued throughout. The subject had no further episodes of abdominal pain and the investigator considered there was no reasonable possibility that the pancreatitis may have been caused by investigational product. In the investigator's opinion, the event was possibly associated with the subject's prior history of pancreatitis.

Patient K

Suspect Drugs: **Mepolizumab**

Serious Events: **Pneumonia, Spinal compression fracture**

This 72-year-old female subject was enrolled in a blinded study for the treatment of hypereosinophilic syndrome. The subject developed a fever, arthralgia, weakness, dry cough, and myalgias 161 days after the start of treatment with intravenous investigational product. She was subsequently hospitalized for evaluation and treatment. Relevant test results revealed leukocytosis and increased neutrophils, and a chest x-ray showed a right upper lobe infiltrate. A sputum culture showed mixed normal flora. A nasopharyngeal wash for rapid RSV and influenza A were negative, as were cultures. She was diagnosed with pneumonia and began treatment with oxygen and levofloxacin (Levaquin). The event resolved after 35 days. The investigational product was continued. Current medical conditions included old age, long-term steroid use, spinal stenosis, and peripheral neuropathy with right foot drop. The investigator considered that there was no reasonable possibility that the pneumonia was related to investigational product, but was possibly associated with exposure to an infected source, as the subject worked in a hospital.

Subsequently, 202 days after the start of investigational product and 7 days after her most recent dose of investigational product, the subject walked to her kitchen without her leg brace, lost her balance, and fell on her back. She presented to the emergency department, where a spinal x-ray revealed a thoracic 12 compression fracture. The event was disabling. The event was resolving at the time of reporting—the subject was in a back brace with limited

mobility and was using a walker. Investigational product was continued. Magnetic resonance imaging 1 week later confirmed the T12 compression fracture but, given the degree of injury close to the spinal cord, surgery was not an option. The subject was treated with acetaminophen (Tylenol), dextropropoxyphene (Darvon), and Lortab plus a chest stabilizer brace and foot brace. The investigator considered there was no reasonable possibility that the T12 compression fracture may have been caused by the investigational product, and that it was possibly associated with trauma.

Patient L

Suspect Drugs: **Placebo**

Serious Events: **Nephrotic syndrome**

This 33-year-old male subject was enrolled in a blinded study for the treatment of hypereosinophilic syndrome. The subject received intravenous investigational product every 4 weeks for 175 days. The subject's past medical history included childhood asthma. Medical conditions at the time of the event included diabetes and hypertension. Concomitant medications included prednisone, Lorcet, glipizide, lisinopril, simvastatin, furosemide, and Hyzaar.

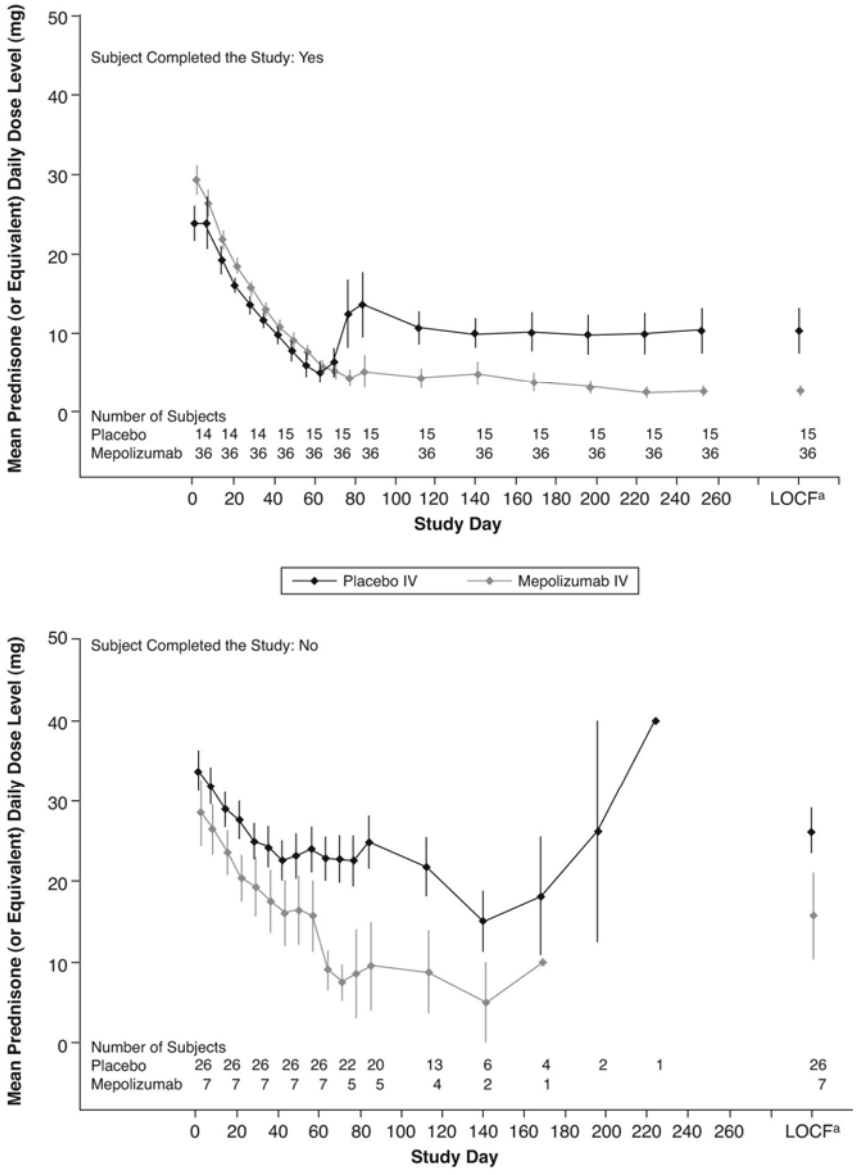
Approximately 18 weeks after the start of investigational product, the subject presented to the emergency department with a 1-week history of pedal edema. He was treated with diuretics, but the edema progressed and 1 week later the subject was admitted to the hospital. Relevant test results included a decreased serum albumin and protein in the urine. The subject was diagnosed with nephrotic syndrome. A renal biopsy was performed, which showed findings diagnostic of a membranous glomerulopathy, stage I to II, with immune complex deposits and 10% to 15% chronicity, evocative of drug-related toxicity. Although a lupus-like condition could not be ruled out, the absence of immunofluoresence staining and reticular aggregates made this diagnosis less likely. There was no segmental glomerulosclerosis. Six of 22 glomeruli were globally sclerosed with periglomerular fibrosis. The findings suggested mild arterionephrosclerosis, but were not diagnostic of diabetic nephropathy. Other tests included negative hepatitis B and C panels and a normal serum electrophoresis. The subject also had a total protein value 5.9 g/L, albumin 2.5 g/L, blood urea nitrogen 26.0

mmol/L, creatinine 1.3 mg/dL, ALT 52.0 U/L, elevated white blood count 14.0×10^{9}/L, and a hemoglobin value of 13.3 g/dL. At the time of the report, the event had improved and the subject had been discharged from the hospital (date not specified). The subject still had ongoing edema. Treatment with investigational product was continued. The investigator considered that there was no reasonable possibility that the nephrotic syndrome may have been caused by investigational product and cited that the event was possibly due to a medical condition and the prednisone taper from his study participation. The investigator reported that the subject was on prednisone 60 mg/day at study entry, which was then tapered to 20 mg/day, but was subsequently increased. The prednisone dose at event onset was 30 mg/day. Treatment with investigational product was discontinued after approximately 6 months, and the subject was withdrawn from the study.

On follow-up, the investigator stated that no clear cause for the nephrotic syndrome could be identified. Also, the subject had no history of nephrotic syndrome or renal disease prior to study participation. At the time of reporting, the event was recovering but had not resolved.

Supplement Appendix 3. Figures 1 to 5 and Tables 1 to 9 Describing Additional Efficacy Data.

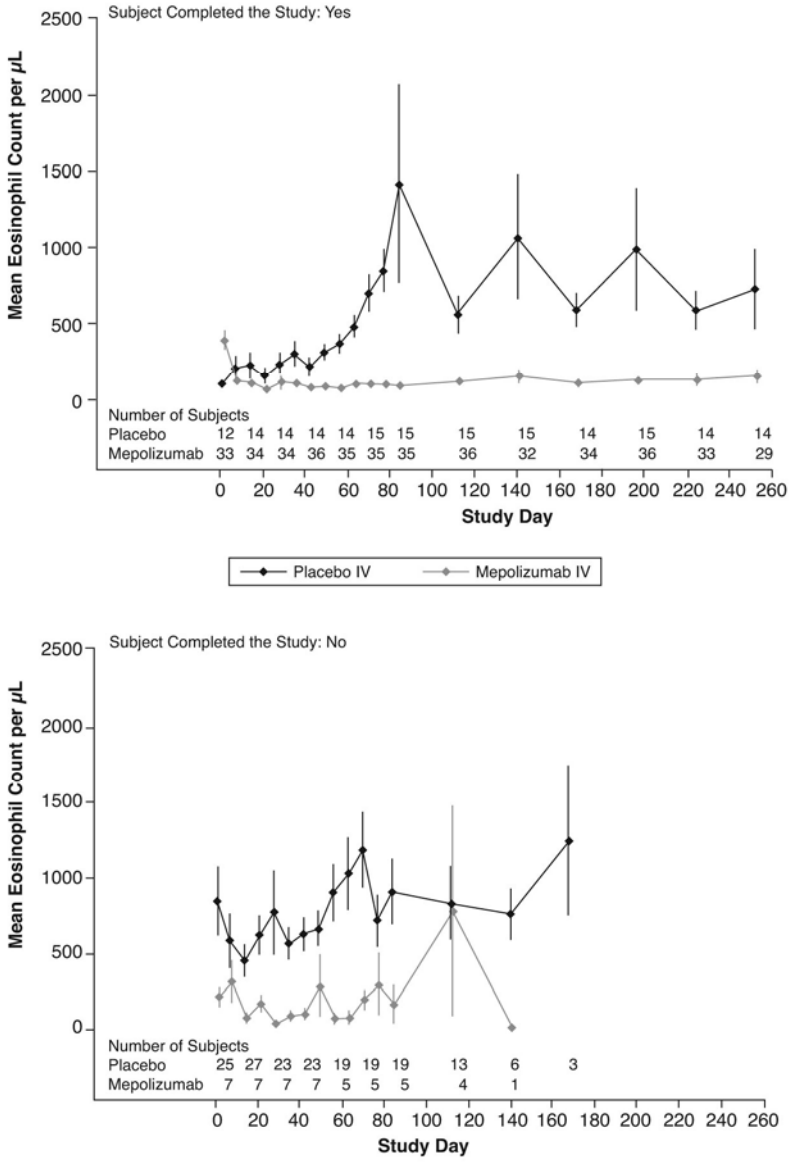
Supplement Figure 1. Steroid Dose for Trial Completers Over Time. Top Panel Shows Patients Who Completed the Trial and Bottom Panel Shows Patients Who Withdrew From the Trial.



[a] LOCF based on data from second infusion onwards.

IV, intravenous; LOCF, last observation carried forward.

Supplement Figure 2. Mean Observed Eosinophil Counts for Trial Completers Over Time. Top Panel Shows Completers and Bottom Panel Shows Noncompleters.



IV, intravenous.

Supplement Table 1a. Date of Withdrawal, Eosinophil Counts, and Steroid Dose for Placebo-Treated Patients Who Withdrew From the Study.

Patient number/ day of withdrawal	Baseline eosinophil count	Last on-treatment eosinophil count	Baseline steroid dose	Last on-treatment steroid dose	Number of day during the treatment period	Cumulative Steroid dose during the treatment period
Pt #15 Day 57	1000	1400	30	20	57	1830
Pt #32 Day 191	730	1120	20	12.5	184	2020
Pt #43 Day 108	790	1210	20	5	108	975
Pt #61 Day 106	370	3830	50	12.5	84	3257.5
Pt #101 Day 146	950	570	50	60	57	3030
Pt #107 Day 29	1090	960	20	10	29	487.5
Pt # 110 Day 85	180	220	45	20	85	1840
Pt #126 Day 134	50	30	20	20	122	2512.5
Pt #130 Day 93	NA	820	35	50	93	3460
Pt # 136 Day 224	4690	2140	60	40	206	7330
Pt #141 Day 113	190	460	25	50	113	4620
Pt #142 Day 113	240	570	30	25	113	1960
Pt # 151 Day 57	70	1440	40	20	57	1467.5
Pt #152 Day 113	1860	3050	50	20	113	3075
Pt #154 Day 66	NA	840	25	30	66	1127.5
Pt #155 Day 83	950	1520	40	25	83	2112.5
Pt #160 Day 129	30	360	NA	25	NA	NA
Pt #163 Day 116	60	560	30	17.5	61	1220
Pt #164 Day 185	180	1170	20	10	175	2180

Pt #165 Day 92	2490	1960	37.5	21.9	88	2268.7
Pt #170 Day 89	240	1450	50	40	88	3300
Pt #171 Day 139	150	570	30	20	139	2877.5
Pt #190 Day 92	3370	1280	50	50	92	3920
Pt #194 Day 143	730	1410	25	17.5	142	3907.5
Pt #200 Day 56	380	760	25	40	56	1720
Pt #201 Day 159	190	730	30	20	120	2180
Pt #227 Day 169	160	420	20	10	169	1864

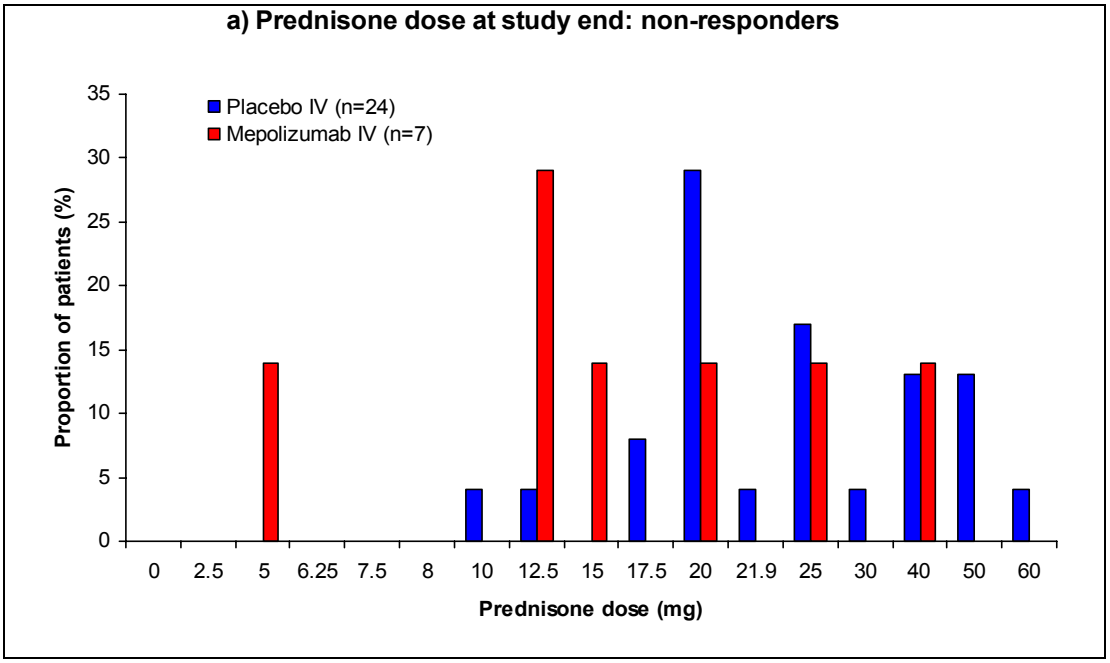
NA, not available.

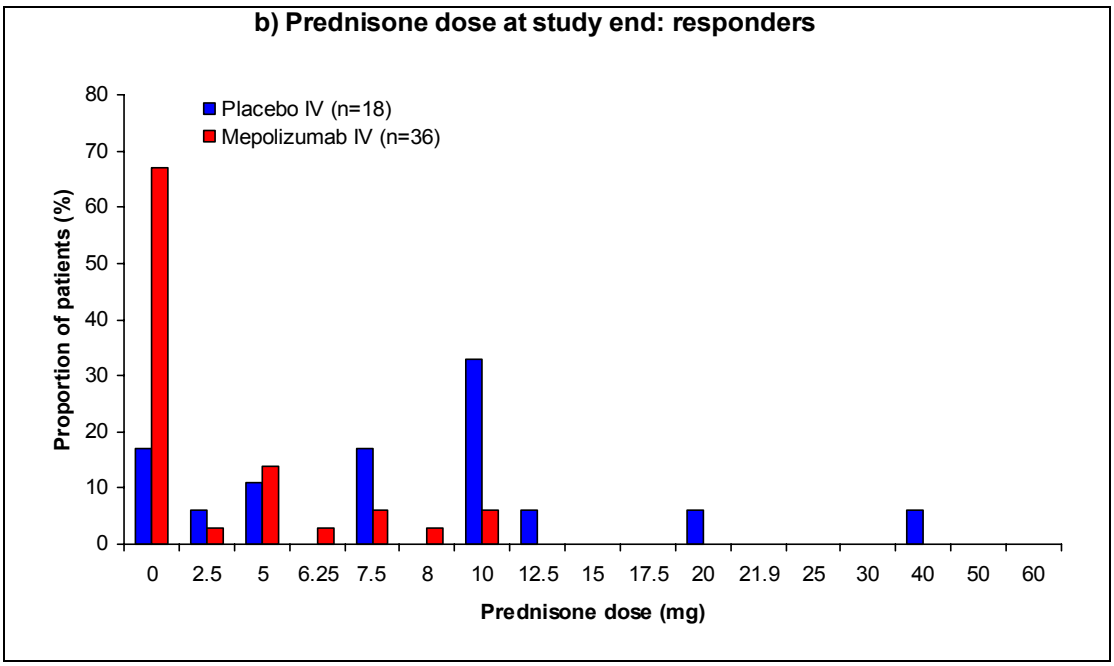
Supplementary Table 1b: Date of Withdrawal, Eosinophil Counts and Steroid Dose for Mepolizumab-treated Patients Who Withdrew From the Study

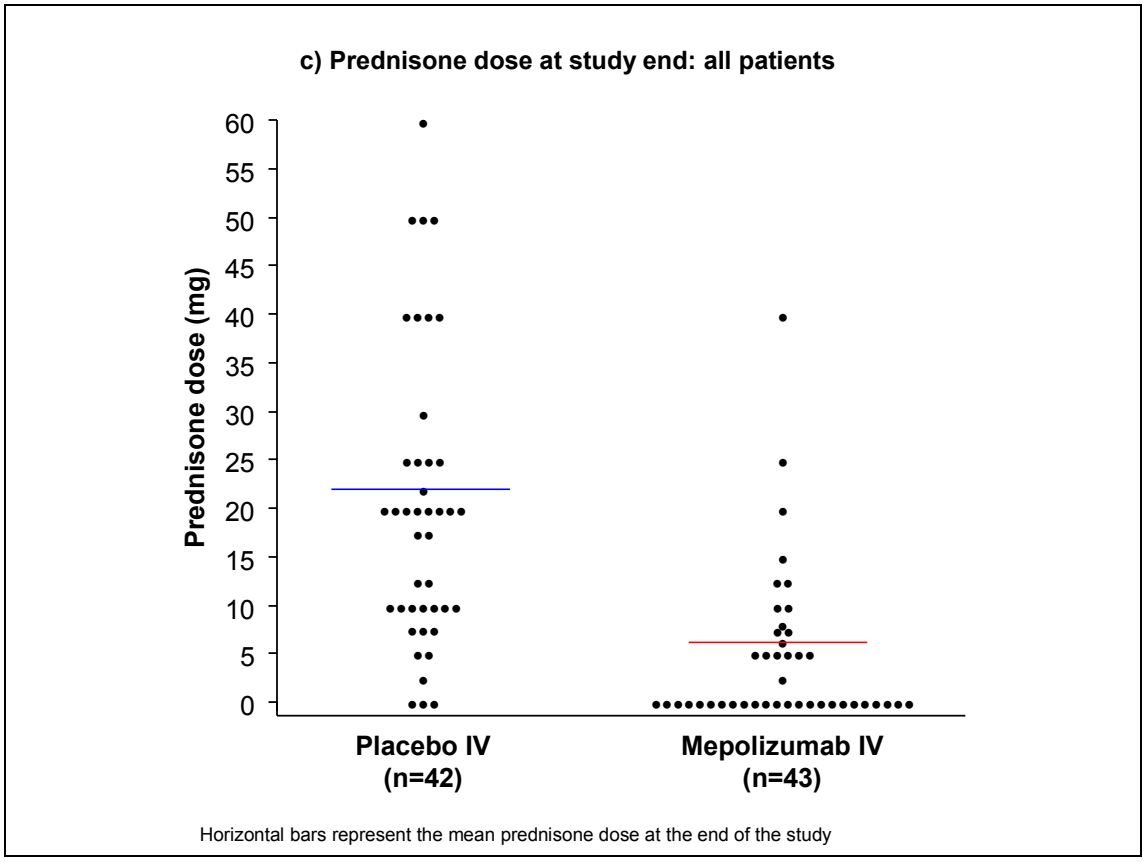
Patient number/ day of withdrawal	Baseline eosinophil count	Last on-treatment eosinophil count	Baseline steroid dose	Last on-treatment steroid dose	Number of day during the treatment period	Cumulative Steroid dose during the treatment period
Pt #17 Day 64	250	90	20	15	58	820
Pt #75 Day 112	100	200	30	0	112	1422.5
Pt #85 Day 57	300	200	30	40	57	2070
Pt #106 Day 225	80	80	20	0	144	1042.5
Pt #125 Day 188	50	20	20	10	172	1935
Pt #193 Day 91	550	40	30	25	91	1975
Pt # 195 Day 111	200	2840	50	20	111	1855

Reasons for withdrawal included lack of efficacy (based on eosinophil counts and HES clinical activity; n=5), adverse events (n=1), and withdrawal of consent (n=1)

Supplement Figure 3: Distribution of Corticosteroid Dose at Study End for a) Patients Who did not Achieve the Primary Endpoint; b) Patients Who did Achieve the Primary Endpoint; c) All Patients. Values Shown as Percent of Patients in Treatment Groups in Panels a) and b), and Individual Patient Values in c).







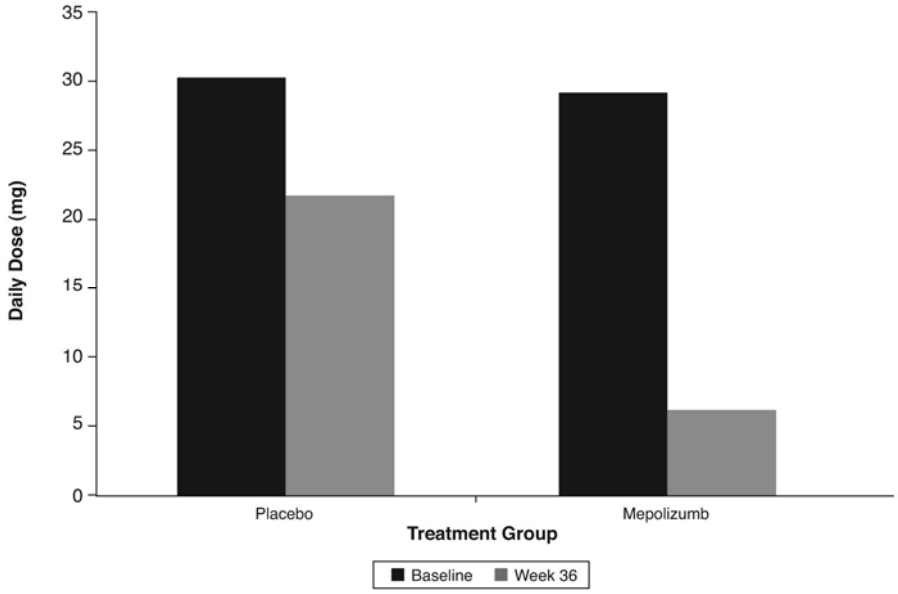
Horizontal bars represent the mean prednisone dose at the end of the study

Supplement Table 2. Summary of Patients Who Became Corticosteroid-Free During Treatment Period.

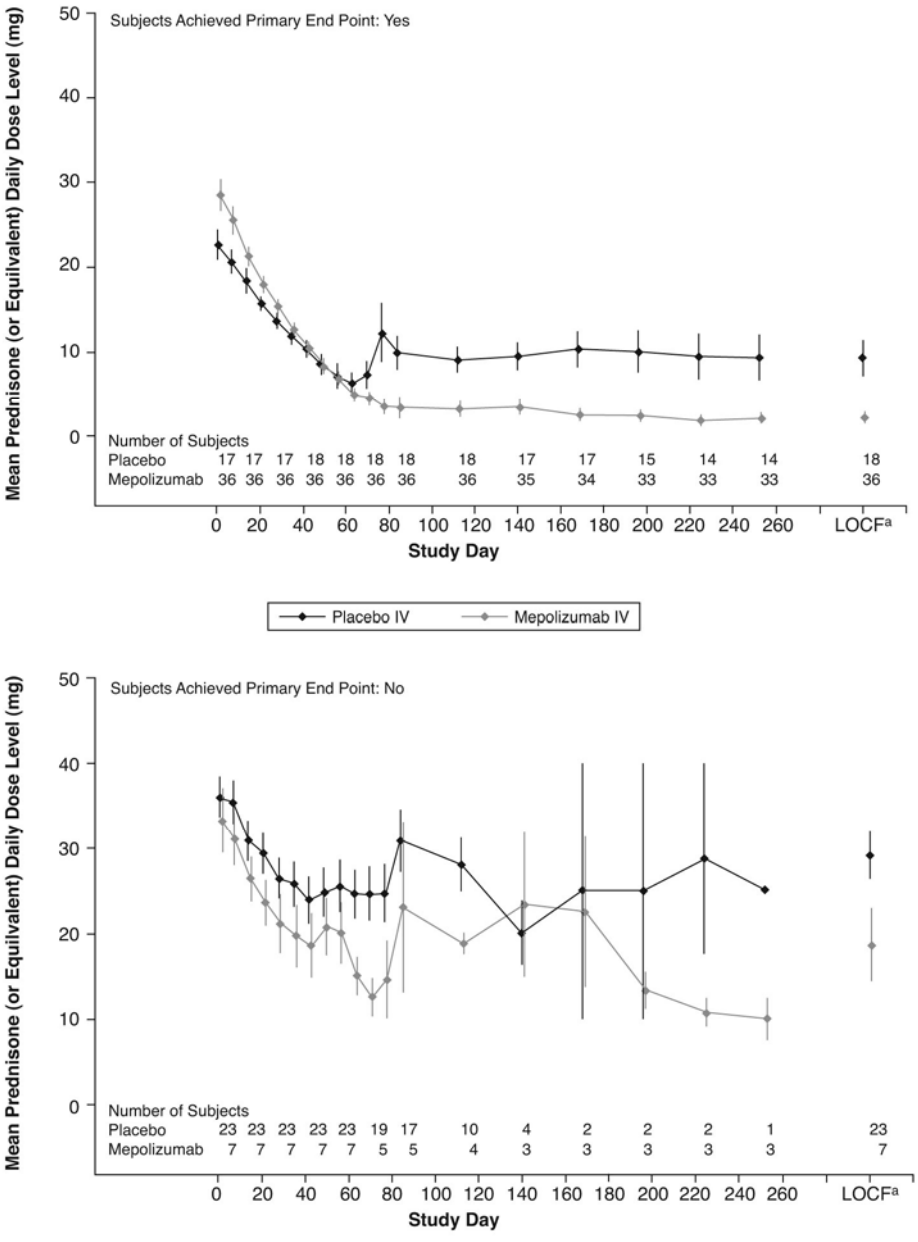
Baseline Prednisone Dose-Level Group	Placebo IV	Mepolizumab IV
All subjects		
Number of subjects analyzed	42	43
Achieved corticosteroid-free status (%)	10 (24)	34 (79)
Odds ratio		12.80
95% confidence interval for odds ratio		(4.39, 37.35)
Chi-square value		26.24
P-value		<0.001

IV, intravenous.

Supplement Figure 4. Change in Mean Prednisone Dose From Baseline to Week 36. Missing data were calculated by last observation carried forward (LOCF).



Supplement Figure 5. Mean Prednisone Dose for Mepolizumab-Treated and Placebo-Treated Patients Comparing Responders and Nonresponders. Top Panel Shows Patients Who Achieved the Primary End Point and Bottom Panel Shows Patients Who Failed to Achieve the Primary End Point.



[a] LOCF based on data from second infusion onwards.

IV, intravenous; LOCF, last observation carried forward.

Supplement Table 3. Mean Laboratory Values of Interest for Inflammation and HES Subtype by Treatment and Response

			Placebo		Mepolizumab	
			Achieved Primary Endpoint	Didn't Achieve Primary Endpoint	Achieved Primary Endpoint	Didn't Achieve Primary Endpoint
IgE antibody (KU/L)	Baseline	N	16	20	32	6
		Mean ± SD	1949±4497	1016±2454	511.4 ± 852	9991±23878
		Median	211	120	154	103
		Range	3,17185	4,9043	9,3165	8,58725
	Week 36	N	13	0	25	3
		Mean ± SD	1429±4508		612±1040	24170±41025
		Median	68		152	788
		Range	6,16415		12,4032	181,71540
Tryptase (UG/L)	Baseline	N	16	20	33	6
		Mean ± SD	6.1±4.16	9.2±12.6	5.6±3.1	6.2±5.3
		Median	6.0	5.0	5.0	4.0
		Range	1,14	2,57	2,14	2,16
	Week 36	N	13	0	23	3
		Mean ± SD	6.5±4.4		5.9±3.3	2.3±0.6
		Median	6.0		5.0	2.0
		Range	2,15		1,13	2,3
Vitamin B12 (PMOL/L)	Baseline	N	16	21	33	6
		Mean ± SD	379±333	394±154	375±342	256±85
		Median	273	376	297	224
		Range	137,1476	207,721	181,2196	170,412
	Week 36	N	13	0	25	2
		Mean ± SD	330±146		435±284	266.0±81
		Median	331		370	266
		Range	130,604		179,1512	209,323

Supplementary Table 4a. Summary of prednisone dose at the end of the study: subjects who did not achieve a total daily prednisone dose of ≤10mg for a period of at least 8 consecutive weeks.

Prednisone dose (mg) at the end of the study, n (%)	Placebo IV (n=24)	Mepolizumab IV (n=7)
0	0/24	0/7
2.5	0/24	0/7
5	0/24	1/7 (14%)
6.25	0/24	0/7
7.5	0/24	0/7
8	0/24	0/7
10	1/24 (4%)	0/7
12.5	1/24 (4%)	2/7 (29%)
15	0/24	1/7 (14%)
17.5	2/24 (8%)	0/7
20	7/24 (29%)	1/7 (14%)
21.875	1/24 (4%)	0/7
25	4/24 (17%)	1/7 (14%)
30	1/24 (4%)	0/7
40	3/24 (13%)	1/7 (14%)
50	3/24 (13%)	0/7
60	1/24 (4%)	0/7

Supplementary Table 4b. Summary of prednisone dose at the end of the study: subjects who did achieve a total daily prednisone dose of ≤10mg for a period of at least 8 consecutive weeks.

Prednisone dose (mg) at the end of the study, n (%)	Placebo IV (n=18)	Mepolizumab IV (n=36)
0	3/18 (17%)	24/36 (67%)
2.5	1/18 (6%)	1/36 (3%)
5	2/18 (11%)	5/36 (14%)
6.25	0/18	1/36 (3%)
7.5	3/18 (17%)	2/36 (6%)
8	0/18	1/36 (3%)
10	6/18 (33%)	2/36 (6%)
12.5	1/18 (6%)	0/36
15	0/18	0/36
17.5	0/18	0/36
20	1/18 (6%)	0/36
21.875	0/18	0/36
25	0/18	0/36
30	0/18	0/36
40	1/18 (6%)	0/36
50	0/18	0/36
60	0/18	0/36

Supplementary Table 4c. Summary of prednisone dose at the end of the study: all patients randomized.

Prednisone dose (mg) at the end of the study, n (%)	Placebo IV (n=42)	Mepolizumab IV (n=43)
0	3/42 (7%)	24/43 (56%)
2.5	1/42 (2%)	1/43 (2%)
5	2/42 (5%)	6/43 (14%)
6.25	0/42	1/43 (2%)
7.5	3/42 (7%)	2/43 (5%)
8	0/42	1/43 (2%)
10	7/42 (17%)	2/43 (5%)
12.5	2/42 (5%)	2/43 (5%)
15	0/42	1/43 (2%)
17.5	2/42 (5%)	0/43
20	8/42 (9%)	1/43 (2%)
21.875	1/42 (2%)	0/43
25	4/42 (10%)	1/43 (2%)
30	1/42 (2%)	0/43
40	4/42 (10%)	1/43 (2%)
50	3/42 (7%)	0/43
60	1/42 (2%)	0/43

Supplement Table 5. Summary of Subjects Achieving the Primary End Point by End Organ Condition.

	Current Condition	Placebo IV	Mepolizumab IV
Cardiac	Yes	4/5 (80%)	5/5 (100%)
	No	14/37 (38%)	31/38 (82%)
Eye	Yes	1/3 (33%)	2/4 (50%)
	No	17/39 (44%)	34/39 (87%)
Gastrointestinal	Yes	2/7 (29%)	8/8 (100%)
	No	16/35 (46%)	28/35 (80%)
Musculoskeletal	Yes	1/7 (14%)	5/6 (83%)
	No	17/35 (49%)	31/37 (84%)
Nervous system	Yes	6/9 (67%)	8/9 (89%)
	No	12/33 (36%)	28/34 (82%)
Respiratory	Yes	7/16 (44%)	17/19 (89%)
	No	11/26 (42%)	19/24 (79%)
Skin	Yes	9/24 (38%)	11/16 (69%)
	No	9/18 (50%)	25/27 (93%)

IV, intravenous.

Supplement Table 6. Summary of Subjects Achieving the Primary End Point by Baseline Prednisone Dose.

	Placebo IV	**Mepolizumab IV**
Total number of subjects achieving primary end point	18/42 (43%)	36/43 (84%)
Baseline prednisone dose (mg)		
12.5	0	1/1 (100%)
17.5	0	1/1 (100%)
20.0	13/15 (87%)	14/15 (93%)
25.0	3/7 (43%)	4/5 (80%)
30.0	0/6	6/8 (75%)
35.0	0/1	1/1 (100%)
37.5	0/1	0/1
40.0	0/2	5/6 (83%)
45.0	0/1	0
50.0	1/6 (17%)	4/5 (80%)
60.0	0/1	0
Missing	1/2 (50%)	0

IV, intravenous.

Results of the Rotterdam Symptom Checklist Subscale Assessments.

At Weeks 24 and 36, greater proportions of subjects treated with mepolizumab reported having no HES symptoms based on the RSCL questions compared with those receiving placebo. However, there were no statistically significant differences in changes from baseline (improvement, no change, or deterioration) for any of the four RSCL subscales in either treatment group (Tables 7a and 7b below). This result is not unexpected since the placebo subjects that remained in the study were stable and responding well to prednisone alone. Further, the RSCL was developed for use in cancer patients with relatively early stage disease undergoing chemotherapy or follow-up. Its relevance and sensitivity in HES patients have not been previously tested and validated.

Supplement Table 7a. Change from Baseline in Rotterdam Symptom Checklist Subscale Scores at the End of Treatment (ITT Population)

	Placebo IV (n=42)		**Mepolizumab IV (n=43)**	
RSCL Subscale, mean (SD)*	**Baseline (n=40)**	**Change at Wk 36; LOCF† (n=35)**	**Baseline (n=42)**	**Change at Wk 36; LOCF† (n=39)**
Physical symptom distress	20.1 (15.4)	2.6 (8.7)	17.9 (13.2)	−1.8 (9.6)
Psychological symptom distress	32.4 (21.7)	−2.3 (17.3)	23.5 (18.7)	−5.1 (17.7)
Activities of daily living‡	6.0 (12.1)	0.4 (13.7)	9.5 (17.7)	0.2 (13.1)
Overall evaluation of life	32.9 (28.4)	8.6 (26.9)	23.0 (15.6)	6.4 (26.7)

* Each of the RSCL subscales was transformed to give a range of scores from 0 to 100, with a higher score indicating a greater level of burden or impairment.

†Last observation carried forward based on data from the 2nd infusion onwards

‡n=41 at baseline for the mepolizumab group

Supplement Table 7b. Shift from Baseline in Rotterdam Symptom Checklist Subscale Scores at Each Visit (ITT Population)

Subscale/Rating, n (%)	Placebo IV (n=42)			Mepolizumab IV (n=43)		
	Wk 12	Wk 24	Wk 36	Wk 12	Wk 24	Wk 36
Physical symptom distress level						
n	30	15	12	36	30	28
Improved	16 (53)	6 (40)	8 (67)	17 (47)	18 (60)	16 (57)
No change	0	0	0	0	1 (3)	4 (14)
Deterioration	14 (47)	9 (60)	4 (33)	19 (53)	11 (37)	8 (29)
Psychological symptom scores						
n	30	15	12	36	30	28
Improved	17 (57)	7 (47)	6 (50)	21 (58)	20 (67)	16 (57)
No change	3 (10)	4 (27)	2 (17)	4 (11)	4 (13)	2 (7)
Deterioration	10 (33)	4 (27)	4 (33)	11 (31)	6 (20)	10 (36)
Activities of daily living						
n	29	15	12	35	29	27
Improved	5 (17)	5 (33)	6 (50)	11 (31)	10 (34)	6 (22)
No change	16 (55)	8 (53)	5 (42)	19 (54)	16 (55)	16 (59)
Deterioration	8 (28)	2 (13)	1 (8)	5 (14)	3 (10)	5 (19)
Overall evaluation of life						
n	30	15	12	36	30	28
Improved	8 (27)	6 (40)	8 (67)	9 (25)	10 (33)	10 (36)
No change	11 (37)	5 (33)	1 (8)	14 (39)	10 (33)	7 (25)
Deterioration	11 (37)	4 (27)	3 (25)	13 (36)	10 (33)	11 (39)

Supplement Table 8a. Summary of subjects who became prednisone-free for ≥1 day, by baseline prednisone dose.

	Placebo IV	Mepolizumab IV
Total subjects achieving endpoint, n (%)	10/42 (24%)	34/43 (79%)
Subjects achieving endpoint by baseline prednisone dose (mg), n (%)		
12.5	0	1/1 (100%)
17.5	0	1/1 (100%)
20	6/15 (40%)	14/15 (93%)
25	3/7 (43%)	3/5 (60%)
30	1/6 (17%)	5/8 (63%)
35	0/1	1/1 (100%)
37.5	0/1	0/1
40	0/2	4/6 (67%)
45	0/1	0
50	0/6	5/5 (100%)
60	0/1	0
Missing	0/2	0

Supplement Table 8b. Summary of subjects who achieved a prednisone dose of ≤10 mg/day for ≥24 weeks, by baseline prednisone dose.

	Placebo IV	Mepolizumab IV
Total subjects achieving endpoint, n (%)	6/42 (14%)	24/43 (56%)
Subjects achieving endpoint by baseline prednisone dose (mg), n (%)		
12.5	0	1/1 (100%)
17.5	0	0/1
20	6/15 (40%)	10/15 (67%)
25	0/7	3/5 (60%)
30	0/6	3/8 (38%)
35	0/1	1/1 (100%)
37.5	0/1	0/1
40	0/2	4/6 (67%)
45	0/1	0
50	0/6	2/5 (40%)
60	0/1	0
Missing	0/2	0

Supplement Table 8c. Summary of subjects who became prednisone-free during the treatment period who remained prednisone-free until study completion, by baseline prednisone dose.

	Placebo IV	Mepolizumab IV
Total subjects achieving endpoint, n (%)	2/42 (5%)	20/43 (47%)
Subjects achieving endpoint by baseline prednisone dose (mg), n (%)		
12.5	0	1/1 (100%)
17.5	0	0/1
20	2/15 (13%)	8/15 (53%)
25	0/7	2/5 (40%)
30	0/6	3/8 (38%)
35	0/1	1/1 (100%)
37.5	0/1	0/1
40	0/2	4/6 (67%)
45	0/1	0
50	0/6	1/5 (20%)
60	0/1	0
Missing	0/2	0

Supplement Appendix 4. Listing of Serious Adverse Events Reported by Investigators from the Ongoing Open-Label Mepolizumab Extension Study, MHE100901, as of 3 September 2007

As of 3 September 2007, the following serious adverse events have been reported by investigators participating in the ongoing extension study MHE100901; 61 of the 78 patients who initially enrolled continue participation in this study.

Patient age, y & gender (M/F)	Serious adverse event (SAE)*	Intensity	Date of 1st mepolizumab dose	Date of last mepolizumab dose prior to onset of SAE	No of doses of mepolizumab prior to SAE onset†	Outcome	Duration, days	Relationship to study drug‡	Action taken
58 (M)	Ataxia	Severe	4 Apr 2005	4 Jun 2007	28	Recovered/resolved	1	Not related	No action
	Confusion	Severe	4 Apr 2005	4 Jun 2007	28	Recovered/resolved	1	Not related	No action
33 (M)	Influenza	Moderate	12 Jan 2006	9 Feb 2006	2	Recovered/resolved	5	Not related	No action
	Nephrotic syndrome	Moderate	12 Jan 2006	2 Jun 2006	6	Not recovered/not resolved	—	Not related	No action
	Adrenal insufficiency	Severe	12 Jan 2006	10 Aug 2006	8	Not recovered/not resolved	—	Not related	No action
	Eosinophilia	Severe	12 Jan 2006	10 Aug 2006	8	Not recovered/not resolved	—	Not related	No action
	Hypertension	Severe	12 Jan 2006	10 Aug 2006	8	Not recovered/not resolved	—	Not related	No action
	Hypoglycemia	Severe	12 Jan 2006	10 Aug 2006	8	Not recovered/not resolved	—	Not related	No action
	Hypokalemia	Severe	12 Jan 2006	10 Aug 2006	8	Not recovered/not resolved	—	Not related	No action
	Nephrotic syndrome	Severe	12 Jan 2006	10 Aug 2006	8	Not recovered/not resolved	—	Not related	No action
	Renal failure	Severe	12 Jan 2006	10 Aug 2006	8	Not recovered/not resolved	—	Not related	No action
	Renal vein embolism	Severe	12 Jan 2006	13 Oct 2006	9	Recovering/resolving	—	Not related	Not applicable
32 (F)	Upper abdominal pain	Severe	30 Sep 2005	29 Aug 2006	10	Recovered/resolved	6	Not related	No action
	Diarrhea	Severe	30 Sep 2005	29 Aug 2006	10	Recovered/resolved	5	Not related	No action
	Pneumonia	Moderate	30 Sep 2005	8 Jan 2007	11	Recovering/resolving	—	Not related	No action
61 (M)	Acute cholecystitis	Moderate	6 Dec 2005	6 Jun 2006	4	Recovered/resolved	2	Not related	No action

Patient age, y & gender (M/F)	Serious adverse event (SAE)*	Intensity	Date of 1st mepolizumab dose	Date of last mepolizumab dose prior to onset of SAE	No of doses of mepolizumab prior to SAE onset†	Outcome	Duration, days	Relationship to study drug‡	Action taken
23 (F)	Thermal burn	Moderate	26 May 2005	20 Oct 2006	21	Recovered/resolved	23	Not related	No action
37 (M)	Optic neuritis	Severe	14 Mar 2005	7 Sep 2006	13	Not recovered/not resolved	—	Related	Dose interrupted
	Spinal disorder	Mild	14 Mar 2005	7 Sep 2006	13	Not recovered/not resolved	—	Related	Dose interrupted
	Myelitis transverse	Severe	14 Mar 2005	7 Sep 2006	13	Not recovered/not resolved	—	Related	Investigational product withdrawn
	Catheter bacteremia	Moderate	14 Mar 2005	7 Sep 2006	13	Recovering/resolving	—	Not related	Not applicable
53 (F)	Pneumonia	Moderate	16 Feb 2006	12 Feb 2007	13	Recovered/resolved	9	Not related	No action
65 (M)	Dyspnea	Moderate	22 Dec 2004	9 May 2005	6	Recovered/resolved	237	Not related	No action
	Status asthmaticus	Severe	22 Dec 2004	9 May 2005	6	Recovered/resolved	220	Not related	Dose interrupted
57 (M)	Fatigue	Severe	12 Apr 2005	5 Dec 2006	21	Recovered/resolved	59	Not related	Dose interrupted
57 (M)	Prostate cancer	Severe	13 Sep 2005	3 Jan 2007	10	Recovered/resolved	74	Not related	No action
43 (F)	Radiculitis brachial	Severe	30 Sep 2004	13 Apr 2005	8	Recovered/resolved	61	Not related	No action
64 (F)	Skin lesion (benign)	Mild	3 Feb 2005	N/A	N/A	Recovered/resolved	N/A	Not related	No action
36 (F)	Asthenia	Moderate	7 Jul 2005	19 Jul 2007	6	Recovered/resolved with sequelae	2	Not related	No action
	Headache	Moderate	7 Jul 2005	19 Jul 2007	6	Recovered/resolved with sequelae	2	Not related	No action
	Transient ischemic attack	Moderate	7 Jul 2005	19 Jul 2007	6	Recovered/resolved with sequelae	2	Not related	No action
58 (F)	Hypertrophic rhinitis	Moderate	21 Sep 2005	23 May 2006	2	Recovered/resolved	2	Not related	No action
62 (F)	Upper respiratory tract infection	Moderate	8 Nov 2005	28 Mar 2006	6	Recovered/resolved	18	Not related	No action
	Eosinophilia	Moderate	8 Nov 2005	28 Mar 2006	6	Recovered/resolved	20	Not related	No action

Patient age, y & gender (M/F)	Serious adverse event (SAE)*	Intensity	Date of 1st mepolizumab dose	Date of last mepolizumab dose prior to onset of SAE	No of doses of mepolizumab prior to SAE onset†	Outcome	Duration, days	Relationship to study drug‡	Action taken
32 (F)	Gastroenteritis	Moderate	24 Mar 2005	28 Jul 2006	16	Recovered/resolved	2	Not related	No action
	Skin erosion	Moderate	24 Mar 2005	28 Jul 2006	16	Not recovered/not resolved	164	Not related	Dose interrupted
	Cardiac failure	Severe	24 Mar 2005	14 Dec 2006	18	Fatal	56	Not related	No action
	Acute renal failure	Moderate	24 Mar 2005	14 Dec 2006	18	Recovered/resolved with sequelae	8	Not related	No action
	Calciphylaxis	Moderate	24 Mar 2005	14 Dec 2006	18	Not recovered/not resolved	44	Not related	No action
	Autoimmune thrombocytopenia	Severe	24 Mar 2005	14 Dec 2006	18	Recovered/resolved	5	Not related	No action
	Respiratory arrest	Severe	24 Mar 2005	14 Dec 2006	18	Recovering/resolving	1	Not related	No action
	Sepsis	Severe	24 Mar 2005	14 Dec 2006	18	Fatal	2	Not related	Not applicable
	Multi-organ failure	Severe	24 Mar 2005	14 Dec 2006	18	Fatal	1	Not related	Not applicable
49 (M)	Eosinophilic gastroenteritis	Severe	22 Dec 2004	2 Oct 2006	14	Recovered/resolved	7	Not related	Not applicable
61 (M)	Arterial occlusive disease	Severe	23 Jun 2004	13 Mar 2006	15	Recovered/resolved with sequelae	249	Not related	Not applicable
	Extremity necrosis	Severe	23 Jun 2004	13 Mar 2006	15	Recovered/resolved	249	Not related	Not applicable
71 (M)	Sclerosing cholangitis	Severe	4 May 2005	23 Aug 2006	12	Not recovered/not resolved	4	Not related	No action
	Hypotension	Severe	4 May 2005	23 Aug 2006	12	Recovered/resolved	10	Not related	No action
	Clostridial gastroenteritis	Severe	4 May 2005	23 Aug 2006	12	Recovered/resolved with sequelae	8	Not related	No action
	Hypotension	Severe	4 May 2005	23 Aug 2006	12	Not recovered/not resolved	14	Not related	Investigational product withdrawn
	Pneumonia aspiration	Severe	4 May 2005	23 Aug 2006	12	Fatal	1	Not related	Not applicable
	Respiratory failure	Severe	4 May 2005	23 Aug 2006	12	Fatal	1	Not related	Not applicable
28 (F)	Depression	Severe	3 Sep 2004	2 Sep 2005	14	Recovered/resolved	6	Not related	No action
	Depression	Severe	3 Sep 2004	2 Sep 2005	14	Recovered/resolved	2	Not related	No action
	Asthma	Severe	3 Sep 2004	30 Mar 2007	19	Recovered/resolved	4	Not related	No action
	Depression	Severe	3 Sep 2004	10 Aug 2007	23	Recovered/resolved	1	Not related	No action
	Self-injurious ideation	Severe	3 Sep 2004	10 Aug 2007	23	Recovered/resolved	1	Not related	No action
38 (M)	Lymphomatoid papulosis	Severe	4 Aug 2004	31 May 2005	11	Not recovered/not resolved	—	Not related	No action

Patient age, y & gender (M/F)	Serious adverse event (SAE)*	Intensity	Date of 1st mepolizumab dose	Date of last mepolizumab dose prior to onset of SAE	No of doses of mepolizumab prior to SAE onset†	Outcome	Duration, days	Relationship to study drug‡	Action taken
44 (M)	Pancreatitis	Severe	19 Oct 2004	7 Jun 2005	9	Recovered/resolved	93	Not related	No action
	Pancreatitis	Severe	19 Oct 2004	5 Oct 2005	11	Recovered/resolved	4	Not related	No action
69 (M)	Myocardial infarction	Moderate	2 Aug 2004	4 Dec 2006	21	Recovered/resolved	1	Not related	No action
45 (M)	Hypereosinophilic syndrome	Severe	10 May 2004	8 Nov 2005	12	Recovered/resolved	8	Not related	No action
	Pyrexia	Severe	10 May 2004	8 Nov 2005	12	Recovered/resolved	8	Not related	No action
34 (F)	Dyspnea	Moderate	28 Feb 2005	5 Dec 2006	13	Recovered/resolved	35	Not related	No action
66 (M)	Influenza-like illness	Mild	17 Nov 2004	6 Apr 2006	11	Recovered/resolved	2	Not related	No action
	Pyrexia	Severe	17 Nov 2004	6 Apr 2006	11	Recovered/resolved	3	Not related	No action
	Osteoarthritis	Severe	17 Nov 2004	6 Apr 2006	11	Recovered/resolved with sequelae	11	Not related	No action
53 (F)	Bronchiectasis	Moderate	10 Feb 2005	1 Sep 2006	12	Not recovered/not resolved	—	Not related	No action
46 (M)	Angioimmunoblastic T-cell lymphoma	Severe	12 Apr 2005	11 Oct 2006	19	Fatal	31	Related	Investigational product withdrawn
	Cardiopulmonary failure	Severe	12 Apr 2005	11 Oct 2006	19	Fatal	8	Not related	Not applicable
38 (M)	Pneumonia	Severe	29 Mar 2005	10 Feb 2006	11	Recovered/resolved	9	Not related	No action

*A serious adverse event is defined as any event that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in a disability/incapacity, is a congenital anomaly/birth defect or is an important medical event

†Total number of mepolizumab infusions in study MHE100185 and MHE100901

‡The relationship between an SAE and the study drug was assessed by the investigator by responding 'yes' or 'no' to the following question, “Is there a reasonable possibility the SAE may have been caused by the study drug?”

N/A, not available. Subject was not receiving mepolizumab when the event occurred (e.g., pre- or post-dosing) or the subject died and there was no prior decision to discontinue mepolizumab

Supplement Appendix 5. Baseline Demographics and Disease Characteristics in Subjects by Baseline Prednisone Dose Group (≤30 mg vs >30 mg).

c	≤30 mg/day prednisone (n=60)	>30 mg/day prednisone (n=25)	Total (n=85)	P-value
Age (yr)	51.3±14.7	40.2±14.1	48.1±15.3	<0.01
Men, n (%)	30 (50)	13 (52)	43 (51)	0.87
Race, n (%)*				**
White/Caucasian	53 (88)	19 (76)	72 (85)	
Black	4 (7)	4 (16)	8 (9)	
Asian†	2 (3)	1 (4)	3 (4)	
Arabic/North African	1 (2)	1 (4)	2 (2)	
Weight (kg)	81.6±20.6	77.3±19.7	80.3±20.3	0.39
Body mass index (kg/m^2)	27.7±6.2	26.8±6.1	27.4±6.1	0.57
Previously treated for HES, n (%)‡	56 (93)	25 (100)	81 (95)	0.19
Most common discontinued previous treatments for HES, n (%)				
Any medication	32 (53)	19 (76)	51 (60)	0.05
Imatinib mesylate	17 (28)	15 (60)	32 (38)	<0.01
Interferon-α	9 (15)	9 (36)	18 (21)	0.03
Hydroxyurea	13 (22)	5 (20)	18 (21)	0.86
Most common ongoing treatments for HES at screening, n (%)				
Any medication	47 (78)	23 (92)	70 (82)	0.13
Systemic corticosteroids	47 (78)	23 (92)	70 (82)	0.13
Interferon-α	2 (3)	1 (4)	3 (4)	0.88
HES duration (yr)	4.6±6.5	7.3±10.3	5.4±7.8	0.14
Age at HES onset (yr)	46.8±15.3	32.9±16.6	42.7±16.9	<0.01

	≤30 mg/day prednisone (n=60)	>30 mg/day prednisone (n=25)	Total (n=85)	P-value
Most prevalent HES-related current clinical conditions, n (%)[§]				
Any condition	49 (82)	21 (84)	70 (82)	0.80
Skin/subcutaneous disorders	22 (37)	18 (72)	40 (47)	<0.01
Respiratory disorders	23 (38)	12 (48)	35 (41)	0.41
Nervous system disorders	13 (22)	5 (20)	18 (21)	0.86
Gastrointestinal disorders	11 (18)	4 (16)	15 (18)	**
Musculoskeletal disorders	7 (12)	6 (24)	13 (15)	**
Cardiac disorders	8 (13)	2 (8)	10 (12)	**
Eye disorders	4 (7)	3 (12)	7 (8)	**
Mean eosinophil count ($\times 10^9$/L)	0.295±0.279	0.812±1.140	0.447±0.694	0.03[††]
Median eosinophil count (GI/L)	0.200	0.260	0.200	
Serum Interleukin 5 (pg/mL)[#]	All <7.8	8.7, 57, 72	N/A	
Mean serum tryptase level (µg/L)	7.3±7.9 (n=56)	5.9±5.6 (n=22)	6.9±7.3 (n=78)	0.16[††]
Median serum tryptase level (µg/L)	5.5	4.0	5.0	

Data are mean±SD unless otherwise specified.

HES, hypereosinophilic syndrome; N/A, not available.

*Assessed by investigator at screening.

[†]Includes East, Southeast, and South Asian.

[‡]Therapy for HES within 5 years prior to screening.

[§]Patients may have had more than one HES-related current clinical condition.

**As >50% of cells have expected counts less than 5, Chi-square test was not performed.

[††]P-value based on Wilcoxon Rank Sum Test.

[#]All but 3 patients were under the level of detection for the assay (7.8 ng/ml). The 3 individual patient levels are reported here.

P-values are based on a 2-sided t-test with pooled variance (continuous data) or Chi-square test (categorical data), unless otherwise specified.