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Mepolizumab

Rec INN

Humanized Anti-IL-5 Monoclonal Antibody Treatment of Hypereosinophilic Syndromes

SB-240563

Immunoglobulin G_1, anti-(human interleukin 5) (human-mouse monoclonal SB-240563 γ1-chain), disulfide with human-mouse monoclonal SB-240563 κ-chain, dimer

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Abstract

Mepolizumab (SB-240563) is a humanized monoclonal antibody that prevents IL-5 from binding to its receptor on eosinophils. The agent was originally developed to treat conditions caused by allergic eosinophilia, such as allergic asthma and atopic dermatitis, but showed little success in treating the clinical symptoms of these conditions. Mepolizumab has shown greater promise in treating hypereosinophilic disorders and has reached phase III trials for the treatment of hypereosinophilic syndromes (HES).

Background

Hypereosinophilia is characterized by abnormally high levels of eosinophils in the blood and/or tissues and is associated with a wide range of clinical conditions, including parasitic infections, allergic diseases, *i.e.*, asthma, allergic rhinitis and atopic dermatitis, drug reactions, malignancies, particularly hematological malignancies, Churg-Strauss syndrome and Loeffler's syndrome (1-3). Hypereosinophilic syndrome (HES) is a subset of the idiopathic eosinophilias with no known cause that is characterized by an absolute eosinophil count of at least 1500/l for more than 6 month and eosinophil-mediated end-organ damage, the major targets being the heart, skin, the nervous system and the respiratory tract. HES is rare in adults and very rare in children and occurs mainly in males, usually between the ages of 20 and 50. The disorder can be fatal, particularly in those resistant to corticosteroid therapy with cardiac involvement. Although the exact etiology of HES is not known, overproduction of cytokines, particularly IL-5, which plays a critical role in eosinophil production, has been implicated (1-10).

Currently, there is no FDA-approved treatment for HES and management involves reducing eosinophil levels and preventing end-organ damage, usually requiring chronic maintenance therapy. Corticosteroids (high-dose prednisone) are considered the first-line therapy of choice, but long-term therapy is associated with potentially serious adverse events and disease recurrence. Second-line therapy consists of interferon alfa and/or cytotoxic drugs such as hydroxyurea, vincristine, cyclophosphamide and chlorambucil, and ciclosporin has also been used; the tyrosine kinase inhibitor imatinib mesilate has also demonstrated some efficacy in HES and is considered the third-line therapy of choice. However, current therapeutic options are not effective in a significant number of patients or are not tolerated as maintenance treatment, and the need exists for safe and effective therapies (1-3, 10, 11).

As previously mentioned, IL-5 plays a crucial role in the maturation, growth and survival of eosinophils and is therefore considered a potential target for the treatment of HES. GlaxoSmithKline developed a fully humanized IgG_1 κ antibody against IL-5, mepolizumab (SB-240563), that binds to IL-5 and blocks its interaction with the IL-5 receptor α-chain present on the surface of eosinophils. Mepolizumab was initially evaluated for its use in asthma but gave disappointing results (2, 3, 10-13). It is currently in phase III evaluation for HES.

Preclinical Pharmacology

The preclinical pharmacology and safety of mepolizumab have been evaluated in cynomolgus monkeys, the only animal model in which the antibody displays cross-reactivity. Using monkeys sensitive to the allergen *Ascaris suum*, a single dose of mepolizumab reduced blood eosinophilia, eosinophil migration to the lungs and the levels of the inflammatory markers RANTES and IL-6 in the lungs for 6 weeks. An indirect pharmacological response model was used to estimate

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an IC_{50} of 1.43 μg/ml for eosinophil reduction based on data from a single s.c. dose of 1 mg/kg mepolizumab. Two doses of mepolizumab, each separated by 1 month, caused dose-dependent decreases in both blood and bronchoalveolar lavage (BAL) eosinophils. Serum eosinophils dropped by up to 94% at doses of 5 mg/kg or higher and were maintained for up to 2 months after dosing. In animals challenged with *A. suum*, mepolizumab had no effect on the acute bronchoconstrictive response. Single- and chronic-dose toxicity studies showed no target organ toxicity, immunotoxicity or bone marrow effects with doses up to 300 mg/kg administered monthly for 6 months (14, 15).

Pharmacokinetics and Metabolism

After a single i.v. injection of 300 mg/kg mepolizumab to cynomolgus monkeys, the C_{max} was 6.7 mg/ml, the $AUC_{0\text{-infinity}}$ was 1450 mg.h/ml, the half-life was 11.7 days, the clearance was 0.2 ml/h/kg and the steady-state volume of distribution was 74.5 mg/kg. Steady-state trough levels were reached after four monthly doses. Exposure was comparable whether mepolizumab was delivered i.v. or s.c., and exposure was roughly dose-proportional over the dose range 0.05-300 mg/kg (14, 15).

A single-dose study explored the pharmacokinetics and pharmacodynamics of mepolizumab in patients with mild allergic asthma. Four male patients each received a dose of 0.5, 2.5 or 10 mg/kg by i.v. infusion. The drug exhibited a mean C_{max} of 12.1, 79.0 and 278 μg/ml, respectively, at these doses and an $AUC_{0\text{-infinity}}$ of 207, 1327 and 4361 μg.h/ml, respectively (16). The plasma clearance was 0.1 ml/h/kg, the steady-state volume of distribution was 60 ml/kg and the terminal half-life was 21 days (17).

Clinical Studies

In the above study, peripheral blood eosinophil counts were reduced dose-dependently by an estimated maximum of 85%, with an estimated IC_{50} of 0.45 μg/ml. The effect was sustained and the treatment was well tolerated (16, 17).

A double-blind, randomized, placebo-controlled, parallel-group trial enrolled 24 men with mild allergic asthma who received a single i.v. infusion of placebo or 2.5 or 10 mg/kg mepolizumab (n=8/group). The subjects were challenged with histamine and inhaled allergen at weeks –2, 1 and 4 with respect to the treatment date. The treatment caused no adverse events, and antibodies did not develop to the drug over the 16-week postdose monitoring period. Mepolizumab produced a profound drop in the peripheral blood and sputum eosinophil counts for at least 4 weeks, and prevented the blood eosinophilia that followed allergen challenge. However, the antibody had no effect on the late asthmatic response or on airways hyperresponsiveness to histamine (18, 19).

Two multiple-dose studies also explored the pharmacodynamic and clinical responses to mepolizumab in patients with mild to moderate allergic asthma. In a double-blind, randomized study, 19 patients received i.v. infusions of mepolizumab (250 or 750 mg) or placebo every 4 weeks for a total of 3 infusions. In line with the previous findings, there was a marked suppression of circulating eosinophils (median values fell from 300 to 45/μl), an effect which persisted for 12 weeks after the termination of treatment. Serum levels of eosinophil cationic protein also dropped, indicating that activation of eosinophils was also suppressed. The treatment had no impact on the distribution of T-cell types, nor on T-cell cytokine production in the peripheral blood (20). In a study of similar design, 24 patients with allergic asthma received either placebo (n=13) or mepolizumab (n=11, 750 mg i.v.) every 4 weeks for a total of 3 doses. Mepolizumab again caused a marked and rapid decrease in the levels of circulating (100% reduction) and sputum (80% reduction) eosinophils, but did not normalize the levels of eosinophils in the airways tissue (55% reduction) or bone marrow (52% reduction). Mepolizumab had minor effects on the numbers of eosinophil-committed progenitor cells in the bone marrow and airways tissue and had no effect on the levels of major basic protein in the lung tissue. In terms of clinical measures of asthma, mepolizumab had no effect on airways hyperresponsiveness or the late-stage asthmatic response. The inability of mepolizumab to fully deplete tissue eosinophils may explain its lack of clinical efficacy (21-23).

In an extension of the latter study, mepolizumab was shown to reduce the levels of the extracellular matrix proteins tenascin, lumican and procollagen III in airways reticular basement membrane tissues. The number and percentage of airways eosinophils expressing transforming growth factor-β_1 (TGF-β_1) were also reduced. These findings suggest a relationship between eosinophilic infiltration and airways remodeling in asthma (24-26).

These same patients were also tested for their response to a cutaneous allergen challenge 2 days before the first infusion and 1-2 weeks after the third infusion of mepolizumab. Similar to the findings in the lungs of these patients, mepolizumab reduced eosinophil infiltration to the skin injection site, as well as the numbers of cells staining positive for tenascin at 48 h after challenge. However, mepolizumab had no effect on the redness, swelling and induration at the injection site at this time point. This study provides further evidence that IL-5 is involved in the repair/remodeling process associated with allergic eosinophilia, but is not critical for the immediate swelling response (27-29).

In a large study in patients with poorly controlled asthma, 362 patients received either mepolizumab (250 or 750 mg) or placebo, administered on 3 occasions at intervals of 4 weeks. Blood and sputum eosinophils were profoundly reduced in both of the mepolizumab-treated groups, but there was no improvement in any of the outcome measures of asthma control (30).

Mepolizumab was also assessed in 43 patients with atopic dermatitis in a double-blind, parallel-group study. Twenty patients were randomized to mepolizumab (2 sin-

gle doses of 750 mg i.v. given 1 week apart) and 23 to placebo. Only mild side effects were reported and there was no difference in the frequency of adverse events between the two groups. Seventeen patients in the mepolizumab group and 22 in the placebo group completed the study; the reason for leaving the study early was lack of effect. Mepolizumab therapy caused a significant decrease in peripheral blood eosinophils but not tissue eosinophils. There was no significant difference between the active and placebo treatment groups in clinical measures of atopic dermatitis, nor in the atopy patch test model of induced eczema (31, 32).

In a case report, a patient with HES with lung disease, biventricular heart failure and lymphomatoid papulosis (characterized by multiple papular eruptions on the skin which can evolve to lymphoma) was treated with mepolizumab (750-mg infusions given 3 times over a 6-week period). Treatment reduced the serum levels of IL-5 and eosinophils, relieved the pulmonary symptoms and cleared the lymphomatoid papulosis, although rebound was seen within a few days of treatment. The patient was subsequently treated successfully with imatinib mesilate (33).

In 3 case reports, patients with HES and dermatological manifestations who had failed corticosteroid therapy received two infusions of mepolizumab (750 mg). All 3 patients experienced a decrease in pruritus and other dermal symptoms, as well as a significant reduction in peripheral and dermal eosinophilia. Other biomarkers of eosinophilia (IL-5, eosinophil cationic protein and eotaxin-1) were also reduced, and cytokine analysis indicated a shift from Th2 to Th1 cells in 2 of the patients. Five weeks after the second infusion of mepolizumab, 2 of the 3 patients experienced a rebound in eosinophil counts and IL-5 levels and worsening of symptoms. Subsequent doses of mepolizumab produced improvement in the symptoms. The treatment was well tolerated (34-36).

In another case report, a patient with angiolymphoid hyperplasia with eosinophilia (ALHE, which manifests as a pinkish-brown nodule several centimeters in size just behind the ear and which is sometimes painful and pulsatile) was treated with a single dose of mepolizumab (750 mg i.v.). The symptoms resolved immediately and the nodule became slightly softer and decreased in size over the subsequent 3-4 weeks. After 3 weeks, the symptoms rebounded (36, 37).

Another patient with HES involving the nose, skin and colon and with severe asthma had been receiving 40 mg prednisone, 1.6 mg budesonide and 48 μg formoterol daily. Treatment with mepolizumab (750 mg i.v. every 1-2 months) allowed a reduction in the prednisone dose to 10 mg daily, indicating its potential as a steroid-sparing supplement to HES therapeutics (38).

In an open-label phase I/II trial, 4 patients with HES (1 with eosinophilic esophagitis and 3 with multiple organ involvement) received mepolizumab at a dose of 750 mg i.v. monthly for a total of 3 doses. Peripheral eosinophil counts declined rapidly and remained low for at least 8 weeks after the final dose of mepolizumab. All 4 patients experienced clinical improvement and reported improvements in their quality of life, as measured by the Short-Form Health Questionnaire (SF-36). In the patient with eosinophilic esophagitis, mepolizumab reduced the levels of tissue eosinophils by > 10-fold and led to improvements in the patient's symptoms and diet (39).

Eight patients with HES and 3 with eosinophilic esophagitis received 3 infusions of mepolizumab (750 mg i.v./dose) with or without changes in their current therapy. Peripheral blood eosinophils fell by 10-fold in all patients, as did the number of cells expressing CCR3 (highly expressed in eosinophils). In an *ex vivo* analysis of the cytokines secreted by PHA-stimulated peripheral blood mononuclear cells (PBMCs) obtained from the patients before and after treatment, the levels of IL-4, IL-5, IL-10, GM-CSF (granulocyte-macrophage colony-stimulating factor) or interferon gamma were unchanged, whereas IL-13 decreased 3-fold. CCR3 and IL-5 receptor levels were unchanged, indicating that the treatment did not alter the receptor expression on the eosinophils. Interestingly, 1 patient had the FIP1L1-PDGFRα rearrangement, indicating potential for mepolizumab therapy in clonal hypereosinophilia (40).

In an open-label phase I/II study, 4 patients with eosinophilic esophagitis received 3 doses of mepolizumab (750 mg i.v. monthly) in addition to their regular antieosinophilic therapy. The treatment was well tolerated. There was a marked drop in both peripheral blood and tissue eosinophilia and in $CCR3^+$ cells, and patient-reported clinical outcomes and quality of life were improved. There was no correlation between plasma IL-5 levels and response to therapy (41, 42).

A multicenter, randomized, double-blind, placebo-controlled, parallel-group phase III study evaluated the safety and corticosteroid-sparing effects of mepolizumab (750 mg i.v. monthly for 36 weeks) in 85 HES patients without the FIP1L1-PDGFR gene rearrangement. Blood eosinophils were stabilized at < 1000 cells/μl by 20-60 mg/day prednisone monotherapy during a 6-week run-in period. The primary endpoint —the proportion of patients with disease control on a dose of prednisone of 10 mg/day or less for at least 8 consecutive weeks— was achieved by 84% of patients in the mepolizumab group *versus* 43% in the placebo group. The time required to achieve this endpoint was shorter in the mepolizumab group than in the placebo group. Secondary endpoints, including peripheral eosinophil counts and other prednisone-sparing measures, were also significantly improved by mepolizumab treatment. Clinical measures of cutaneous disease showed no difference between the treatment groups. Mepolizumab was safe and well tolerated in this study. There was no difference in the incidence of adverse events (98% of placebo-treated patients *vs.* 93% of mepolizumab-treated patients). Five patients reported 7 serious adverse events in the placebo-treated group, and 7 patients reported 14 serious events in the mepolizumab group, including 1 who died of cardiac arrest; however, none were considered treatment-related. The most frequent adverse events were

fatigue (30% on mepolizumab *vs.* 26% on placebo), pruritus (28% *vs.* 21%), headache (23% *vs.* 21%) and arthralgia (21% *vs.* 17%). Laboratory tests and vital signs raised no major safety concerns (43-49). An open-label extension of the above study is evaluating the long-term safety, efficacy and optimal dosing frequency of 750 mg of mepolizumab (50).

Ongoing phase I/II and II trials are assessing mepolizumab in the treatment of eosinophilic esophagitis, eosinophilic bronchitis and other types of HES, as well as Churg-Strauss syndrome (51-55), and a compassionate-use trial of mepolizumab is evaluating its safety and efficacy in patients with severe or life-threatening HES with limited treatment options and previously demonstrated benefit from anti-IL-5 therapy (56).

Source

GlaxoSmithKline (GB).

References

1. Tefferi, A., Patnaik, M.M., Pardanani, A. *Eosinophilia: Secondary, clonal and idiopathic*. Br J Haematol 2006, 133(5): 468-92.

2. Sutton, S.A., Assa'ad, A.H., Rothenberg, M.E. *Anti-IL-5 and hypereosinophilic syndromes*. Clin Immunol 2005, 115(1): 51-60.

3. Wilkins, H.J., Crane, M.M., Copeland, K., Williams, W.V. *Hypereosinophilic syndrome: An update*. Am J Hematol 2005, 80(2): 148-57.

4. Hardy, W.R., Anderson, R.E. *The hypereosinophilic syndromes*. Ann Intern Med 1968, 68(6): 1120-9.

5. Chusid, M.J., Dale, D.C., West, B.C., Wolff, S.M. *The hypereosinophilic syndrome: Analysis of fourteen cases with review of the literature*. Medicine (Baltimore) 1975, 54(1): 1-27.

6. Assa'ad, A.H., Spicer, R.L., Nelson, D.P., Zimmermann, N., Rothenberg, M.E. *Hypereosinophilic syndromes*. Chem Immunol 2000, 76: 208-29.

7. Fauci, A.S., Harley, J.B., Roberts, W.C., Ferrans, V.J., Gralnick, H.R., Bjornson, B.H. *NIH conference. The idiopathic hypereosinophilic syndrome. Clinical, pathophysiologic, and therapeutic considerations*. Ann Intern Med 1982, 97(1): 78-92.

8. Sanderson, C.J. *Interleukin-5, eosinophils, and disease*. Blood 1992, 79(12): 3101-9.

9. Weller, P.F., Bubley, G.J. *The idiopathic hypereosinophilic syndrome*. Blood 1994, 83(10): 2759-79.

10. Tefferi, A. *Modern diagnosis and treatment of primary eosinophilia*. Acta Haematol 2005, 114(1): 52-60.

11. Kalac, M., Quintas-Cardama, A., Vrhovac, R., Kantarjian, H., Verstovsek, S. *A critical appraisal of conventional and investigational drug therapy in patients with hypereosinophilic syndrome and clonal eosinophilia*. Cancer 2007, 110(5): 955-64.

12. Holgate, S.T. *Cytokine and anti-cytokine therapy for the treatment of asthma and allergic disease*. Cytokine 2004, 28(4-5): 152-7.

13. O'Byrne, P.M. *Cytokines or their antagonists for the treatment of asthma*. Chest 2006, 130(1): 244-50.

14. Hart, T.K., Cook, R.M., Zia-Amirhosseini, P. et al. *Preclinical efficacy and safety of mepolizumab (SB-240563), a humanized monoclonal antibody to IL-5, in cynomolgus monkeys*. J Allergy Clin Immunol 2001, 108(2): 250-7.

15. Zia-Amirhosseini, P., Minthorn, E., Benincosa, L.J., Hart, T.K., Hottenstein, C.S., Tobia, L.A.P., Davis, C.B. *Pharmacokinetics and pharmacodynamics of SB-240563, a humanized monoclonal antibody directed to human interleukin-5, in monkeys*. J Pharmacol Exp Ther 1999, 291(3): 1060-7.

16. Walls, C.M., Patel, B., Hart, T.K. et al. *SB-240563, an anti-IL-5 monoclonal antibody: Tolerability, activity and pharmacokinetic assessment in patients with asthma*. Eur Respir J 1999, 14(Suppl. 30): Abst P1988.

17. Zia-Amirhosseini, P., Walls, C.M., Patel, B., Cowley, H.C., Minthorn, E., Hottenstein, C.S. *Pharmacokinetics and pharmacodynamics of SB-240563, a humanized monoclonal antibody directed to human interleukin-5, in mild asthmatics*. 100th Annu Meet Am Soc Clin Pharmacol Ther (ASCPT) (March 18-20, San Antonio) 1999, Abst PII-2.

18. Leckie, M.J., ten Brinke, A., Khan, J. et al. *Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response*. Lancet 2000, 356(9248): 2144-8.

19. Leckie, M.J., ten Brinke, A., Lordan, J. et al. *SB 240563, a humanized anti-IL-5 monoclonal antibody. Initial single dose safety and activity in patients with asthma*. Am J Respir Crit Care Med 1999, 159(3, Part 2): A624.

20. Buttner, C., Lun, A., Splettstoesser, T., Kunkel, G., Renz, H. *Monoclonal anti-interleukin-5 treatment suppresses eosinophil but not T-cell functions*. Eur Respir J 2003, 21(5): 799-803.

21. Flood-Page, P.T., Menzies-Gow, A.N., Kay, A.B., Robinson, D.S. *Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway*. Am J Respir Crit Care Med 2003, 167(2): 199-204.

22. Menzies-Gow, A., Flood-Page, P., Sehmi, R. et al. *Anti-IL-5 (mepolizumab) therapy induces bone marrow eosinophil maturational arrest and decreases eosinophil progenitors in the bronchial mucosa of atopic asthmatics*. J Allergy Clin Immunol 2003, 111(4): 714-9.

23. Menzies-Gow, A., Flood-Page, P., Compton, C. et al. *A double blind, placebo-controlled, parallel group study to assess the effect of mepolizumab (humanised monoclonal anti-IL-5 antibody) on bone marrow and peripheral blood eosinophils and eosinophil progenitors in atopic asthmatics*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst H47.

24. Flood-Page, P., Menzies-Gow, A., Phipps, S. et al. *Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics*. J Clin Invest 2003, 112(7): 1029-36.

25. Flood-Page, P., Menzies-Gow, A., Phipps, S. et al. *Anti-IL-5 treatment (mepolizumab) reduces eosinophil-associated TGF-beta: Relationship to deposition of extracellular matrix proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics*. J Allergy Clin Immunol 2004, 113(2, Suppl.): Abst 271.

26. Phipps, S., Flood-Page, P., Menzies-Gow, A. et al. *Anti-IL-5 (mepolizumab) reduces the expression of tenascin, procollagen III and lumican in the reticular basement membrane of human*

atopic asthmatics. J Allergy Clin Immunol [59th Annu Meet Am Acad Allergy Asthma Immunol (AAAAI) (March 7-13, Denver) 2003] 2003, 111(2, Part 2): Abst 839.

27. Phipps, S., Flood-Page, P., Menzies-Gow, A., Ong, Y.E., Kay, A.B. *Intravenous anti-IL-5 monoclonal antibody reduces eosinophils and tenascin deposition in allergen-challenged human atopic skin*. J Invest Dermatol 2004, 122(6): 1406-12.

28. Ong, Y.E., Menzies-Gow, A., Flood-Page, P. et al. *A randomized double-blind, placebo-controlled, parallel group study to assess the effect of mepolizumab (humanized monoclonal anti-IL-5 antibody) on the allergen-induced late-phase skin response*. 21st Congr Eur Acad Allergol Clin Immunol (June 1-5, Naples) 2002, Abst 210.

29. Flood-Page, P., Phipps, S., Menzies-Gow, A., Ong, Y.E., Kay, A.B. *Effect of intravenous administration of an anti-IL-5 mAb (mepolizumab) on allergen-induced tissue eosinophilia, the late-phase allergic reaction and the expression of a marker of repair/remodeling in human atopic subjects*. J Allergy Clin Immunol [59th Annu Meet Am Acad Allergy Asthma Immunol (AAAAI) (March 7-13, Denver) 2003] 2003, 111(2, Part 2): Abst 774.

30. Flood-Page, P., Swenson, C., Faiferman, I. et al. *A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma*. Am J Respir Crit Care Med 2007, Epub ahead of print.

31. Oldhoff, J.M., Darsow, U., Werfel, T. et al. *Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis*. Allergy 2005, 60(5): 693-6.

32. Oldhoff, J.M., Darsow, U., Werfel, T. et al. *No effect of anti-interleukin-5 therapy (mepolizumab) on the atopy patch test in atopic dermatitis patients*. Int Arch Allergy Immunol 2006, 141(3): 290-4.

33. Koury, M.J., Newman, J.H., Murray, J.J. *Reversal of hypereosinophilic syndrome and lymphomatoid papulosis with mepolizumab and imatinib*. Am J Med 2003, 115(7): 587-9.

34. Plotz, S.G., Simon, H.U., Darsow, U. et al. *Use of an anti-interleukin-5 antibody in the hypereosinophilic syndrome with eosinophilic dermatitis*. N Engl J Med 2003, 349(24): 2334-9.

35. Ploetz, S.G., Darsow, U., Simon, H.U., Hein, R., Smith, T., Behrendt, H., Ring, J. *Efficacy of an interleukin-5 blocking monoclonal antibody on eosinophils in hypereosinophilic syndrome*. 22nd Congr Eur Acad Allergol Clin Immunol (June 7-11, Paris) 2003, Abst 256.

36. Ring, J., Plotz, S., Darsow, U., Braun-Falco, M., Simon, H.U., Behrendt, H. *Anti-interleukin-5 in the treatment of hypereosinophilic skin diseases*. 25th Symp Coll Int Allergol (Aug 24-30, Bornholm) 2004, Abst 75.

37. Braun-Falco, M., Fischer, S., Plotz, S.G., Ring, J. *Angiolymphoid hyperplasia with eosinophilia treated with anti-interleukin-5 antibody (mepolizumab)*. Br J Dermatol 2004, 151(5): 1103-4.

38. Hargreave, F.E., Smith-Blackwell, R. *Prednisone-sparing effect of anti-interleukin-5 in asthma*. Annu Conf Br Soc Allergy Clin Immunol (July 12-14, Loughborough) 2004, Abst.

39. Garrett, J.K., Jameson, S.C., Thomson, B. et al. *Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes*. J Allergy Clin Immunol 2004, 113(1): 115-9.

40. Stein, M.L., Villanueva, J.M., Jameson, S.C. et al. *Anti-IL-5 therapy (mepolizumab) in hypereosinophilic syndromes and eosinophilic esophagitis: Cytokine secretion and decreased peripheral blood eosinophilia*. J Allergy Clin Immunol [62nd Annu Meet Am Acad Allergy Asthma Immunol (AAAAI) (March 3-7, Miami Beach) 2006] 2006, 117(2, Suppl. 1): Abst 225.

41. Stein, M.L., Collins, M.H., Villanueva, J.M. et al. *Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis*. J Allergy Clin Immunol 2006, 118(6): 1312-9.

42. Stein, M.L., Villanueva, J.M., Filipovich, A.H., Collins, M.H., Buckmeier, B., Assa'ad, A., Rothenberg, M.E. *Anti-IL-5 therapy (mepolizumab) for eosinophilic esophagitis: Cytokine secretion and decreased peripheral blood and esophageal eosinophilia*. Clin Immunol [Annu Meet Fed Clin Immunol Soc (FOCIS) (June 1-5, San Francisco) 2006] 2006, 119(Suppl. 1): Abst Sa.49.

43. *Intravenous mepolizumab in subjects with hypereosinophilic syndromes (HES) (NCT00086658)*. ClinicalTrials.gov Web site, Last updated April 18, 2006.

44. Gleich, G.J., Schwartz, L.B., Busse, W.W., Huss-Marp, J., Walsh, S.R. *Baseline demographics and disease characteristics of patients with hypereosinophilic syndrome in a placebo-controlled trial evaluating the steroid-sparing effects of the anti-IL-5 monoclonal antibody, mepolizumab*. Blood [48th Annu Meet Am Soc Hematol (Dec 9-12, Orlando) 2006] 2006, 108(11): Abst 4899.

45. Klion, A.D., Rothenberg, M.E., Murray, J.J., Singh, A., Simon, H.U. *Safety and tolerability of anti-IL-5 monoclonal antibody (mepolizumab) therapy in patients with HES: A multicenter, randomized, double-blind, placebo-controlled trial*. Blood [48th Annu Meet Am Soc Hematol (Dec 9-12, Orlando) 2006] 2006, 108(11): Abst 2694.

46. Rothenberg, M.E., Gleich, G.J., Roufosse, F.E., Rosenwasser, L.J., Weller, P.F. *Steroid-sparing effects of anti-IL-5 monoclonal antibody (mepolizumab) therapy in patients with HES: A multicenter, randomized, double-blind, placebo-controlled trial*. Blood [48th Annu Meet Am Soc Hematol (Dec 9-12, Orlando) 2006] 2006, 108(11): Abst 373.

47. Rosenwasser, L.J., Schwartz, L.B., Sheikh, J., Klion, A.D., Rothenberg, M.E. *Corticosteroid-sparing effects of mepolizumab, an anti-interleukin-5 monoclonal antibody, in patients with hypereosinophilic syndrome*. J Allergy Clin Immunol [63rd Annu Meet Am Acad Allergy Asthma Immunol (AAAAI) (Feb 23-27, San Diego) 2007] 2007, 119(1, Suppl.): Abst 628.

48. Weller, P.F., Gleich, G., Busse, W.W., Rothenberg, M.E. *Effects of mepolizumab, an anti-interleukin-5 monoclonal antibody, on blood eosinophil counts in patients with hypereosinophilic syndrome*. J Allergy Clin Immunol [63rd Annu Meet Am Acad Allergy Asthma Immunol (AAAAI) (Feb 23-27, San Diego) 2007] 2007, 119(1, Suppl.): Abst 821.

49. Shear, N., Gleich, G., Leiferman, K., Ring, J. *Rationale and design of a placebo-controlled trial to evaluate the steroid-sparing effects of anti-IL5 monoclonal antibody (mepolizumab): Focus on cutaneous outcomes in patients with hypereosinophilic syndrome (HES)*. J Am Acad Dermatol [65th Annu Meet Am Acad Dermatol (AAD) (Feb 2-7, Washington, D.C.) 2007] 2007, 56(2, Suppl. 2): Abst P716.

50. *Open-label extension of intravenous mepolizumab in patients with hypereosinophilic syndrome (NCT00097370)*. ClinicalTrials.gov Web site, September 28, 2007.

51. *Anti-interleukin-5 (IL-5) study for hypereosinophilic syndrome (NCT00266565)*. ClinicalTrials.gov Web site, September 28, 2007.

52. *An evaluation of mepolizumab in therapy of eosinophilic esophagitis in adult patients (NCT00274703)*. ClinicalTrials.gov Web site, September 28, 2007.

53. *Intravenous mepolizumab in children with eosinophilic esophagitis (NCT00358449)*. ClinicalTrials.gov Web site, September 28, 2007.

54. *Mepolizumab as a steroid-sparing treatment option in the Churg Strauss syndrome (MATOCSS) (NCT00527566)*. ClinicalTrials.gov Web site, September 28, 2007.

55. *The prednisone-sparing effect of anti-IL-5 antibody (SB-240563) (NCT00292877)*. ClinicalTrials.gov Web site, September 28, 2007.

56. *Compassionate use of mepolizumab in subjects with hypereosinophilic syndrome (HES) (NCT00244686)*. ClinicalTrials.gov Web site, September 28, 2007.