Pharmacokinetics and Pharmacodynamics of SB-240563, a Humanized Monoclonal Antibody Directed to Human Interleukin-5, in Monkeys


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ABSTRACT

The pharmacokinetics (PK) of SB-240563 have been investigated after i.v. and s.c. administration to cynomolgus monkeys. Approximately linear PK was observed following i.v. administration over a 6000-fold dose range (0.05–300 mg/kg). After i.v. dosing, SB-240563 concentration declined in a biexponential manner with a mean terminal half-life of 13 ± 2 days. The plasma clearance and volume of distribution at steady state were 0.2 ml/h/kg and 70 ml/kg, respectively. Following s.c. administration, SB-240563 was completely absorbed into the systemic circulation. Because interleukin-5 is known to stimulate production, activation, and maturation of eosinophils, eosinophil counts were measured to assess pharmacologic activity of SB-240563. The maximal response (81–96% decrease in eosinophil count relative to baseline) following a single s.c. administration occurred at 3 weeks postdosing. Suppression of eosinophil count also was observed following multiple monthly administrations of SB-240563 to monkeys. The pharmacokinetic/pharmacodynamic relationship was generally well described with an indirect pharmacologic response model with an estimated IC50 value of 1.43 μg/ml. The combination of a low IC50 value for reduction of circulating eosinophils and a long terminal half-life suggests the possibility of an infrequent dosing regimen for SB-240563 for treatment of diseases associated with increased eosinophil function such as asthma.

SB-240563 is a humanized monoclonal antibody (IgG1) with specificity for human interleukin-5 (IL-5). IL-5 is a cytokine produced primarily by T lymphocytes and mast cells (Takatsu et al., 1988; Galli et al., 1994). Binding to the IL-5 receptor on eosinophils, IL-5 plays an essential role in the differentiation and functional maturation of eosinophils (Dent et al., 1990; Sanderson, 1990; Tominaga et al., 1991; Takatsu et al., 1994). In addition to IL-5, other cytokines such as IL-3 and granulocyte macrophage-colony stimulating factor influence the development and maturation of eosinophils in the bone marrow, and postmitotic functional activation of eosinophils in tissues (Saito et al., 1988; Clutterbuck et al., 1989; Goodall et al., 1993). Even though IL-3 and granulocyte macrophage-colony stimulating factor play a role in the proliferation and commitment of progenitors to the eosinophil lineage, IL-5 is necessary and sufficient for eosinophil development (Sanderson, 1990, 1991). IL-5 is overexpressed in many eosinophil-associated diseases (Owen et al., 1989, 1990; Sanderson, 1992) and development of profound eosinophilia has been observed in IL-5 transgenic mice (Dent et al., 1990; Tominaga et al., 1991). Thus, IL-5 appears to play essential roles in promoting the production and function of eosinophils in vivo. This cytokine also has been shown to enhance survival of mature eosinophils (Tai et al., 1991).

Activated eosinophils release proinflammatory molecules and cytotoxic agents that are not only toxic to helminthic parasites but also can cause tissue damage in allergic inflammations such as asthma (Lopez et al., 1988; Bousquet et al., 1990; Reed, 1994). Antibodies to IL-5 have been shown to block peripheral eosinophilia in recombinant IL-2-treated mice (Yamaguchi et al., 1990) and to be beneficial in reducing eosinophil recruitment into the lung in murine models of allergic disease (Hamelmann et al., 1997).

In this article, the pharmacokinetics (PK) of SB-240563 following single or repeated i.v./s.c. administrations to monkeys has been described. Additionally, the bioavailability of SB-240563 and its effect on eosinophils following s.c. administration are discussed. The monkey was chosen as the appropriate preclinical species because SB-240563 cross-reacts with monkey IL-5 but not with recombinant rat or guinea pig IL-5. The presented data have been collated

ABBREVIATIONS: IL-5, interleukin 5; PK, pharmacokinetic(s); ECL, electrochemiluminescent; PD, pharmacodynamic(s); Cmax, maximum plasma concentration; Tmax, time at which Cmax occurs; AUC, area under the plasma concentration-time curve; Vss, volume of distribution at steady state; CL, clearance; T1/2, terminal half-life.
from four different preclinical studies conducted with SB-240563.

**Materials and Methods**

**Chemicals.** SB-240563 is a Chinese hamster ovary-derived IgG1 humanized monoclonal antibody directed to human IL-5. Drug was supplied as a sterile solution in phosphate-buffered saline. The concentration of SB-240563 solutions (original or diluted) were confirmed by UV absorption spectrometry. The mouse monoclonal antibody to human IL-5 was purchased from Zymed Laboratories Inc. (South San Francisco, CA). The ruthenium label was from IGEN, Inc. (Rockville, MD). Streptavidin-coated microbeads (2.8-μm paramagnetic polystyrene beads) were purchased from DYNA, Inc. (Great Neck, NY). Assay buffer for the Origen analyzer was purchased from IGEN, Inc. Tween 20 was purchased from Sigma Chemical Co. (St. Louis, MO). All other chemicals were of reagent grade or better.

**Electrochemiluminescent (ECL) Immunoassay.** Plasma concentrations of SB-240563 were determined with an ECL immunoassay. Briefly, plasma samples were diluted to within the calibration range and reacted with biotin-conjugated human IL-5 and paramagnetic microbeads conjugated to streptavidin. The microbeads were then reacted with a ruthenium-labeled mouse monoclonal antibody to human IgG1 (Fc CH2 region), and the ECL response was recorded on an Origen analyzer. The lower limit of quantification of the assay was 50 ng/ml.

Reproducibility and accuracy of the assay were determined by spiking control monkey plasma with SB-240563 and analyzing replicates (n = 6, stored frozen as authentic plasma samples at −20°C or below). These samples were stable for at least the time period spanning the collection and analysis of authentic plasma samples. The within-run and between-run coefficients of variation ranged from 2.3 to 9.5% and 1.9 to 5.6%, respectively, in the concentration range of 10 to 5000 ng/ml. Average assay accuracy ranged from 93.7 to 111%.

**Animal Husbandry.** Cynomolgus monkeys weighing 2 to 5 kg were used. Animals were housed in stainless steel cages in a controlled environment (68–76°F; 40–70% relative humidity) on a 12-h light/dark cycle in the Department of Laboratory Animal Sciences at SmithKline Beecham. Approximately six to eight biscuits of Purina certified monkey chow or monkey diet 5038 (PMI Feeds, Inc., St. Louis, MO) were provided to each monkey twice a day and filtered tap water was available ad libitum from an automatic watering system. Additionally, a daily allotment of fresh fruit was offered to each monkey. On the day of dosing, food was withdrawn at least 1 h before drug administration and then again provided 6 h after drug administration.

**Dose Administration and Blood Samples.** In a single dose i.v. study, two dose levels of 3 and 300 mg/kg (0.2 ml/kg bolus and 20 ml/kg at 10 ml/min, respectively) were administered on study day 1. Two cynomolgus monkeys (one male and one female) were used for each dose group. Blood samples were obtained before and immediately after dose administration, and at 3- and 6-h postdosing on day 1. Additional samples were collected on days 3, 8, 15, and 28.

In a repeat-dose study where two monthly doses were given, four dose levels (0.05, 0.5, 5.0, and 50.0 mg/kg with a 2.0 ml/kg dose volume) were injected i.v. on days 1 and 29. Four cynomolgus monkeys (two males and two females) were used for each dose group. Blood samples were obtained before dose administration and at 5-min and 3- and 6-h postdosing. Additional samples were collected on days 2, 7, 13, 27, 29 (5 min before administration of the second dose), 30, 35, 41, 56, 77, 99, and 120.

In a 6-month repeat-dose study, six cynomolgus monkeys (three males and three females) were injected with 10 mg/kg (injection volume of 0.5–1.0 ml given at two injection sites each) monthly doses of SB-240563 via the s.c. route. Blood samples for PK analysis were obtained before each dose administration, and at 24 h and 1 week following the first and fifth doses of SB-240563. Eosinophil count was measured before each dose administration.

In a separate crossover i.v./s.c. study, four female cynomolgus monkeys each received a 1 mg/kg dose of SB-240563 that was administered as an i.v. bolus (total injection volume of 0.6 ml). Approximately 3 months after the administration of the i.v. dose, these monkeys each received a second 1 mg/kg dose of SB-240563 administered s.c.. For the i.v. arm of this study, blood sample collection was performed at the following times postdosing: 0 (predose), 0.5, 0.5, 1, 2, 4, 6, 8, 24, 72, and 120 h, and at 1, 2, 3, 4, 5, 6, and 7 weeks. For the s.c. arm of the study, blood sample collection was performed at the following times postdosing: 0 (predose), 2, 4, 6, 8, 24, 48, 72, and 96 h, and at 1, 2, 3, 4, 5, 6, and 8 weeks. Additional blood samples were collected for hematology before dose administration and −10-weeks postdosing for the i.v. arm, and before dosing and at 1, 3-, 5-, 8-, and 14-weeks postdosing for the s.c. arm.

**Pharmacokinetics and Pharmacodynamics (PD).** Noncompartmental PK analysis of SB-240563 plasma concentration-time data was performed using traditional methods (Chiu, 1978). The following PK parameters are reported: maximum observed plasma concentration (Cmax), the time to reach Cmax (Tmax), the area under the plasma concentration-time curve from time zero to infinity [AUC(0–inf)] and apparent terminal elimination half-life (T1/2). In addition, the following parameters were calculated from data obtained following i.v. administration of SB-240563: plasma clearance (CL) and volume of distribution at steady state (Vss). Compartamental analysis of concentration-time data obtained following i.v. administration was performed with a two-compartment model in the curve-fitting program MODFIT (Allen, 1990).

Bioavailability of SB-240563 following s.c. administration in the crossover study was computed as follows:

\[
F = \frac{AUC_{iv} - AUC_{sc}}{AUC_{iv} - AUC_{sc}} \times \frac{Dose_{iv}}{Dose_{sc}}
\]

To assess the effect of SB-240563 on eosinophils, eosinophil count data obtained following a single s.c. administration were plotted versus time. A time lag was evident between the measured maximal decrease in SB-240563 concentration and the observed maximal decrease in eosinophil count data. This delayed effect is consistent with the TABLE 1

<table>
<thead>
<tr>
<th>Monkey</th>
<th>Volume/F</th>
<th>k_{a1} (day⁻¹)</th>
<th>k_{e1} (day⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>92.5 (6.2)</td>
<td>1.99 (20.5)</td>
<td>0.0288 (15.8)</td>
</tr>
<tr>
<td>2</td>
<td>73.5 (4.0)</td>
<td>3.28 (13.1)</td>
<td>0.0286 (10.8)</td>
</tr>
<tr>
<td>3</td>
<td>100.7 (6.0)</td>
<td>4.69 (19.2)</td>
<td>0.0393 (17.7)</td>
</tr>
<tr>
<td>Mean</td>
<td>89.1 (15.8)</td>
<td>3.24 (11.1)</td>
<td>0.0341 (0.0057)</td>
</tr>
</tbody>
</table>

* k_{a1} is the first-order rate constant for the absorption of drug into the systemic circulation.

* k_{e1} is the first-order rate constant for the elimination of drug from the systemic circulation.

<table>
<thead>
<tr>
<th>Monkey</th>
<th>k_{m}</th>
<th>k_{out} (day⁻¹)</th>
<th>IC_{50}</th>
<th>10⁴ count/1/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.06 (24)</td>
<td>0.19 (22)</td>
<td>1.51 (22)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.21 (37)</td>
<td>0.31 (36)</td>
<td>1.46 (27)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.04 (27)</td>
<td>0.15 (26)</td>
<td>1.62 (27)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.19 (217)</td>
<td>0.65 (217)</td>
<td>1.13 (32)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.13 (0.09)</td>
<td>0.33 (0.23)</td>
<td>1.43 (0.21)</td>
<td></td>
</tr>
</tbody>
</table>
mechanism of action of SB-240563, i.e., its effect on eosinophils via binding to IL-5. Therefore, the PK/PD relationship was described with an indirect response model with inhibition of the production of response (eosinophils) via the inhibition of $k_{in}$ (eq. 2) (Dayneka et al., 1993):

$$\frac{dR}{dt} = k_{in} \left( 1 - \frac{C_p}{IC_{50} + C_p} \right) - k_{out} \cdot R(t)$$ (2)

where $R$ is the measured response (eosinophil count), $k_{in}$ is the zero-order constant for production of response, $k_{out}$ is the first-order rate constant for loss of response, $IC_{50}$ is the concentration that produces 50% of maximal inhibition in the eosinophil production rate, and $C_p$ is the predicted SB-240563 plasma concentration. The above-mentioned PD model assumes that $k_{in}$ and $k_{out}$ completely account for production and loss of response. Equation 2 assumes maximal response is one or complete suppression (i.e., 100% reduction in eosinophil count). Inclusion of an $I_{max}$ term, the maximal inhibitory capability of the drug (Sharma and Jusko, 1996), did not improve the quality of the fit and $I_{max}$ was estimated as one.

Before the PK/PD analysis, a one-compartment model with first-order absorption was fitted to the observed SB-240563 concentration-time data with nonlinear regression analysis (WinNonlin, version 1.1; Apex, NC). The PK parameters obtained from this exercise were used to predict drug concentrations ($C_p$) for the PD model. The indirect response model was fitted to the eosinophil time course data obtained following a single s.c. dosing with nonlinear regression analysis. For these analyses, uniform weighting and the Gauss-Newton (Levenberg and Hartley) minimization algorithm were used. The goodness of fit was judged by examination of the predicted values, residual plots, and precision of parameter estimates (%S.E.).

The mean PK parameters obtained from the modeling exercise (Table 1) were used to simulate (WinNonlin Pro., version 1.5; Apex, NC) an average concentration-time profile following multiple s.c. injections of a 10 mg/kg dose. Additionally, the mean parameters obtained following the PK/PD modeling of the single-dose data (Table 2) were used to simulate (WinNonlin Pro., version 1.5; Apex, NC) an average eosinophil count-time profile following multiple dosing of SB-240563.

**Results**

Following i.v. administration, SB-240563 exhibited approximately dose-proportional PK over the dose range from 0.05 to 300 mg/kg. After the injection, concentrations declined in a biexponential manner with an average initial half-life of 12.9 ± 9.4 h (Figs. 1 and 2). The second phase of
the concentration-time profile accounted for the majority of AUC (≥86%). SB-240563 concentration-time profiles were similar between male and female monkeys (Fig. 1). The mean CL and $V_{ss}$ were relatively constant across the examined dose groups (0.05–300 mg/kg) and ranged from 0.157 to 0.217 ml/h/kg and 65.6 to 82.1 ml/kg, respectively (Tables 3–5). The mean overall terminal half-life following i.v. dosing was 13.0 ± 2.2 days.

After s.c. dosing, maximal concentrations were observed 2- to 4-days postinjection (Table 4). Following the absorption phase, SB-240563 concentration appeared to decline in a mono-exponential manner with an apparent half-life (14.5 ± 3.8 days) similar to that observed after i.v. dosing (Fig. 2 and Table 4). SB-240563 appeared to be completely absorbed ($F = 1.18 ± 0.16$) following s.c. administration (Table 4).

Following a single s.c. injection, peripheral eosinophil count decreased in a time-dependent manner (Fig. 3). The maximum percentage of decrease (81 to 96%) relative to baseline (just before administration of the s.c. dose) was observed at 3-weeks postdosing, whereas maximal concentrations were observed at 2- to 4-days postdosing. Thus, an inhibitory indirect model with inhibition of production of response (eosinophil count) was used to describe the data.

**Fig. 2.** Mean concentration-time profiles following i.v. (○) or s.c. (●) administrations of a single 1 mg/kg dose of SB-240563 to cynomolgus monkeys.

**TABLE 3**
Mean PK data following single i.v. administration of SB-240563 to cynomolgus monkeys

<table>
<thead>
<tr>
<th>Dose</th>
<th>300 mg/kg$^{a,b}$</th>
<th>3 mg/kg$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{max}$ (µg/ml)</td>
<td>6700</td>
<td>89.1</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$ (µg·h/ml)$^c$</td>
<td>1,405,000</td>
<td>14,600</td>
</tr>
<tr>
<td>$T_{1/2}$ (days)</td>
<td>11.7</td>
<td>11.2</td>
</tr>
<tr>
<td>CL (ml/h/kg)</td>
<td>0.217</td>
<td>0.208</td>
</tr>
<tr>
<td>$V_{ss}$ (ml/kg)</td>
<td>74.6</td>
<td>82.1</td>
</tr>
</tbody>
</table>

$^a$ Actual dose = 304 mg/kg.
$^b$ n = 1/sex/group; sexes combined because no marked differences between sexes.
$^c$ AUC$_{0-\infty}$ estimated with data obtained on study days 1–28.

**TABLE 4**
Individual and mean (S.D.) PK parameters obtained with noncompartmental analysis of concentration-time data following i.v. and s.c. dosing of 1 mg/kg of SB-240563 to female monkeys

<table>
<thead>
<tr>
<th>Monkey</th>
<th>Intravenous</th>
<th>Subcutaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C_{max}$ µg/ml</td>
<td>CL ml/h/kg</td>
</tr>
<tr>
<td>1</td>
<td>28.80</td>
<td>0.155</td>
</tr>
<tr>
<td>2</td>
<td>26.12</td>
<td>0.132</td>
</tr>
<tr>
<td>3</td>
<td>27.14</td>
<td>0.165</td>
</tr>
<tr>
<td>4</td>
<td>28.72</td>
<td>0.174</td>
</tr>
<tr>
<td>Mean</td>
<td>27.70</td>
<td>0.157</td>
</tr>
</tbody>
</table>

(S.D.) (1.30) (0.018) (5.0) (1.5) (1.87) (23.0) (3.8) (0.16)
A one-compartment PK model with first-order absorption fitted the concentration-time profiles obtained following s.c. administration reasonably well as indicated by the low standard errors of the parameter estimates (%S.E. < 21%) (Table 1). As evidenced by the close agreement between the observed and predicted eosinophil counts, the indirect response model as described by eq. 2 generally described the PD data well (Fig. 4, A–D). The standard errors associated with the parameter estimates were <40% in three of four animals (Table 2). In one animal, the standard errors were large compared with the remaining animals; nonetheless, the model appeared to adequately describe the data in this animal (Fig. 4D) and the parameter estimates were similar to those obtained in the other animals. An IC$_{50}$ value of 1.43 μg/ml was observed for reduction in eosinophil count by SB-240563 (Table 2). This value is 2- to 4-fold lower than the observed plasma concentrations during the first month after i.v. or s.c. administration of a 1-mg/kg dose. During the first 2 months after a single s.c. administration of 1 mg/kg SB-240563, eosinophil counts were suppressed to ~30–70% of the baseline level (Fig. 3).

Following six monthly repeated administrations of SB-

### Table 5
Mean (S.D.) PK data obtained following administration of repeated i.v. doses of SB-240563 to cynomolgus monkeys

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>$C_{\text{max}}$ (μg/ml)</th>
<th>$AUC_{(0-\infty)}$ (μg · h/ml)</th>
<th>$T_{1/2}$ (days)</th>
<th>CL (ml/h/kg)</th>
<th>$V_d$ (ml/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>1220 (141)</td>
<td>310,466 (25,935)</td>
<td>13.3 (0.6)</td>
<td>0.162 (0.014)</td>
<td>72.4 (5.6)</td>
</tr>
<tr>
<td>5</td>
<td>137 (19)</td>
<td>27,961 (3280)</td>
<td>11.9 (2.7)</td>
<td>0.181 (0.021)</td>
<td>69.8 (9.9)</td>
</tr>
<tr>
<td>0.5</td>
<td>13.0 (1.5)</td>
<td>2991 (383)</td>
<td>12.5 (1.3)</td>
<td>0.169 (0.022)</td>
<td>70.9 (3.8)</td>
</tr>
<tr>
<td>0.05</td>
<td>1.2 (0.1)</td>
<td>251 (34)</td>
<td>9.7 (0.9)</td>
<td>0.203 (0.031)</td>
<td>66.2 (4.3)</td>
</tr>
</tbody>
</table>

$a$ $n = 5$ two/sext/group; sexes combined because no marked differences between sexes.  
$b$ First dose of drug administered on day 1; second dose administered on day 29.  
$c$ $AUC_{(0-\infty)}$ after first dose was estimated with data obtained on study days 1–27 and after the second dose with data obtained on days 29–120.  
$d$ $n = 5$ three for this group because $AUC$ and $T_{1/2}$ could not be determined for one male animal.

**Fig. 3.** Eosinophil count versus time profiles following s.c. administration of a single 1 mg/kg dose of SB-240563 to cynomolgus monkeys. ○, eosinophil data from monkey 1; ■, data from monkey 2; △, data from monkey 3, and ●, data from monkey 4.
240563 at 10 mg/kg, the observed eosinophil counts were persistently <20% of the baseline levels over the entire 6-month dosing period (Fig. 5). The estimated PK and PD parameters obtained from modeling the concentration and eosinophil count data following a single s.c. administration of drug were used to simulate concentration and eosinophil count data following s.c. administration of six monthly 10-mg/kg doses. Although a significant suppression in eosinophil count was observed following multiple dose administration, the PD model developed with the single-dose data predicted a somewhat greater decrease in eosinophil count after administration of all six doses, including the first dose. This observation may reflect a higher IC₅₀ value in the monkeys used in the repeat-dose study.

**Discussion**

Following i.v. administration, SB-240563 exhibited relatively low clearance and volume of distribution. The observed volume of distribution (66 to 82 ml/kg) was slightly higher than the typical plasma volume (45 ml/kg) but lower than the typical extracellular fluid volume (200 ml/kg) in monkeys (Davies and Morris, 1993). The mean terminal half-life values were similar following i.v. (~13 day) and s.c. (14.5 day) administrations. These half-life values are within the range of values (9–30 days) reported for other monoclonal antibodies in the monkey (Ehrlich et al., 1987; Muraszko et al., 1993; Cavacini et al., 1994; Davis et al., 1995). SB-240563 was completely bioavailable following s.c. administration.

Consistent with similar results obtained following i.v. administration of SB-240653 (Hart et al., 1998), s.c. administration of a relatively low dose of 1 mg/kg was effective in reducing circulating eosinophils. The drop in circulating eosinophils does not appear to be due to redistribution of eosinophils because complete histopathology assessments were conducted with no remarkable accumulation or absence of eosinophils in any organs (data not shown). Thus, the drop in circulating eosinophils appears to represent an absence of or a decreased signal for eosinophil recruitment from the bone marrow to areas in the body where they may be needed.

A time delay in the manifestation of maximal effect (decrease) on basal eosinophil count was noted relative to the observed time for maximal drug concentrations. The relationship between drug concentrations and eosinophil count was generally well described with an indirect PD response model. A steady-state concentration of ~1.5 μg/ml SB-240563 would decrease and sustain peripheral eosinophil counts by 50% relative to that observed before drug administration. It is
worth noting that the IC$_{50}$ is a term that not only reflects the binding equilibrium between the antibody and IL-5 but also the interaction of IL-5 with its receptor on the eosinophil surface. The $k_{\text{out}}$ represents the rate constant for the elimination of eosinophils from the body. Based on the estimated value of $k_{\text{out}}$, the elimination half-life of eosinophils in monkey blood is 2.1 days (~50 h). In human blood, eosinophils have a half-life of 18 h (Steinbach et al., 1979) and we suspect that their half-life in monkey would be similar to that in humans. Considering the observed variability (up to 5-fold) in baseline eosinophil count, which is a reflection of variability in $k_{\text{in}}$ and $k_{\text{out}}$, the estimated half-life of 2 days is a reasonable estimate of the monkey eosinophil half-life.

The combination of the availability of SB-240563 via the s.c. route, its long terminal half-life, and low IC$_{50}$ value (~1–2 µg/ml) for reduction of circulating eosinophils make this compound a viable candidate for treatment of diseases associated with exaggerated eosinophil function, e.g., asthma. The link between depression of eosinophil count following administration of SB-240563 and pulmonary function tests is currently being investigated in clinical trials.

References
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