

Safety and Pharmacokinetics of an Intramuscular Monoclonal Antibody (SB 209763) against Respiratory Syncytial Virus (RSV) in Infants and Young Children at Risk for Severe RSV Disease

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We conducted a multicenter, double-blind, placebo-controlled, randomized trial of a humanized monoclonal antibody against a respiratory syncytial virus (RSV) fusion protein (SB 209763) to evaluate its safety, pharmacokinetics, and fusion inhibition and neutralization titers. Forty-three infants who were either delivered prematurely (≤ 35 weeks' gestation) or exhibited bronchopulmonary dysplasia were administered either single or repeat (two doses, 8 weeks apart) intramuscular injections of SB 209763 at a concentration of 0.25, 1.25, 5.0, or 10.0 mg/kg or of a placebo. Four of 229 adverse events were considered related to the study drug, including purpura ($n = 3$) and thrombocytosis ($n = 1$). No subject developed a detectable level of anti-SB 209763 antibody. Approximately 1 week after administration of the second dose of SB 209763 at 10 mg/kg, the mean plasma concentration ($n = 9$) was 68.5 $\mu\text{g/ml}$. The terminal half-life ($T_{1/2}$) determined by noncompartmental analysis ranged from 22 to 50 days. The population pharmacokinetics for SB 209763 following intramuscular administration was appropriately described by a one-compartment model with first-order input and elimination. Higher values for clearance and volume of distribution at steady state were observed for younger patients, with values decreasing to 0.143 (ml/h)/kg and 161 mL/kg, respectively, by a mean age of 298 days (~ 10 months). The mean $T_{1/2}$ of SB 209763 for the study population was 32.5 days. No other factor (dose, weight, gender, race, premature birth, or bronchopulmonary dysplasia) was observed to alter the population pharmacokinetics of SB 209763 in this study of infants and young children. The mean neutralization titer on day 6 was 286, and the mean fusion inhibition titer was 36. At least 57% of subjects dosed at 1.25 to 10.0 mg of SB 209763 per kg of body weight who were seronegative at baseline experienced a fourfold or greater increase in fusion inhibition titer. Nine RSV infections were documented during the 16-week course of the study; the numbers of RSV infections were similar for the different regimens, including the placebo. The doses of SB 209763 studied may have been insufficient to confer protection against RSV lower respiratory tract disease; these results suggest that additional trials using higher doses of monoclonal antibody for immunoprophylaxis should be considered.

Respiratory syncytial virus (RSV) remains one of the most important infectious causes of hospitalization of infants and young children (8). Seasonal outbreaks of RSV disease result in infection in over 90% of children by 2 years of age. The outcome varies from a mild upper respiratory tract illness in approximately 75% of infected infants and children to a severe, life-threatening disease in a small percentage of infected patients. Infants at particular risk of severe disease include prematurely born children, children born with congenital heart disease, and children with chronic lung disease, particularly bronchopulmonary dysplasia (BPD) (10).

Despite the importance of RSV as a pathogen in the pediatric age group, options for treatment and prevention of RSV disease are limited. Active immunization to prevent severe RSV disease has not yet proven successful (7). Two clinical trials with a polyclonal, hyperimmune RSV globulin have demonstrated safety and efficacy for prophylaxis in carefully selected children at increased risk for severe RSV infection (6, 13). The results of these clinical trials led to Food and Drug Administration licensure of this RSV antibody-enriched immune globulin in January 1996.

A second-generation product for immunoprophylaxis against RSV disease is a monoclonal antibody directed against a highly immunogenic RSV surface glycoprotein (12, 15). Monoclonal antibodies to the fusion protein have been shown to be effective in preventing RSV infection in animal models (3, 17–19) and in humans (9). During the 1995–1996 respiratory virus season, a multicenter, double-blind, placebo-controlled,

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TABLE 1. Randomization of infants

Inoculum (dose, mg/kg)		No. of subjects
First	Second	
SB 209763 (0.25)	SB 209763 (0.25)	6
SB 209763 (1.25)	SB 209763 (1.25)	9
SB 209763 (5.0)	SB 209763 (5.0)	8
SB 209763 (10.0)	SB 209763 (10.0)	10
Placebo	SB 209763 (0.25)	2
Placebo	SB 209763 (1.25)	2
Placebo	SB 209763 (5.0)	3
Placebo	SB 209763 (10.0)	3 ^a

^a Includes one subject who was withdrawn from the study prior to receiving the second dose.

randomized trial was conducted with SB 209763, a humanized murine monoclonal antibody directed against the RSV fusion glycoprotein. The primary objectives of this phase I trial were to evaluate the safety and pharmacokinetics of single and repeat intramuscular (i.m.) doses of SB 209763 in a pediatric population at risk for severe RSV disease. The secondary objectives included measurement of fusion inhibition titers and neutralization titers and assessment of anti-idiotypic anti-SB 209763 antibodies.

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MATERIALS AND METHODS

Patients. Infants and young children less than 37 months of age were eligible for enrollment at one of the seven participating sites if they were born prematurely (≤ 35 weeks), with a chronological age of ≤ 6 months, and/or had a history of BPD. Eligible subjects were required to have a life expectancy of at least 6 months. The protocol was approved by the institutional review board at each site, and informed consent was obtained from all participating families. Exclusion criteria included known preexisting heart, liver, or renal disease; a recognized immune system abnormality; severe respiratory illness requiring assisted ventilation; or previous gamma globulin infusion.

Randomization. Participants were randomly assigned to one of four monoclonal antibody dosage groups (0.25, 1.25, 5.0, or 10.0 mg of SB 209763 per kg of body weight) or to a placebo group according to a randomization schedule provided by SmithKline Beecham. Each dosage group included at least eight subjects; within each dosage group, at least six infants received SB 209763 at the first administration while at least two subjects received the placebo (Table 1). Eight weeks after administration of the first dose, a second i.m. injection was given. Subjects who were randomized to received the monoclonal antibody initially received a repeat dose identical to the initial dose. Subjects who initially received the placebo were crossed over and received SB 209763 at a dosage consistent with that for the group to which they were initially assigned.

The 8-week dosing interval was identical to the dosing interval examined in an earlier study of adults (unpublished data). Results from this study and an additional trial involving adults demonstrated that plasma levels of SB 209763 remain above 10 $\mu\text{g/ml}$ 8 weeks after i.m. administration for at least some of the dosages used in the present study (4). This concentration has been associated with protection in murine and rat models of RSV infection *in vivo* (19).

Study drug. SB 209763 lyophilate (lot no. U-94045), reconstituted with sterile water to a concentration of 45 mg/ml, and a placebo (a solution containing all components of the active preparation except SB 209763) were used in this study. Doses of 0.25 and 1.25 mg of SB 209763/kg were administered as single i.m. injections into one thigh muscle. Doses of 5.0 and 10.0 mg/kg were divided and administered as separate injections into each thigh muscle to maintain reasonable injection volumes. Placebo subjects were injected with a volume of placebo equivalent to the volume of active drug that would have been received by a subject of identical weight assigned to that dosage group. At the highest dose, a volume of 0.22 ml of either active drug or placebo per kg was administered.

Higher doses of SB 209763 were not administered within a randomization regimen until at least three subjects within the regimen's dosage group had received a lower dose and were evaluated through 24 h postdosing (thus ensuring that at least two of the three dosed individuals received the active drug). This evaluation included an assessment of the results of laboratory studies for patient safety, conducted 24 h after injection of the study medication. The following laboratory tests were performed: complete blood count; differential blood count; platelet count; determination of alanine aminotransferase, aspartate aminotrans-

ferase, total bilirubin, alkaline phosphatase, and creatinine levels in serum; and urinalysis. Dose escalation was halted and reevaluated in a consultation with the study sponsor upon occurrence of a serious adverse response.

Safety parameters. Screening visits included a medical history and physical examination. A physical examination was performed and blood and urine samples were collected for laboratory tests for determination of patient safety prior to administration of each dose of the study medication. Blood and urine samples were also obtained for laboratory testing at 24 h and 2 weeks after administration of the first dose and at 2 weeks after administration of the second dose of the study medication. A physical examination was also performed at the 2-week-postdose visit. Injection sites were examined for local reactions at approximately 5 min, 2 h, and between 4 and 7 days after each injection. Vital signs were measured prior to and at 15, 30, 45, 60 and 120 min following administration of each dose of the study drug.

Blood samples were obtained prior to and approximately 6 days and 2 and 8 weeks following administration of each dose for assessment of the presence of anti-SB 209763 antibodies. Plasma was analyzed for anti-SB 209763 antibodies by sandwich enzyme-linked immunosorbent assay. Serial dilutions of plasma samples were added to microtiter plates coated with SB 209763. Anti-SB 209763 antibodies present in plasma were allowed to bind; the sandwiched anti-SB 209763 was detected by binding of biotin-labeled SB 209763 followed by the use of an avidin-biotinylated alkaline phosphatase system. The positive controls, a bovine monoclonal anti-idiotypic antibody and a rabbit polyclonal anti-SB 209763 antibody, were included in each assay.

Subjects were monitored during the RSV season for the presence of RSV disease symptoms through biweekly telephone contacts. If a subject developed respiratory symptoms, attempts were made to obtain a nasopharyngeal aspirate, which was tested for the presence of RSV by antigen detection assay. Samples testing positive were transported to a central processing laboratory for RSV culture and titer determination. Pairs of tubes of Hep2 cells (in 1.5 ml of basal medium [Eagle minimal medium supplemented with 2% fetal calf serum, 2% L-glutamine, and 1% penicillin-streptomycin-Fungizone]) were each inoculated with 0.2 ml of 10^0 to 10^{-6} dilutions of the nasopharyngeal aspirate specimen. The inoculated cells were then incubated at 34°C for 3 weeks and observed three times per week for development of cytopathic effects. The maintenance medium was changed two times per week. Observed virus titers were expressed as 50% tissue culture infective doses per milliliter.

Pharmacokinetic parameters. For analysis of plasma SB 209763 concentrations, venous blood samples were collected in sodium citrate tubes prior to administration of the first dose and at approximately 24 h, 6 days, and 2 and 8 weeks after the first dose of study medication was administered. The 8-week sample was drawn just prior to administration of the second dose. Blood samples were also drawn at approximately 6 days and 2 and 8 weeks after administration of the second dose of the study medication.

Plasma SB 209763 concentrations were quantified by an enzyme-linked immunosorbent assay based on the simultaneous binding of SB 209763 to two bovine anti-idiotypic monoclonal antibodies, B11 and B12 (3). Briefly, SB 209763 was captured from plasma in a microtiter plate to which B11 had been bound. The B11-SB 209763 complex was then probed with biotinylated B12, forming a sandwich which was detected with horseradish peroxidase-conjugated streptavidin. The lower limit of detection of SB 209763 in 10% (vol/vol) phosphate saline buffer was 0.030 $\mu\text{g/ml}$. A low predose response was noted in one patient in the 1.25-mg/kg group. However, this value had no effect on the data analysis, since all postdosing SB 209763 concentrations in this patient were at least 30-fold higher than the predose level. Typical within- and between-run precision values (coefficients of variation) for this assay were 2.8 to 8.4% and 0.8 to 12.9%, respectively. Typical average accuracy values were 94 to 105%.

Concentration-time data for each subject in each dose group were analyzed by noncompartmental methods. The area under the plasma concentration-time curve from immediately predose (time zero) to the last quantifiable concentration (AUC_{0-t}), the peak concentration of SB 209763 (C_{max}), and the apparent terminal elimination phase half-life ($T_{1/2}$) were determined for both the first and second doses of SB 209763. The AUC for the first dose was calculated by using samples obtained prior to administration of the second dose. The AUC following administration of the second dose (the sum of the AUC for the second dose plus that remaining from the first dose) was calculated by using blood samples obtained immediately before administration of the second dose as well as samples obtained at 6 days and at 2 and 8 weeks after administration of the second dose. The apparent terminal elimination phase rate constant, λ_z , was derived from the log-linear disposition phase of the concentration-time curve by least-squares regression analysis with visual inspection of the data to determine the appropriate number of data points for the calculation of λ_z . At least three points in the terminal elimination phase were required for calculation of λ_z . The AUC_{0-t} was calculated by using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid. The $T_{1/2}$ was calculated as $\ln 2/\lambda_z$.

The plasma concentration-time data were further analyzed by using nonlinear mixed-effect modeling as implemented in the NONMEM computer program (1, 2). Based on a visual examination of these data and data from a previous study of healthy adults, a one-compartment model with first-order input and elimination was used to describe the data. This model was parameterized in terms of the apparent clearance (CL/F), the volume of distribution at steady state (V_{ss}/F),

TABLE 2. Patient demographics by dosage group

Enrollment status	Dose (mg/kg)			
	0.25	1.25	5.0	10.0
Age at time of enrollment				
Mean (months)	6.0	9.8	9.8	5.4
Range (months)	4 to 11	0.75 to 30	0.25 to 33	0.75 to 13
Mean weight at time of enrollment (kg)	5.3	6.3	5.1	4.5
Male/female ratio	3/5	5/6	3/8	10/3
Race (white/black/other)	7/1/0	7/2/2	7/1/3	11/1/1
RSV risk factor(s)				
Prematurity	2	3	4	2
BPD plus prematurity	5	2	2	6
BPD alone	1	6	5	5

and the absorption rate (k_a) following i.m. administration. The effects of patient demographics and other factors (dose, age, weight, gender, race, premature birth, and BPD) on the pharmacokinetic parameters CL/F and V_{ss}/F were assessed to determine whether these factors should be retained in the final model. To examine the potential effect of these factors on the pharmacokinetics of SB 209763, the value of k_a was fixed at 0.0469 liters/h.

The primary consideration in selecting which model to use in analyzing the data (including selection of the factors to be included in the model) involved a statistically significant change in the objective function as implemented by Beal and Sheiner (2). For hierarchical models, a difference of 8 in the objective function was assumed to be significant at the 95% level when there was a change of 1 degree of freedom. Nonhierarchical models were assessed by direct comparison of the log likelihood values. The following were also crucial to the selection of a model: (i) assessment of the weighted residual plots showing any variability as featureless random noise; (ii) increased precision in parameter estimates, resulting in smaller values for standard error; and (iii) reduction in estimates of interindividual variances.

Pharmacodynamic parameters. Venous blood samples for analysis of fusion inhibition and plasma neutralization antibody titers were obtained prior to administration of each dose and at approximately 6 days and 2 and 8 weeks after administration of SB 209763 or the placebo. In vitro microneutralization assays were used to measure the ability of SB 209763 to inhibit the growth of RSV (4). Fusion inhibition and plasma neutralization titers were expressed as the reciprocal of the dilution which caused a 50% reduction in the optical density at 450 nm based on regression analysis of the dose titration.

RESULTS

Enrollment. Forty-three infants and children were enrolled in this study (11 premature infants without BPD and 32 infants with BPD). The subjects ranged in age from 8 days to 33 months and weighted between 1.1 and 15.5 kg (mean, 5.3 kg) at the time of enrollment. The racial demographics were as follows: 74% white, 12% black, 12% Oriental, and 2% other. Forty-two subjects completed the study. One subject was withdrawn due to noncompliance with the follow-up protocol after receiving one 10-mg/kg dose of SB 209763. This subject was included in the analysis as if the 10-mg/kg treatment regimen had been completed. The number of subjects who received each treatment regimen is shown in Table 1. The patient demographics as a function of dosage group are shown in Table 2. Although it is difficult to assess homogeneity across dosage groups given the relatively small sample size, it appears that the groups were fairly well balanced in terms of mean age and weight. The racial compositions of the groups were also relatively balanced; participants in all four dosage groups were predominantly white. The gender distributions of the three lowest-dosage groups were similar, with more females being enrolled than males; the highest-dosage group was skewed in the opposite direction. The majority of subjects in each group had chronic lung disease (BPD).

Safety results. Single and repeat doses of 0.25 to 10.0 mg of SB 209763 per kg were safe and well tolerated. There were no deaths during the study. There were 229 adverse events re-

TABLE 3. Frequency of RSV-positive episodes by dosage

Group	No. infected/total (%)	<i>p</i> value ^a	95% CI ^b
Placebo	2/10 (20%)		
SB 209763			
0.25 mg/kg	2/14 (14%)	0.72	0.07–5.75
1.25 mg/kg	2/20 (10%)	0.46	0.05–3.74
5.0 mg/kg	2/19 (11%)	0.49	0.05–3.97
10.0 mg/kg	1/22 (5%)	0.20	0.01–2.40

^a Logistic regression analysis was used to compare each group with the placebo group.

^b CI, confidence interval.

ported for 41 subjects over the 16 weeks following treatment with the study medication. Thirty-seven adverse events occurred in 10 subjects who received the placebo, and 192 were reported in 35 subjects who received SB 209763. Most were mild to moderate in severity. Four adverse events were considered by the investigators to be related to the study drug. These included three episodes of mild to moderate purpura, which occurred in two subjects, and thrombocytosis, which occurred in one subject. The purpura developed at the site of blood sampling. All adverse events had resolved by the end of the study surveillance period. Nineteen laboratory test values were considered clinically relevant by the investigator. Two of these, granulocytopenia and thrombocytosis, were considered to be related to the study medication. The administration of the study drug was not altered in any patient due to side effects.

Erythema or induration at the injection site was observed at 30% of placebo injection sites and at 48% of SB 209763 injection sites at 5 min postadministration. Most reactions consisted of erythema without induration. No adverse reactions were evident in placebo recipients after 5 min. Eight percent of SB 209763 injection sites continued to show a response at 2 h postadministration. No reactions were evident at the final scheduled assessment (between 4 and 7 days postadministration). These reactions were not reported to be associated with obvious pain or discomfort and were not considered by the investigators to be clinically relevant.

None of the subjects' plasma samples tested positive for anti-SB 209763 antibodies.

RSV infection. Sixty-five episodes of respiratory illness occurred. During 40 of these episodes, nasopharyngeal specimens were obtained, and RSV was recovered from nine specimens, as shown in Table 3. Although there were fewer RSV infections in the group receiving SB 209763 at 10 mg/kg (1 of 22) than in the placebo group (2 of 10), the difference was not statistically significant ($P = 0.20$).

Pharmacokinetic evaluation. Following noncompartmental analysis of the SB 209763 concentration data, C_{max} values and total exposure (as indicated by the AUC) of SB 209763 following i.m. administration increased with increasing dosages of SB 209763 (Table 4). All subjects had quantifiable concentrations of SB 209763 at the last sampling times for the first and second doses of SB 209763. The $T_{1/2}$ was calculated only if at least three time-concentration values were present in the terminal phase. This resulted in the $T_{1/2}$ being estimated for 21 of 75 concentration-time profiles derived from 43 subjects, ranging from 22 to 50 days. Concentrations of SB 209763 were available on days 1 and 6 after the first dose of SB 209763 was administered in 19 of the 43 subjects. All 19 of the subjects had higher concentrations on day 6 than on day 1. Mean concentrations in specimens obtained on day 56 (± 7 days), as shown in Table 4, ranged from 0.50 to 21.1 $\mu\text{g/ml}$ for dosages of 0.25

TABLE 4. Pharmacokinetic parameters for SB 209763 after single and repeat i.m. doses

Parameter	Single or repeat administration	Mean value \pm SD (<i>n</i>) at a dose of (mg/kg) ^a :			
		0.25	1.25	5.0	10.0
C_{max} ($\mu\text{g/ml}$)	Single	1.77 \pm 0.54 (8)	6.84 \pm 2.07 (11)	22.6 \pm 14.0 (11)	40.9 \pm 12.6 (13)
	Repeat	2.33 \pm 0.65 (6)	8.51 \pm 3.27 (9)	28.0 \pm 14.0 (8)	68.5 \pm 18.0 (9)
Concn, day 56 ($\mu\text{g/ml}$)	Single	0.50 \pm 0.24 (8)	2.50 \pm 0.94 (9)	8.48 \pm 5.97 (10)	14.4 \pm 6.52 (11)
	Repeat	0.77 \pm 0.21 (6)	2.85 \pm 1.28 (7)	11.42 \pm 6.18 (6)	21.1 \pm 10.6 (8)
AUC_{0-t} ($\mu\text{g} \cdot \text{h/ml}$)	Single	1,313 \pm 384 (8)	5,611 \pm 1,655 (11)	17,197 \pm 10,912 (11)	35,794 \pm 10,098 (13)
	Repeat	1,829 \pm 454 (6)	7,166 \pm 2,556 (9)	23,059 \pm 14,078 (7)	57,363 \pm 10,483 (9)

^a Values are provided for concentrations obtained on day 56 (\pm 1 week). Parenthetic.

to 10 mg/kg. Mean plasma SB 209763 concentrations following single and repeat i.m. doses are shown in Fig. 1.

Based on NONMEM analysis, the SB 209763 plasma concentration-time data in this patient population were adequately described by a one-compartment model with first-order input. A covariate evaluation showed that the CL/F and V_{SS}/F values were higher for younger patients, with values decreasing with increasing age to 0.143 (ml/h)/kg and 161 ml/kg, respectively, by a mean age of 298 days (\sim 10 months). The corresponding $T_{1/2}$ for a mean age of 298 days was 32.5 days. The relationship between age and CL/F was described as follows: $CL/F = 0.143 \cdot (\text{age}/298)^{-0.316}$. For V_{SS}/F , the model which included age was described as follows: $V_{SS}/F = 161 \cdot (\text{age}/298)^{-0.306}$. The exponential equations permitted predictions for CL/F and V_{SS}/F to increase for newborns through the age of 298 days and to level off as the age increased beyond 298

days. Between-subject variabilities described by coefficients of variation for CL/F and V_{SS}/F were estimated to be 34 and 33%, respectively. No other factor (dose, weight, gender, race, premature birth, or BPD) was observed to alter the population pharmacokinetics of SB 209763 in this study of infants and young children. Dose linearity is supported by the fact that changes in CL/F and V_{SS}/F were not related to dose amounts.

Pharmacodynamic evaluation. The mean and median neutralization and fusion inhibition antibody titers on day 6 are shown, in comparison to the corresponding predose titers, in Table 5. Increases in most of the titers were observed for recipients of each of the four dosing regimens. In the 10 placebo recipients, median titers did not significantly change between predose and 6-day-postdose specimens. Among infants who received a dose of 10 mg/kg, there was typically a two- to fourfold increase over predose titers. The wide range of pre-

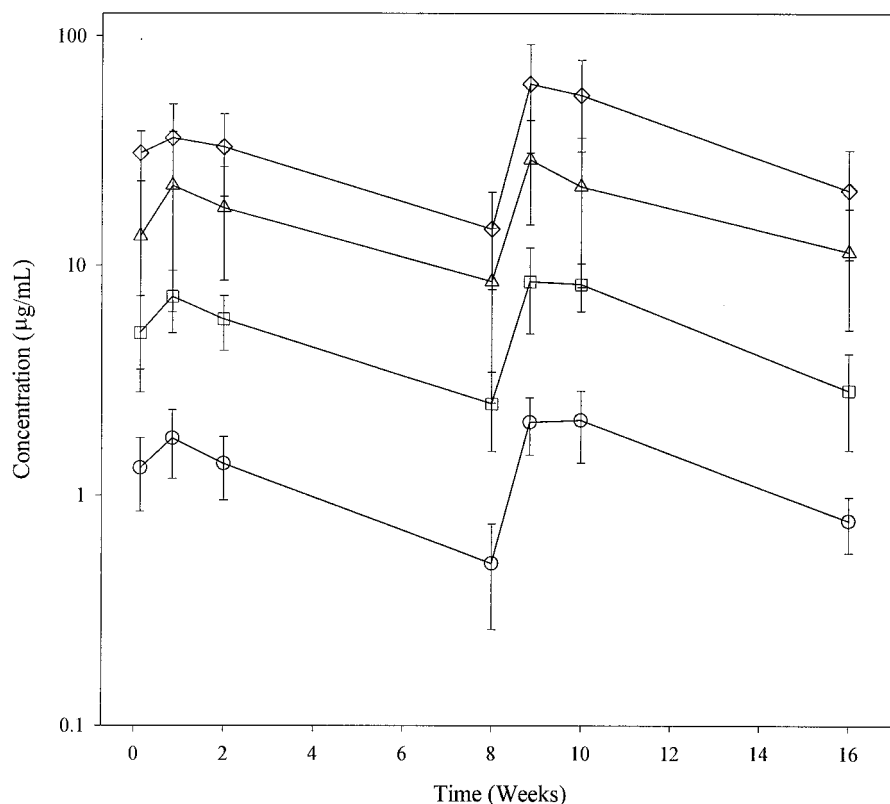


FIG. 1. Mean SB 209763 concentrations, \pm standard deviations, versus time for subjects receiving doses of 0.25 mg/kg (○), 1.25 mg/kg (□), 5 mg/kg (△), or 10 mg/kg (◇).

TABLE 5. Neutralization and fusion inhibition antibody titers

Titer type	Antibody titer for study group administered:				
	SB 20973 at dose of:				Placebo (n = 10)
	10 mg/kg (n = 11)	5 mg/kg (n = 11)	1.25 mg/kg (n = 9)	0.25 mg/kg (n = 7)	
Neutralization titer					
Mean (SD)					
Predose	155 (66)	228 (89)	704 (338)	278 (119)	1,255 (984)
Day 6 postdose	286 (89)	375 (102)	508 (185)	304 (127)	1,146 (985)
Median (range)					
Predose	67 (2-675)	109 (2-877)	234 (2-3,098)	234 (2-855)	129 (2-10,000)
Day 6 postdose	131 (32-961)	242 (32-1,130)	310 (59-1,890)	132 (11-770)	104 (2-10,000)
Fusion titer					
Mean (SD)					
Predose	11 (4)	22 (13)	35 (19)	52 (25)	26 (15)
Day 6 postdose	36 (9)	96 (41)	76 (33)	72 (33)	12 (5)
Median (range)					
Predose	2 (2-37)	2 (2-137)	18 (2-179)	48 (2-189)	16 (2-160)
Day 6 postdose	34 (2-86)	52 (2-467)	45 (2-268)	39 (2-233)	2 (2-42)

dose neutralization and fusion inhibition antibody titers among infants in different dosing groups explains at least some of the variation in peak titers after dosing.

To further evaluate the change in the levels of both neutralizing antibodies and fusion inhibition antibodies, the same data were analyzed as ratios of the concentrations on day 6 to the predose titers (Table 6). This analysis also shows the difference between predose and day 6 concentrations in those subjects who were seronegative prior to the first dose. Although the number of SB 209763 recipients who were seronegative before administration of the first dose was small in each category, the majority of seronegative subjects who received SB 209763 at a dose of 1.25 mg/kg or higher demonstrated more than a four-fold increase in neutralizing and fusion inhibition antibody titers on day 6.

DISCUSSION

In the absence of a safe and effective vaccine, passive immunoprophylaxis holds the greatest promise for the prevention of severe RSV illness in high-risk children. Studies have shown that immunoprophylaxis with a polyclonal, hyperimmune RSV globulin is effective in attenuating RSV disease both in animal

models and in high-risk infants and children. However, there are several disadvantages to this product, including the need for intravenous administration, the fluid volume associated with its administration, the less-than-complete protection against RSV disease achieved, and the issue of safety in children with cyanotic heart disease (11). An effective monoclonal antibody can be administered i.m., thereby avoiding many of these difficulties.

Monoclonal antibodies of purely murine origin have not been widely used in clinical trials due to concerns with regard to the development of anti-murine antibodies. Substitution of human sequences for the murine sequences within the non-antigen-binding region of the molecule results in a lower degree of immunogenicity relative to that of unmodified murine monoclonal antibodies. In the present trial, single and repeat doses of 0.25 to 10.0 mg of SB 209763, a humanized murine monoclonal antibody against the RSV fusion protein, per kg were safe and well tolerated when administered i.m. to high-risk infants. Evaluation of the local and systemic anti-SB 209763 immune response failed to reveal evidence of an immune reaction against this humanized antibody. These results are similar to those of previous studies of healthy male subjects

TABLE 6. Numbers and percentages of subjects with two- or fourfold increases in antibody titers.

Titer increase seen	No. of subjects with indicated titer increase/no. tested (%) for group administered:				
	SB 209763 at dose of:				Placebo
	10 mg/kg	5 mg/kg	1.25 mg/kg	0.25 mg/kg	
Neutralization ratio					
All subjects					
>2-fold	5/11 (45)	5/11 (45)	3/9 (33)	2/7 (29)	1/10 (10)
>4-fold	4/11 (36)	4/11 (36)	2/9 (22)	2/7 (29)	1/10 (10)
Seronegative subjects, predose					
>2-fold	3/3 (100)	2/2 (100)	2/2 (100)	2/2 (100)	1/2 (50)
>4-fold	3/3 (100)	2/2 (100)	2/2 (100)	2/2 (100)	1/2 (50)
Fusion ratio					
All subjects					
>2-fold	6/11 (55)	7/11 (64)	5/9 (56)	1/7 (14)	1/10 (10)
>4-fold	5/11 (45)	5/11 (45)	5/9 (56)	0/7 (0)	0/10 (0)
Seronegative subjects, predose					
>2-fold	4/7 (57)	5/8 (63)	2/3 (67)	0/3 (0)	0/4 (0)
>4-fold	4/7 (57)	5/8 (63)	2/3 (67)	0/3 (0)	0/4 (0)

who received single and multiple doses of SB 209763 and did not develop a detectable anti-idiotypic reaction (4). Another humanized RSV monoclonal antibody, directed against the F protein, showed a similar lack of immunogenicity (16).

Although the number of sampling times in this study was limited ($n = 7$) in comparison to many studies examining pharmacokinetics, sufficient information was available to provide individual values of C_{max} and AUC_{0-t} by utilizing non-compartmental pharmacokinetic methods. However, parameter estimates for AUC_{0-t} and C_{max} should be considered as approximations of the values that would be obtained with a more intensive sampling schedule. By the use of population modeling, estimates of CL/F and V_{ss}/F were obtainable. The predicted CL/F of 0.143 (ml/h)/kg for the mean age of 298 days is similar to values of intravenous clearance (CL) reported for healthy adults who were administered intravenous doses of SB 209763 (15). In this earlier study, mean CL values ranged from 0.122 to 0.142 (ml/h)/kg for similar doses of 0.25 to 10.0 mg/kg. Mean estimates for V_{ss}/F from the earlier, intravenous study of healthy adults ranged from 87.5 to 104 ml/kg for doses of 0.25 to 10.0 mg/kg. This is in contrast to a mean V_{ss}/F of 161 ml/kg for the present study population. These differences could be in part due to the larger proportion of total and extracellular body water in infants and young children (5).

Analysis of plasma neutralization and fusion inhibition antibody levels following administration of a single dose of the study medication suggests that doses of as little as 1.25 mg of SB 209763 per kg may be associated with some increase in antiviral activity. However, given the relatively low neutralization and fusion inhibition antibody titers that were achieved with the highest dosing regimen, it is not surprising that differences in RSV attack rates were not observed. Also, the high predose neutralization-antibody titer in placebo recipients may have conferred some degree of protection, making it difficult to detect a difference in RSV infection rates between groups. Experience with a polyclonal, hyperimmune RSV globulin indicates that serum neutralizing-antibody titers of greater than 1:200 are necessary to limit RSV replication in the lower respiratory tract. Because of the presence of functionally distinct populations among the RSV-neutralizing antibodies in a polyclonal antibody preparation, only a subset of neutralizing antibodies may actually be protective (14). In this trial, the absence of a cumulative effect on antibody concentration that would be derived from serial doses of SB 209763 also may have contributed to the lack of an effect on RSV infection rates. However, the lack of toxicity and the relative ease of i.m. administration justify further consideration of RSV prophylaxis with a monoclonal antibody.

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