Proposed Dosage[2]

For EIB, the recommended dosing is 1 inhalation (50 mcg) at least 30 minutes prior to exercise, with protection claimed for the majority of patients out to 9 hours in 12 and above, and to 12 hours in 4 to 11 year olds.

Specific comments on the proposed changes in the labeling are contained in section 11.0 of this review.

Formulation

There are no differences proposed for this indication compared with that of the marketed Serevent Diskus formulation.

4.0 CHEMISTRY / MANUFACTURING CONTROLS

Formulation

The relevant formulation used in the US clinical trials was the same formulation as the marketed Serevent Diskus (i.e., salmeterol 50 mcg in lactose to 12.5 mg weight) with the placebo Diskus containing the lactose, but no active drug substance. An exception is that the 100 mcg and 25 mcg doses administered as comparators in some trials were achieved by altering the amount of active drug / blister. Note that MDI formulations of Serevent and Ventolin were used as positive controls, as was the Serevent [redacted] for Diskhaler. The latter is not a US approved product, but has a similar drug formulation to the Diskus (lactose/salmeterol xinafoate blend).

5.0 PRECLINICAL PHARMACOLOGY / TOXICOLOGY

There are no additional toxicology issues for this sNDA (except for labeling regarding multiples of human exposure for children aged 4 years) given the recent approval for the drug product, along with the fact that the proposed pediatric indication is only down to age 4 (i.e., not down below 2 years of age for which specific young juvenile animal studies might be needed).

7.0 CONDUCT OF THE REVIEW

This medical officer review was conducted in the following manner:

a) 45-day filing review - This review was conducted by Sue Johnson, clinical reviewer from DPDP, and identified no filing issues. At this time, there was also a decision not to seek DSI auditing of the study sites.

b) A full review of the five US pivotal studies (see table) was conducted first to evaluate the claimed indications. Note that the sponsor considers SLGA2002 to be supportive, but was considered by the reviewer to be pivotal because it is an adequate and well-controlled US study of the relevant dose done in an appropriate setting. The non-US studies and other data were considered as supportive and reviewed in an concise fashion, mainly focusing on safety or any efficacy data

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2 **(vol 1.001, page 27 - proposed labeling) of SE1-001**

which refute or augment the data from the pivotal trials.

Table 1

Study Number	Study design	Doses Examined	Patients Enrolled	Age Range
SLGA2013	Randomized, double-blind (DB), double-dummy (DD), X-over	50, 100 mcg Diskus, 42 mcg MDI, placebo	24	12 - 35
SLGA2017	Rand, DB, DD, XO	50, 100 mcg Diskus, 42 mcg MDI, placebo	29	12 – 38
SLGA2002	Rand, DB, DD, XO	50 mcg via Diskus, Diskhaler, vs. placebo	22	15-36
SLGA2003	Rand, DB, DD, XO	50 mcg [redacted] 50 mcg Diskus, placebo	24	4 – 11
SLGA2014	Rand, DB, DD, XO	25, 50 mcg Diskus, albuterol 180 mcg, placebo	26	4 - 11

c) A review of the sponsor's ISE was conducted. The total amount of data, particularly in terms of exposure and number of similar studies, was limited, so that the integration was also limited in scope as was the resultant information.

d) The total amount of safety data for this collection of single dose studies was not substantive. Therefore, the ISS for the pediatric indication (submitted with SE1-002) contains a comprehensive ISS, covering both supplements. The FDA perspective on the ISS will be found in Dr. Johnson's medical review for 20-692 SE1-002.

d) Finally, a limited audit/check of the data provided in study report line-listings was conducted utilizing CRFs. The purpose of this 'random' audit was to assure that the primary data as represented in the CRF was accurately reflected in the line-listings and study report. No patients withdrew or died in the newly submitted studies, so the sponsor provided no CRFs with the submission. However, they were asked to provide CRFs randomly chosen from the pivotal studies: patients 9956 from SLGA2013 (study site – Kemp) and 12579 (site – Blake) from SLGA2013. A full check of demographic recordings, medical history, vital signs at screening and visit 1 and spirometry listings for visit 1 and Serevent Diskus administration show no discrepancies with line listings, and the calculations of all in FEV_1 appear accurate. No signal of problems with data transcription / representation were found from these random checks.

No auditing by DSI of study sites was requested for this application, since this moiety is already approved for this indication in ages 12 and above in an MDI formulation and given the divisional experience and past audit results of trials submitted by this sponsor. No reasons for requesting an audit were identified in the course of the review.

Abbreviations used: AE - adverse event; ATS - American Thoracic Society; EIB – exercise-induced bronchospasm; ECG - electrocardiogram; FEF25-75% - forced expiratory flow in the middle half of forced vital capacity; FEV1 - forced expiratory volume in one second; FVC - forced vital capacity; LOCF - last observation carried forward; PEFR - peak expiratory flow rate; PFT - pulmonary function test; MDPI – multi-dose dry powder inhaler; DD – double-dummy; DB – double-blind, XO – cross-over; MDPI 50 – 50 mcg/blister Serevent Diskus product; MDPI 100 – 100 mcg Serevent Diskus product; MDI – metered-dose inhaler

8.0 CLINICAL STUDIES SUPPORTING THE EFFICACY AND SAFETY OF SEREVENT DISKUS IN THE PREVENTION OF EXERCISE-INDUCED BRONCHOSPASM IN PATIENTS AGES 4 YEARS AND ABOVE

8.1 STUDY SLGA2013[3]

"A Randomized, Double-blind, Double-Dummy, Single-Dose, Four-Way Crossover Comparison of Salmeterol 50 and 100 mcg via the Diskus, Salmeterol 50 mcg via the metered-Dose Inhaler, and Placebo for the Prevention of Exercise-Induced Bronchospasm in Adults and Adolescents with Asthma." [sponsor title]

8.1.1 Objectives/Rationale

1. To compare the clinical efficacy of 42 mcg from the salmeterol MDI and 50 and 100 mcg doses via the Diskus to that of placebo in the prevention of EIB in patients 12 - 40 years of age with asthma.
2. To compare the safety and tolerability of single doses of salmeterol administered via the MDI to two doses from the Diskus.

8.1.2 Design

This was a two-center (Austin TX – Howland PI; San Diego CA – Kemp PI), randomized, double-blind, placebo and positive-controlled, 4-way cross-over conducted in the US between the dates of June 15 and December 18, 1995. Enrollment was planned for 24 evaluable patients 12 – 40 years of age with a diagnosis of EIB. Note that although the sponsor terms this a double-dummy design, it actually utilized three devices – one MDI and two Diskus devices - in each patient.

8.1.3 Summary of the Study Protocol (including amendments)

8.1.3.1 Population

Non-smoking patients of the appropriate age were recruited if they had a diagnosis of asthma by ATS criteria and a history of EIB. At baseline, patients were to have an FEV_1 of at least 70% of predicted and had to have a demonstrated fall in FEV_1 with exercise of at least 20% from the pre-exercise testing. Patients had to be able to withhold medications prior to testing (notably, albuterol – 8 hours, salmeterol for 48 hours) and were restricted from receiving any inhaled, parenteral or oral corticosteroids for 4 weeks prior to testing.

8.1.3.2 Treatment Visits

Single blind dose of placebo (baseline) for Visit 1 (to replicate the FEV_1 response) – followed in random sequence by:

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3 **(vol 1.006, page 33) of SE1-001**

- salmeterol MDI 42 mcg plus Diskus placebo;
- salmeterol Diskus 50 mcg plus MDI placebo;
- salmeterol Diskus 100 mcg plus MDI placebo.
- Diskus placeboes plus MDI placebo

There was to be at least a 3-day and no more than a 14-day period between test days, with subjects using Ventolin dosed as needed between visits.

8.1.3.3 Assignment to Treatment

All eligible patients were to receive all treatments over the course of the study. Patients who dropped out, however, were not to be replaced.

8.1.3.4 Blinding

Active medications and their matching placebos were supplied in identical metered dose inhalers/canisters and dry-powder inhalers. Since the two salmeterol products (MDI vs. MDPI) were so different, a multi-dummy design was used.

8.1.3.5 Dosing

Three devices were distributed to each patient, for administration as follows the morning of test days (between 0600 and 0830):

Table 2

Treatment	Device A	Device B	Device C
	MDI	Diskus 50 mcg	Diskus 100 mcg
MDPI 50	2 puffs placebo	1 blister active	1 blister placebo
MDPI 100	2 puffs placebo	1 blister placebo	1 blister active
MDI	2 puffs active (42 mcg)	1 blister placebo	1 blister placebo
Placebo	2 puffs placebo	1 blister placebo	1 blister placebo

8.1.3.6 Exercise Testing

Serial spirometry was to be performed immediately pre-exercise, and at 5, 10, 15, 30 and 60 minutes post-exercise. Triplicate determinations were performed at each time point with the highest of the three FEV_1 readings recorded. The exercise challenge was a stepped technique utilizing a treadmill, changing the speed and incline to achieve a heart rate of at least 80% of the predicted maximum for age. The duration was to be 10 minutes (2 at minimal workload, 2 minutes at 2/3 target work load and 6 minutes at target conditions), although exercise in step III could be stopped if the subject became too symptomatic. The patients breathed from a 170-liter reservoir containing compressed air, to standardize for humidity.

To be considered for enrollment, all patients had to have a drop in FEV_1 of at least 20% following exercise compared to the pre-exercise value. Any subject who experienced a fall of more than 40% was to receive rescue treatment, with isoproterenol MDI (Isuprel) if within 3 hours of initial exercise testing for that day, or Ventolin if beyond the second exercise testing. Any patient

needing therapy between 3 hours after the first challenge and before the second challenge, or needing therapy beyond the standard dose of rescue (2 puffs) was not to continue testing that day.

On treatment visits, patients underwent predose FEV_1 assessment to assure stability of disease (within 12% of screening FEV_1). If the patient met the stability criterion, the first of the two exercise challenges was to be done at approximately 0900, timed for 30 minutes following dosing with study medications. The second was performed 8.5 hours following dosing, if the patient had recovered to at least 70% of the baseline FEV_1 recorded pre-exercise on that day.

8.1.3.7 **Assessments**

Efficacy Evaluations

The primary efficacy measure for this study was the percent fall in FEV_1 following exercise. Also analyzed was the minimum FEV_1 achieved (as a % of predicted) and a categorical analysis of patients who fell <10 %, those who fell between 10% and <20%, and those who fell 20% or more in their FEV_1.

Safety Evaluations

The following safety measures were collected in the study: adverse events, physical findings; and pre / post-study clinical laboratory evaluations and 12-lead ECG.

8.1.3.8 Medication/Exposure Restrictions

- 8 or more hours since any back-up Ventolin use
- 6 or more hours post-caffeine exposure
- 4 or more hours since strenuous activity or exercise
- 2 or more hours since more than 15 minutes of cold exposure
- 5 or more days since completing treatment for an asthma exacerbation

8.1.3.9 Endpoints

Efficacy parameters:

The primary variable was an assessment of the percent fall in FEV_1 following exercise, based on the lowest value recorded during the first hour post-exercise. The percent fall was to be compared amongst treatments utilizing an analysis of variance F-test based on a crossover model with terms for subject, treatment, period and carryover. The minimum FEV_1 was assessed using the same testing. The categorical comparisons of FEV_1 were based on non-parametric statistical testing. No correction for multiple comparisons was planned by the sponsor.

8.1.3.10 Statistical / Power considerations

Sample size calculation: data from previous EIB studies indicated that 14% was a reasonable assumption for the SD of the fall in FEV_1 post-exercise. Based on this and the ANOVA F-test crossover model with a significance level of 0.05, a sample size of 24 was reported by the sponsor to offer a >80%

power to detect a 12% difference between any two treatments.

The analysis was designed to be an intent-to-treat analysis, based on the available data from any patient who received study treatment.

8.1.3.13 Amendments to the protocol

There was 1 protocol amendment instituted after enrollment began to clarify laboratory / ECG criteria that should have no significant impact in the interpretation of the results.

Figure 1 **Procedure Graphic**

	Screening	Treatment Visit 1	Treatment Visit 2	Treatment Visit 3	Treatment Visit 4	Treatment Visit 5	Post-Treatment Follow-up	Subject Discontinuation
Informed Consent	x[c]							
Medical History	x							
Vital Signs	x						x	x
Physical Examination	x						x	x
Spirometry	x							x
FEV$_1$ Reproducibility Assessment		x	x	x	x	x		
Serial Vital Signs and Spirometry	x	x	x	x	x	x		
Exercise Challenge	x[d]	x	x	x	x	x		
Adverse Event Assessment		x	x	x	x	x	x	x
Concomitant Medications	x	x	x	x	x	x	x	x
12-lead ECG	x						x	x
Clinical Laboratory Tests	x						x	x
Serum Pregnancy Test (all females)	x						x	x
Chest X-ray	x[e]							
Review MDPI Inhalation Technique	x	x	x	x	x	x		
Review MDI Inhalation Technique	x	x	x	x	x	x		
Issue Ventolin® MDI	x	x[b]	x[b]	x[b]	x[b]	x[b]		

8.1.4 **Results**

8.1.4.1 Study population characteristics:

Twenty-four subjects between the ages of 12 to 35 years were enrolled into the study and randomized. An additional 6 were screened, but never randomized due to unsuccessful exercise challenges at screening or treatment visit 1 (5 patients) and an adverse event (1 patient). All 24 who received randomized treatment completed the study. Only 3 visits were not conducted within the 3 – 14 days called for in the protocol, one each at visits 3, 4, and 5, and all three cases were beyond the 14 days (none were less than 3 days).

Demographics tabulations reveal most patients were male and Caucasian (19 and 22 out of 24m, respectively). There were 4 subjects 15 years or below in age, with 2 more additional teenagers. The majority of subjects were in their 20's. Most patients had a long history of asthma (more than 5 years), with the mean screening FEV$_1$ equal to 3.71L (85.5% of predicted),and a mean maximal fall post-exercise of 31.5%.

8.1.4.1.1 Concurrent Illness / Drugs

The sponsor lists a summary of concurrent illnesses by body system. A majority of subjects had concurrent illnesses, but these fell primarily into the neurologic, skin or musculoskeletal systems.

Concurrent medication use was largely unremarkable, primarily consisting of oral contraceptives, OTC headache, and vitamins. Notably, few patients needed rescue medications at study visits, except for the screening visits, the single blind visit 1 and the placebo visits (where 3, 5 and 7 patients respectively needed rescue, primarily with Ventolin). During the active treatment visits, only 1 subject needed intra-testing treatment with Isuprel (during an MDI active treatment visit).

8.1.4.2 Efficacy Analysis

8.1.4.2.1 *Data set analyzed*

All 24 subjects who were randomized completed the study and these formed the intent-to-treat population, the only population analyzed and presented by the sponsor.

8.1.4.2.2 FEV_1 response to exercise challenge

The primary analysis for efficacy was the maximum percent fall in FEV_1 within the first hour following exercise testing. Note that the line listings for PFTs gave time of dosing and the time of testing. The investigators did a consistent job of timing of the tests (that is, patients tended to commence at the same time on differing days, often to within a few minutes). The tests were also consistently conducted at or very near 30 minutes and 8.5 hours post-dosing, despite the allowances in the protocol for a wider spread in the time window.

These resulting primary endpoint data are summarized in the table below:

Table 3

Exercise Challenge	Spirometry assessment	Visit 1 FEV_1 [SE] (%)	Placebo	MDI	MDPI 50	MDPI 100
#1 *0.5 hr*	Pre-exer.	3.72 L	3.61 L	4.01	3.97	3.98
	Post-exer.	2.64 [2.44](-29%)	2.45 [3.39](-32)	3.66 [2.59](-9)	3.41 [3.54](-13)	3.54 [2.69](-11)
#2 *8.5 hr*	Pre-exer.	3.68 L	3.63	4.07	3.96	4.08
	Post-exer.	2.63 [1.68](-29%)	2.60 [3.01](-29)	3.53 [2.67](-13)	3.28 [3.21](-17)	3.45 [2.94](-16)

For the 8.5 hour challenge, the placebo data were contributed by only 23 and 22 patients respectively for the pre and post-exercise studies (due to patients exacerbating prior to completing the exercise challenge), the n = 24 for all other data. In all cases, active treatment beat placebo in pairwise testing of the mean maximal percent fall in FEV_1, with p values less than 0.001 for all such comparisons at both 0.5 and 8.5 hours.

Note that, per Dr. Gebert's review, the p-value for the most relevant comparison - placebo vs. MDPI 50 – would remain statistically significant at both time points, even if adjusted for multiple comparisons by any of the usual

multiple comparison corrections.

Note also that these patients displayed a very reproducible response to exercise, with the screening mean fall in FEV_1 = 31%, the Visit 1 single-blind test showing 29%, and the placebo testing being in the 30% range as well.

For pairwise testing between actives, the trend towards superiority of the MDI compared to MDPI 50 was statistically significant at the first test (p = 0.037) and close to significant at the second (p = 0.055). Otherwise, all pairwise comparisons of active were not significant. It is interesting to note, however, that in addition to the MDI appearing more efficacious than the 50 mcg Diskus dose, there is a trend towards the 42 mcg MDI dose providing more protection with a longer duration of that protection than with the 100 mcg Diskus dose.

Similar data were seen for the minimum FEV_1 analysis, with all active doses beating placebo at both time points, and with the MDI superior to the 50 mcg Diskus at both time points (p = 0.026, 0.027 respectively), with no other significant pairwise differences seen.

The categorical analysis provided similar and complimentary data to the analysis of the mean response. These data are summarized in the table below (note that patients unable to conclude an exercise challenge were included in the ≥ 20% category):

Table 4

Challenge	Placebo		MDI		MDPI 50		MDPI 100	
% fall	**(N)**	**(% total)**	**(N)**	**(% total)**	**(N)**	**(% total)**	**(N)**	**(% total)**
0.5 hour	24		24		24		24	
< 10%	**4**	**(17)**	**16**	**(67)**	**15**	**(63)**	**15**	**(63)**
≥ 10%, < 20%	1	(4)	6	(25)	2	(8)	4	(17)
≥ 20%	**19**	**(79)**	**2**	**(8)**	**7**	**(29)**	**5**	**(21)**
8.5 hour								
< 10%	**3**	**(13)**	**12**	**(50)**	**11**	**(46)**	**10**	**(42)**
≥ 10%, < 20%	2	(8)	7	(29)	6	(25)	8	(33)
≥ 20%	**19**	**(79)**	**5**	**(21)**	**7**	**(29)**	**6**	**(25)**

This analysis revealed significant differences for all active treatments vs. placebo, though there were no differences in pairwise testing of the active treatments.

A few things regarding the data analyzed in this fashion are worth noting. First, these data confirm the well-described finding that the fall in FEV_1 from an exercise challenge is a variable response, since 5 of the placebo patients failed to fall by 20% or more at either time point (despite having done so at screen and Visit 1). Second, although salmeterol is still somewhat protective at the 8.5 hour time point, if one focuses mainly on "fully protected patients" (i.e., those with < 10% maximum fall in FEV_1), there is a waning of the response to where the minority of patients are "fully protected" in the Diskus groups. Third, salmeterol in any formulation is not entirely protective for all patients, with between 8 – 29% of patients still having a positive exercise

challenge following dosing. Both of these latter two points need to be captured in labeling (as they are in the current Serevent MDI labeling).

8.1.4.3 Safety Analysis

The safety analysis included all patients who received any study drug, a total of 24 subjects, with each patient receiving all treatments over the course of the study. No deaths or serious AEs were reported in this study, and no patients were withdrawn for an AE.

8.1.4.3.1 Adverse Event Occurrences

The following table depicts all AEs that were either reported in more than one treatment group or in a single active treatment group where no occurrence had been noted with placebo:

Table 5

Adverse Event		Placebo N (%)	MDI N (%)	MDPI 50 N (%)	MDPI 100 N (%)
Total Pt. Numbers		24	24	24	24
Number of patients with any event		5 (21)	7 (29)	3 (13)	4 (17)
ENT	All	1 (4)	3 (13)	0	3 (13)
throat irritation		0	2 (8)	0	3 (13)
nasal congestion		1 (4)	1 (4)	0	0
Neuro	headache	1 (4)	1 (4)	1 (4)	1 (4)
sleep disturbance		1 (4)	1 (4)	0	0
Respiratory	cough	0)	1 (4)	1 (4)	0
GI	pain/discomfort	1 (4)	1 (4)	0	0
CV	extrasystoles (vent.)	0	1 (4)	0	0
Musculoskeletal	cramps/spasm	0	0	1 (4)	0
GU	uterine cramping	0	0	0	1 (4)

Overall, these data show reasonably comparable tolerability, with only throat irritation appearing to be related to active treatment. It is notable that the total number of AE reports for the MDI is higher than either dose of the MDPI, particularly the proposed dose. Clearly this database allows no firm conclusions about relative safety or even tolerability of formulations, however, due to its small size and the limited exposure to each formulation, as well as due to the triple-placebo design (i.e., three placebo devices utilized). The ventricular extrasystoles were noted over 2 minutes during exercise for the patient listed, and only noted during the MDI arm. This at least raises the possibility of greater salmeterol systemic exposure for this patient from the MDI compared to either dose of the MDPI.

8.1.4.3.2 Laboratory Abnormalities / Changes

There were no signals detected in laboratory examinations. Since laboratories were done only pre and post-study, attribution of any abnormalities would be difficult in any case.

8.1.4.3.3 Vital Signs

Mean values for blood pressure and pulse rate were presented pre- and post-exercise by treatment and showed no clear treatment response when compared to the data from the placebo group (with no clear indication of more systemic effects of the MDI compared to the Diskus).

8.1.4.3.4 ECGs

ECGs, like the laboratories, were only performed pre and post-treatment, and therefore would not be likely to reveal any information which would be discriminative for relative effects of the 3 formulation tested. There were some minor ECG changes noted in 3 patients, 2 developed changes from pre-study to post-study, one reverted from abnormal to normal over the course of the study. None of these appear to be convincing for a causal connection to study drug exposure.

8.1.5 Conclusions

8.1.5.1 Efficacy Conclusions

Study 2013 supports the efficacy of salmeterol 50 mcg via the Diskus in the prevention of EIB for patients prone to exercise-related fall in FEV_1 when used episodically and when delivered 30 minutes prior to exercise. Although this protection clearly wanes by 8.5 hours, most patients still have less than a 20% fall in FEV_1 at that time point (though the minority fell by less than 10%).

Although the MDI appeared numerically (and by some few analyses, statistically) superior to the MDPI, it is clear that the Diskus considered on its own was effective. Interestingly, there is little indication from this study that the 100 mcg dose confers much additional protection when compared to the 50 mcg dose of the Diskus. Both appeared numerically inferior to the MDI.

8.1.5.2 Overall Safety Conclusions

The safety data generated in this sort of study are limited in their utility, since the exposures are brief and the sample size is small by design. There does not appear to be any clear signal of a problem with tolerability of the formulations. If total numbers of AEs are considered, there were many fewer in the MDPI 50 group compared to placebo, and the MDI – already approved for this indication – had the highest occurrence of AEs overall.

8.2 **STUDY SLGA2017[4]**

"A Randomized, Double-blind, Double-Dummy, Single-Dose, Four-Way Crossover Comparison of Salmeterol 50 and 100 mcg via the Diskus, Salmeterol 50 mcg via the metered-Dose Inhaler, and Placebo for the Prevention of Exercise-Induced Bronchospasm in Adults and Adolescents with Asthma." [sponsor title]

8.2.1 **Objectives/Rationale**

1. To compare the clinical efficacy of salmeterol MDI 42 mcg versus treatment with 50 and 100 mcg via the Diskus to placebo in the prevention of EIB in patients 12-40 years of age with asthma.
2. To compare the safety and tolerability of single doses of salmeterol administered via the MDI to two doses from the Diskus.

8.2.2 **Design**

This was a two-center (Jacksonville FL – Blake PI; Aurora, CO – Pearlman PI), randomized, double-blind, double-dummy, placebo and positive-controlled, 4-way cross-over conducted in the US between the dates of July 17, 1995 and April 8, 1996 (essentially, it ran concomitantly with study 2013). Enrollment was planned for 24 evaluable patients 12 – 40 years of age with a diagnosis of EIB.

8.2.3 **Summary of the Study Protocol (including amendments)**

Note: This protocol was a replicate of the former (intended for that purpose) and therefore no reiteration of the protocol is given in the review. Please refer to sections 8.1.3 of this review for any details.

8.2.3.1 Amendments to the protocol

As with the former protocol, there was 1 amendment instituted just as enrollment began that clarified laboratory / ECG criteria.

8.2.4 **Results**

8.2.4.1 Study population characteristics:

Twenty-nine subjects between the ages of 12 to 38 years were enrolled into the study and randomized (one of these 29 was discontinued due to a failure to return). 6 additional patients were screened, but not enrolled, with 5 of these failing to be enrolled due to failure to complete the exercise challenge either at screening (3 patients) or at Visit 1 (2 patients). One patient failed to be enrolled for "other" reasons. A total of 9 treatment visits – excluding the follow-up and screening visits - were not conducted within the 3 – 14 day window called for in the protocol, with one visit occurring before the 3 day target at visit 5. Overall, though, compliance with visit dates was quite high (86 – 100%).

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4 **(vol 1.008, page 1) of SE1-001**

As opposed to study 2013, the demographics revealed a more even balance in gender, with somewhat more females than males (17 and 12 respectively). 90% of subjects were Caucasian, 10% (3 patients) were Black, and no Asians or Hispanics were enrolled. The mean age was approximately 24, with a range of 12 – 38 years. There were 7 subjects who were 15 years old or less, with the majority of the subjects in their twenties.

Comment – As opposed to the prior study, the demographics of this study were a bit more varied, with more females, a more heterogeneously aged population and a few more minorities. Whether any differences in treatment effects seen in this study compared to the former can be attributed to the demographics is a bit speculative. This issue may be better addressed in the ISE, since this study helps make the summed demographics of the two studies more balanced and therefore renders the results of the combined analysis more generalizable.

Most patients had a long history of asthma (23 with asthma for 5 or more years), with the mean screening FEV_1 equal to 3.29 L (90.4% of predicted) with a mean maximal fall post-exercise of 28.3%.

8.2.4.1.1 Concurrent Illness / Drugs

The sponsor lists a summary of the concurrent illnesses by body system. Although the majority of subjects had concurrent illnesses, they fell primarily into the ENT or musculoskeletal systems.

Concurrent medication use was largely unremarkable, primarily consisting of oral contraceptives and OTC headache/pain remedies.

Notably, few patients needed rescue medications at study visits, except for the screening visits, the single blind visit 1, and the placebo visits. However, in contrast to 2013, during the active treatment visits subjects received rescue on 5 occasions with either Ventolin (4 times, 2 with MDPI 50, 2 with MDPI 100) or Isuprel (1 time in the MDPI 50 group) – all in the Diskus groups.

Note – this pattern of rescue supports that the MDI is relatively more effective than either Diskus product, as hinted at numerically in the prior study.

8.2.4.2 Efficacy Analysis

8.2.4.2.1 Data set analyzed

As previously stated, of the 29 subjects who were randomized, only 28 completed the study as one patient failed to return following treatment visit 2. All 29 patients formed the intent-to-treat population, with all available data considered.

8.2.4.2.2 FEV_1 response to exercise challenge

The primary analysis for efficacy was the maximum percent fall in FEV_1 within the first hour following exercise testing. Review of line listing shows a reasonable job in conducting the tests with respect to the targeted start times and time of dosing.

The % fall in FEV_1 data are summarized in the table below:

Table 6

Exercise Challenge	Spirometry assessment	Visit 1 FEV_1 [SE] (%)	Placebo	MDI	MDPI 50	MDPI 100
#1 *0.5 hr*	Pre-exer.	3.20 L	3.20 L	3.42	3.36	3.40
	Post-exer.	2.51 [2.34](-21%)	2.59 [2.54](-19)	3.27 [1.53](-4)	3.08 [1.61](-8)	3.16 [1.72](-7)
#2 *8.5 hr*	Pre-exer.	3.22 L	3.22	3.51	3.96	3.47
	Post-exer.	2.45 [2.20](-25%)	2.60 [3.08](-20)	3.20 [2.12](-19)	2.91 [2.57](-14)	3.08 [2.15](-12)

Note that for screening, visit 1 and the MDPI 100 groups, data are contributed by all 29 patients, but only 28 contributed to the placebo, MDI and MDPI 50 assessments. In all cases, active beat placebo in pairwise testing of the mean maximal percent fall in FEV_1. For the MDPI 50 comparison at the 0.5 and 8.5 hour time points, the results of significance testing showed a $p<0.001$ and $p = 0.047$, with p values of <0.001 and $= 0.006$ for the MDPI 100 comparisons. The p values for the MDI vs. placebo comparison were less than 0.001 at both time points. The MDI was statistically superior to the MDPI 50 at the 8.5 hour time point, with all other pairwise comparisons of actives insignificant.

In this study, adjustments for multiple comparisons, such as the Bonferroni technique, would have rendered the MDPI 50 vs. placebo pairwise results at 8.5 hours insignificant.

Similar data were seen for the minimum FEV_1 analysis, with all active doses beating placebo at both time points, but with the MDI superior to the Diskus at both time points ($p = 0.050$, 0.003 respectively), with no other significant pairwise differences seen.

The categorical analysis provided similar and complimentary data to the analysis of the mean response, although in this analysis, the MDPI 50 did not statistically beat placebo at 8.5 hours ($p = 0.055$) even without correction for multiple comparisons, nor did the MDPI 100 ($p = 0.135$). No significant differences were seen between actives by this analysis. These data are summarized in the table below (note that any patient unable to conclude a challenge were included in the ≥ 20% category):

Table 7

Challenge % fall	Placebo (N)	Placebo (% total)	MDI (N)	MDI (% total)	MDPI 50 (N)	MDPI 50 (% total)	MDPI 100 (N)	MDPI 100 (% total)
0.5 hour	28		28		28		29	
< 10%	**11**	**(39)**	**20**	**(71)**	**16**	**(57)**	**21**	**(72)**
≥ 10%, < 20%	2	(7)	6	(21)	9	(32)	4	(14)
≥ 20%	**15**	**(54)**	**2**	**(7)**	**3**	**(11)**	**4**	**(14)**
8.5 hour								
< 10%	**9**	**(32)**	**19**	**(68)**	**15**	**(54)**	**13**	**(45)**
≥ 10%, < 20%	5	(18)	5	(18)	6	(21)	8	(28)
≥ 20%	**14**	**(50)**	**4**	**(14)**	**7**	**(25)**	**8**	**(28)**

This analysis of the data helps explain why there may have been a less convincing effect of the proposed dose of the Diskus relative to placebo

coming from this study. The population enrolled may not have been sufficiently diseased to sensitively identify drug effect, since only about 50% of subjects had a 'positive' exercise test by the sponsor's criterion at the placebo visit. (This could be inferred from the mean % FEV_1 results as well). In any case, judging from placebo data presented in the above analyses, there were many fewer patients who clearly maintained a positive exercise challenge with repeat testing in this study than in 2013. Hence, it would have been harder for the actives to show clear superiority. In fact, the percent of patients maintaining a fully protected status (i.e., fall of FEV_1 < 10%) in the MDPI 50 group was numerically higher in this study than in 2013, yet statistically, the comparison to placebo at 8.5 hours in this study would not be significant by an adjusted p-value. If one considered this a 'failed study' for supporting the 8.5 hour duration of action, it could be argued that this was more on the basis of the population enrolled rather than a true failure of the drug to "work."

8.2.4.3 Safety Analysis

The safety analysis included all patients who received any study drug treatment, a total of 29 subjects, with each patient receiving all treatments over the course of the study. No deaths or serious AEs were reported in this study, and no patients were withdrawn for an AE.

8.2.4.3.1 Adverse Event Occurrences

The following table depicts all AEs that were reported either in more than one treatment group, or in a single active treatment group where no occurrence had been noted with placebo:

Table 8

Adverse Event	Placebo N (%)	MDI N (%)	MDPI 50 N (%)	MDPI 100 N (%)
Total Pt. Numbers	28	28	28	29
Number of patients with any event	0 (0)	1 (4)	3 (11)	1 (3)
ENT Throat Irritation	0	0 (0)	0	1 (3)
URTI -	0	0	1 (4)	0
GI viral GI infection	0	0	1 (4)	0
Nausea/vomiting	0	1 (4)	0	0
Musculoskeletal pain	0	0	1 (4)	0

As in the previous study, these data show reasonably comparable tolerability. There seems to be no signal of any clear treatment-related occurrences, though there was an extraordinarily low reporting rate for AEs compared to the prior study. As opposed to the prior study's AE tabulation, here the highest reported number of AEs overall is in the MDPI 50 group, albeit still a very low number. In looking at these data, one wonders whether the investigators for this study were less rigorous in eliciting AEs than the prior study, but that is speculative.

8.2.4.3.2 Laboratory Abnormalities / Changes

There were no safety signals detected from laboratory examinations. Since laboratories were done only pre and post-study, attribution of any abnormalities would have been difficult in any case.

8.2.4.3.3 Vital Signs

Mean values for blood pressure and pulse rate were presented pre and post-exercise by treatment and showed no clear treatment response when compared to the data from the placebo group. There was, however, in the summary heart rate data at least some indication of more of a systemic response with the MDI compared to the Diskus (either dose) as the post-exercise heart rate (2 minutes after cessation) was highest in the MDI group. These data are shown in the following table:

Table 9

Challenge	Placebo	MDI	MDPI 50	MDPI 100
0.5 hour	28	28	28	29
End of exercise	159	161	158	158
2 minutes post-exercise	115	119	115	113
8.5 hours				
End of exercise	155	162	158	157
2 minutes post-exercise	117	122	118	115

8.2.4.3.4 ECGs

ECGs, like the laboratories, were only performed pre- and post-treatment, and therefore would not be likely to reveal any information that would be discriminative for relative effects of the 3 formulations tested. There was only one remarkable change over the course of the study and this was the appearance of new Q-waves in a 37-year-old female in the precordial leads. The cardiology work-up done as a result of this change was unremarkable.

8.2.5 Conclusions

8.2.5.1 Efficacy Conclusions

Study 2017 supports the efficacy of salmeterol Diskus 50 mcg in the prevention of EIB in patients prone to exercise-related fall in FEV_1 when used episodically and delivered 30 minutes prior to exercise. The support for the durability of protection beyond the first challenge is less clear in this study, but this in part may be due to the population enrolled (and will be addressed in part by supportive studies).

The MDI again appeared numerically (and by many analyses, statistically) superior to the MDPI. There was also little indication from this study that the 100 mcg Diskus confers additional protection when compared to the 50 mcg dose of the Diskus – particularly in the categorical analysis where at 8.5 hours there were a higher percentage of patients protected in the MDPI 50 mcg dose testing than the 100 mcg dose.

8.2.5.2 Overall Safety Conclusions

From the safety data generated, there does not appear to be any clear signal of a problem with tolerability of the formulations. It does appear from the vital signs data that the MDI may be more bioavailable, but this is a weak signal and, if reflective of a true pharmacokinetic phenomenon, did not translate into any defined clinical effect otherwise.

8.3 **STUDY SLGA2002**[5]

"A Randomized, Double-blind, Double-Dummy, Single-Dose, Three-Way Crossover Comparison of Salmeterol Xinafoate 50 mcg and Placebo Given by the Multidose Dry Powder Inhaler and the Diskhaler, for the Prevention of Exercise-Induced Bronchospasm in Adolescent and Adult Patients with Asthma." [sponsor title]

This study was submitted as a part of the PD linkage of the Diskhaler and Diskus in the original Diskus NDA. It is reviewed here because of its relevance to this supplement (it was not reviewed except for safety in the original NDA review because it was neither a pivotal efficacy study nor was it pivotal to the PD linkage). By agreement with DPDP , the sponsor did not resubmit these data in the supplement, but rather referenced their prior submission.

8.3.1 **Objectives/Rationale**

- To compare the efficacy and safety of salmeterol 50 mcg via the Diskus (MDPI) and the Diskhaler (DH) versus placebo in the prevention of EIB in patients 12-40 years of age with asthma.

8.3.2 **Design**

This was a two-center, randomized, double-blind, double-dummy, placebo and positive-controlled, 4-way cross-over conducted in the US between the dates of December 11, 1993 and June 30, 1994. Enrollment was planned for 24 evaluable patients 12 – 40 years of age with a diagnosis of EIB.

8.3.3 **Summary of the Study Protocol (including amendments)**

Note – there were substantial similarities between this and the prior protocols, so that only a brief discussion is given below, focusing on the important changes from those protocols previously reviewed. For ease of cross-reference, the enumeration has been kept consistent.

8.3.3.2 Treatment Visits

Single blind dose of placebo (baseline) – followed in random sequence by:

- salmeterol Diskus 50 mcg plus MDI placebo;
- salmeterol Diskhaler 50 mcg plus MDI placebo;
- Diskus plus Diskhaler placeboes (lactose only).

There was to be at least a 2-day and no more than a 14-day period between test days, with subjects only using *prn* Ventolin between visits.

8.3.3.5 Dosing

Two devices were distributed to each patient, for administration as follows the morning of test days:

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5 **(vol 1.130, page 276) of NDA 20-692 (submitted 6-19-96)**

Table 10

Treatment	Device A	Device B
	Diskus 50 mcg	Diskhaler 50
MDPI 50	1 blister active	1 blister placebo
DH 50	1 blister placebo	1 blister active
Placebo	1 blister placebo	1 blister placebo

8.3.3.6 Exercise Testing

The main difference in this study regarding the exercise testing was that rescue medication was not given unless the FEV_1 had dropped by ≥ 55% or if the PI felt that the patient otherwise warranted treatment.

Also, the exercise challenges were to be performed at 0.5, 5.5, and 11.5 hours post-dosing on treatment visit days.

8.3.3.9 Endpoints

The primary variable was the same as the prior studies.

8.3.3.13 Amendments to the protocol

There was 1 protocol amendment instituted after enrollment began regarding concomitant medications, treatment of exacerbations and power analyses, but these should have had no major impact in the interpretation of the results.

8.3.4 **Results**

8.3.4.1 Study population characteristics:

Twenty-two subjects between the ages of 15 and 36 years were enrolled into the study. Two patients were excluded from the efficacy population by the sponsor (1 failed to return, the other exacerbated, needed corticosteroids and therefore was in violation of the protocol). Twenty-two subjects participated in visit 1, 21 - visit 2 and 20 - visit 3 (with 19 completing the follow-up visit). A total of 8 visits were not conducted within the 2 – 14 days called for in the protocol, though none occurred before 2 days.

Demographics of the population revealed most patients were male (13 out of 22) and all were Caucasian. There were 6 subjects between the ages of 15 and 18, all from one site. The majority of subjects were in their 20's. Most patients had a long history of asthma (87% had a history more than 5 years), with the mean screening FEV_1 equal to 3.73 L (88.5% of predicted) with a mean maximal fall post-exercise of 35.5%.

8.1.4.1.2 Concurrent Illness / Drugs

The sponsor lists a summary of the concurrent illnesses by body system. Although the majority of subjects had concurrent illnesses, they fell primarily into the ocular, skin or ENT systems.

Concurrent medication use was largely unremarkable, primarily consisting of oral contraceptives, headache/pain preparations, and vitamins. Interestingly,

unlike the other studies above, NSAIDs were allowed in this trial and 4 subjects did take concomitant NSAIDs. Also unlike the previous studies, many subjects required RX for exacerbations in clinic (from the exercise-testing) despite the more liberal fall in FEV_1 allowed, with a total of 17 of the subjects receiving at least some treatment (mostly Isuprel) treatment during the course of the treatment visits. Additionally, one patient had a URI with a true exacerbation requiring prednisone treatment.

8.3.4.2 Efficacy Analysis

8.3.4.2.1 *Data set analyzed*

Results from both an Intent-to-Treat and an efficacy population were presented by the sponsor (the latter excluding all data on patients who withdrew early, and data for patients that did not complete a particular exercise test). This review will focus primarily on the ITT population, and on the MDPI vs. placebo data, since this is the most relevant to this review.

8.3.4.2.2 FEV_1 response to exercise challenge

The primary analysis for efficacy was the maximum percent fall in FEV_1 within the first hour following exercise testing and the sponsor focused on the efficacy population data. The investigators did a reasonable job of timing of the tests, particularly with the spacing of the testing post-dosing.

The FEV_1 data (ITT) are summarized in the table below:

Table 11

Exercise Challenge	PFT		Placebo FEV_1 [SE] (%)		MDPI 50		DH 100
#1 *0.5 hr*	Pre.	N=21	3.72 L	N=20	3.60	N=21	3.70
	Post	N=21	2.69 [4%] (-29)	N=21	3.31 [4%] (-10)	N=21	3.40 [4%] (-9)
#2 *5.5 hr*	Pre	N=19	3.80	N=20	4.05	N=21	4.01
	Post	N=17	3.01 [4%] (-25)	N=21	3.32 [4%] (-17)	N=21	3.44 [4%] (-15)
#3 *11.5 hr*	Pre	N=16	3.87	N=21	3.81	N=21	3.90
	Post	N=16	3.08 [4%] (-20)	N=20	3.06 [4%] (-22)	N=21	3.17 [3%] (-20)

For the pairwise testing between the MDPI and placebo, there was statistical separation at the 0.5 and 5.5 hour tests ($p<0.001$ and $= 0.002$ respectively), but not at the 11.5 hour test ($p = 0.239$). Though not directly relevant, similar statistical results were seen with the Diskhaler. Although the numerical trends looked better in the sponsor's efficacy-population analysis (with only a mean percent drop of 13% at 12 hours), there was still no statistical separation at that time point.

Similar data were seen for the minimum FEV_1 analysis, although all three time periods were statistically significant for the Diskus vs. placebo comparisons. Numerically, however, the results were unconvincing - with the mean minimum FEV_1 = 3.08 L for placebo from a 3.87 L baseline compared to a minimum of 3.06 L for the Diskus from a baseline of 3.81L.

The categorical analysis again provided similar data to the analysis of the mean response. These data are summarized in the table below (note that

patients unable to conclude an exercise challenge were included in the ≥ 20 % category):

Table 12

Challenge		Placebo		MDPI 50		DH 50	
% fall		(N)	(% total)	(N)	(% total)	(N)	(% total)
0.5 hour		21		21		21	
	< 10%	4	(19)	14	(67)	10	(48)
	≥ 10%, < 20%	6	(29)	1	(5)	7	(33)
	≥ 20%	11	(52)	6	(29)	4	(19)
5.5 hour							
	< 10%	4	(19)	10	(48)	11	(52)
	≥ 10%, < 20%	3	(14)	4	(19)	3	(14)
	≥ 20%	14	(67)	7	(33)	7	(33)
11.5 hour							
	< 10%	6	(29)	7	(33)	7	(33)
	≥ 10%, < 20%	2	(10)	3	(14)	5	(24)
	≥ 20%	13	(62)	11	(52)	9	(43)

In this analysis, the Diskus separated from placebo only at the immediate (0.5 hour) test. However, numerically, there is still an apparent effect with many more < 10% patients and many fewer >=20% patients in the Diskus group than placebo at the 5.5 hour test. There is very little evidence of protection out to 11.5 hours in these adolescent and adult patients, however.

Comment – undoubtedly, these data caused the sponsor to rethink a claim of 12 hours duration for the Diskus for EIB (though they have established that duration for bronchodilation). Therefore, the labeling for the Diskus will have to be different from the MDI, where a 12-hour duration for EIB has been approved.

8.3.4.3 Safety Analysis

The safety analysis included all patients who received any study drug, a total of 24 subjects, with each patient receiving all treatments over the course of the study. No deaths or serious AEs were reported in this study, and no patients were withdrawn for an AE.

8.3.4.3.1 Adverse Event Occurrences

Relatively few AEs were reported in this study (6 during the treatment phase), though all arose in the active treatment groups. Of those that could plausibly be treatment-related (i.e., excluding a cataract) – the three worth noting are:

a case of pharyngitis in a DH patient; a case of nasopharyngitis in a Diskus patient, and a case of palpitations in a Diskus patient. This latter event was deemed by the investigator as possibly related to treatment and lasted 6 hours.

8.3.4.3.2 Laboratory Abnormalities / Changes

There were no signals detected in laboratory examinations.

8.3.4.3.3 Vital Signs

Mean values for blood pressure and pulse rate were presented pre- and post-exercise by treatment and showed no clear treatment response when compared to the data from the placebo group.

8.3.4.3.4 ECGs

ECGs were conducted at each treatment visit pre-exercise and 0.5 hours post-exercise for each challenge. The QTc data shows an increase in the mean QTc and median QTc for this Diskus formulation compared to placebo at the 30 post-exercise evaluation following exercise #1 (that is, approximately 1 hour post-dosing). The mean is 6 msec longer than placebo and the median is 8, with 3 patients having QTc's exceeding 440 in the Diskus group compared with only 1 in placebo.

8.3.5 Conclusions

8.3.5.1 Efficacy Conclusions

Study 2002 supports the efficacy of salmeterol Diskus 50 mcg in the prevention of EIB in patients prone to exercise-related fall in FEV_1 when used episodically and delivered 30 minutes prior to exercise. The results from this study support protection against EIB out to 5.5 hours, but certainly not out to 11.5 hours, where very little residual effect was observed.

8.3.5.2 Overall Safety Conclusions

The limited safety data generated in this study suggest some possibility of minor attributable local effects such as pharyngitis, and also the possibility of systemic effects, since one patient experienced palpitations and there was an apparent effect on QTc at 30 minutes after the first challenge for the Diskus. These issues will be better addressed when looking at the integrated data for safety.

8.4 **STUDY SLGA2003[6]**

"A Randomized, Double-blind, Double-Dummy, Single-Dose, Three-Way Crossover Comparison of Salmeterol Xinafoate 50 and Placebo given by the Multi-dose Powder Inhaler and Diskhaler for the Prevention of Exercise-Induced Bronchospasm in Pediatric Subjects with Asthma." [sponsor title]

8.4.1 **Objectives/Rationale**

- To compare the efficacy and safety single doses of salmeterol 50 mcg via the Diskus and the [redacted] via Diskhaler (DH) with placebo in the prevention of EIB in patients 4 - 11 years of age with asthma.

8.4.2 **Design**

This was a two-center, randomized, double-blind, double-dummy, placebo and positive-controlled, 3-way cross-over conducted in the US between the dates of Feb. 10th and Aug. 12th, 1994. Enrollment was planned for 24 evaluable patients 4 - 11 years of age with a diagnosis of asthma and EIB.

8.4.3 **Summary of the Study Protocol (including amendments)**

8.4.3.1 Population

Patients of the appropriate age were recruited if they had a diagnosis of asthma by ATS criteria and EIB. At baseline, patients were to have an FEV_1 of at least 70% of predicted and had to have a demonstrated fall in FEV_1 with exercise of at least 20% from the pre-exercise testing. Patients had to be able to withhold medications prior to testing (notably, albuterol for at least 8 hours) and not have received any inhaled, parenteral or oral corticosteroids or cromone drug for 4 weeks prior to testing (stable doses of BDP intranasally were allowed). Environmental tobacco smoke exposure was an exclusion criterion if the exposure was 8 hours of more/day.

8.4.3.2 Treatment Visits

Random sequence of:

- salmeterol Diskus 50 mcg plus [redacted] placebo;
- salmeterol [redacted] 50 mcg via DH plus Diskus placebo.
- Diskus plus [redacted] placeboes

There was to be at least a 2-day and no more than a 14-day period between treatment days, with subjects using *prn* Ventolin and any other allowed medications (theophylline, oral beta agonists) between visits so long as the proper withholding was observed.

8.4.3.3 Assignment to Treatment

All eligible patients were to receive all treatments over the course of the study. Patients who dropped out, however, were not to be replaced.

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6 **(vol 1.010, page 1) of SE1-001**

8.4.3.4 Blinding

Active medications and their matching placebos were supplied in identical, double-blind Diskus and/or Diskhalers. Since the two salmeterol DPIs were so different, a double-dummy design was used.

8.4.3.5 Dosing

Two devices were distributed to each patient, for administration as follows the morning of test days (targeted for approximately 0800):

Table 13

Treatment	Device A	Device B
	MDPI	DH
MDPI 50	1 blister active	1 blister placebo
DH 50	1 blister placebo	1 blister active
Placebo	1 blister placebo	1 blister placebo

8.4.3.6 Exercise Testing

Serial spirometry was to be performed immediately pre-exercise (preceded immediately in each case by vital signs), and at 5, 10, 15, 30 and 60 minutes post-exercise. Duplicate determinations were performed (3 if necessary due to inconsistency) with the highest of the three FEV_1 readings recorded. Note that Polgar criteria were used to predict normal values.

To be considered for enrollment, all patients had to have a drop in FEV_1 following exercise at the screening visit of at least 20% from the pre-exercise value. The exercise challenge was a stepped technique utilizing a treadmill, changing the speed and incline to achieve a heart rate of at least 85% of the predicted maximum for age. The duration was to be 10 minutes (2 at minimal work load, 2 at 2/3 target work load and 6 at target conditions), although exercise in step III could be stopped if the subject became too symptomatic. An attempt was made to control head and humidity to the ranges of 20 – 25 C for temperature and humidity between 50 – 60% RH.

Any subject who experienced a fall of more than 40% were to receive rescue treatment, with isoproterenol MDI if between the first challenge and second challenge or between the second and third, or Ventolin if beyond the third exercise test.

On treatment visits, patients underwent predose FEV_1 assessment to assure stability of disease (within 15% of screening FEV_1). If the patient met the stability criterion, the first of the two exercise challenges was to be done at approximately 0830, timed for 30 minutes following dosing with study medications. The second was performed 5.5 hours following dosing with the third at 11.5 hours. These latter tests were only performed if the FEV_1 had returned to 90% of the pre-exercise level. Patients were to remain sedentary in between exercise tests.

8.4.3.7 Assessments

Efficacy Evaluations

The primary efficacy measure for this study was also the maximum percent fall in FEV_1 following exercise. Also analyzed was the minimum FEV_1 achieved (unadjusted for baseline) and a categorical analysis of patients who fell <10 %, those who fell between 10% and <20%, and those who fell 20% or more in their FEV_1.

Safety Evaluations

The following safety measures were collected in the study: adverse events, physical findings; and pre / post-study clinical laboratory evaluations. 12-lead ECGs were performed at screening, and at each visit prior to and 0.5 hours post-exercise.

8.4.3.8 Medication/Exposure Restrictions

- 8 or more hours since any back-up Ventolin use
- 12 or more hours since any short-acting oral beta agonist use
- 24 or more hours since any twice daily oral beta agonist use or any Serevent use (the latter per amendment)

8.4.3.9 Endpoints

Efficacy parameters:

The primary variable was an assessment of the percent fall in FEV_1 following exercise, based on the lowest value recorded during the first hour post-exercise. The percent fall will be compared amongst treatments utilizing an analysis of variance F-test based on a crossover model with terms for subject, treatment, period and carryover. The minimum FEV_1 unadjusted for baseline will be assessed using the same testing. The categorical comparisons of FEV_1 were based on non-parametric statistical testing.

8.4.3.10 Statistical / Power considerations

Sample size: Data from previous EIB studies indicated that 14% is a reasonable assumption for the SD of the fall in FEV_1 post-exercise. Based on this and the ANOVA F-test crossover model with a significance level of 0.05, a sample size of 24 was reported by the sponsor to offer a >80% power to detect a 12% difference between any two treatments.

The analysis was designed to be an intent-to-treat analysis, based on the available data from any patient who received study treatment.

8.4.3.13 Amendments to the protocol

There was 1 protocol amendment instituted on March 23, 1994 after enrollment began. Though extensive, this should not have altered the interpretability of the results. Note that per this amendment, at least 33% of the subjects were to be less than 9 years old.

8.4.4 **Results**

8.4.4.1 Study population characteristics:

Twenty-four subjects between the ages of 4 to 11 years were screened and enrolled into the study. All 24 completed the study. Only 8 visits were not conducted within the 2 – 14 days between visits called for in the protocol, none were less than the 2 days.

Demographics revealed most patients were Caucasian (92%) and there were slightly more males (58%). The mean age was 9, with 38% of subjects under the age of 9, with the remainder between 9 – 11 years of age. The majority of subjects had a history of asthma of more than 2 years, with the mean screening FEV_1 equal to 1.81L (88.2% of predicted) with a mean maximal fall post-exercise of 30.6% at screening.

8.4.4.1.1 Concurrent Illness / Drugs

The sponsor lists a summary of the concurrent illnesses by body system. Although the majority of subjects had concurrent illnesses, they fell primarily into the ENT and neurologic systems.

Concurrent medication use was largely unremarkable, primarily consisting of headache/pain medications and beclomethasone nasal spray. A total of 13 subjects had an 'exacerbation' during the study (i.e., required Isuprel or Ventolin rescue): 8 at the screening challenge, 2 during placebo treatment only and 1 each during - screen, placebo and Diskus; screen placebo and DH; and screen, placebo and both active periods

8.4.4.2 Efficacy Analysis

Comment: *Although the Diskhaler data will be presented below because of the similarities in the formulations, since these data are not strictly relevant to this application from the regulatory standpoint, they will not be the focus of the discussion.*

8.4.4.2.1 *Data set analyzed*

All 24 subjects who were randomized completed the study and these formed the intent-to-treat population, the only population analyzed and presented by the sponsor.

8.4.4.2.2 FEV_1 response to exercise challenge

The primary analysis for efficacy was the maximum percent fall in FEV_1 within the first hour following exercise testing.

These data are summarized in the table below:

Table 14

Exercise Challenge	Spirometry assessment	Placebo FEV_1 [SE%] (%)	MDPI 50 FEV_1 [SE%] (%)	DH 50 FEV_1 [SE%] (%)
#1 *Initial*	Pre-exer.	1.73 L	1.76	1.75
	Post-exer.	1.50 [3] (-13%)	1.72 [2] (-2%)	1.74 [0] (1%)
#2 *5.5 hr*	Pre-exer.	1.76 L	1.89	1.94
	Post-exer.	1.55 [2] (-13%)	1.77 [1] (-6%)	1.82 [19] (-6%)
#2 *11.5 hr*	Pre-exer.	1.75 L	1.85	1.87
	Post-exer.	1.50 [4] (-14%)	1.71 [2] (-6%)	1.78 [2] (-5%)