Note that for the second and third challenges (5.5. and 11.5 hr), the data were from 21 and 20 patients respectively for all treatment groups.

The pairwise testing of the Diskus against placebo was positive at all tests, with p-values of 0.002, 0.017 and 0.024 for the initial, 5.5 and 11.5-hour challenges respectively. This is despite a very strong placebo response (i.e., the fall in FEV_1 on placebo was only in the range of 13 percent, when it had been in the range of 30% at screening). This might be expected to have rendered the study less sensitive to detecting a treatment response. A subset analysis of the 9 patients between ages 4 – 8 years yielded numerically similar results and support efficacy in that population.

Similar data were also seen for the minimum FEV_1 analysis with the Diskus beating placebo at all three time points.

The categorical analysis again 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 15

Challenge % fall	Placebo (N)	Placebo (% total)	MDPI 50 (N)	MDPI 50 (% total)	DH 50 (N)	DH 50 (% total)
0.5 hour	24		24		24	
< 10%	**13**	**(54)**	**22**	**(92)**	**21**	**(88)**
≥ 10%, < 20%	7	(29)	0	(0)	0	(0)
≥ 20%	**4**	**(17)**	**2**	**(8)**	**3**	**(13)**
5.5 hour						
< 10%	**9**	**(38)**	**16**	**(67)**	**17**	**(71)**
≥ 10%, < 20%	7	(29)	5	(21)	4	(17)
≥ 20%	**8**	**(33)**	**3**	**(13)**	**3**	**(13)**
11.5 hour						
< 10%	**11**	**(46)**	**16**	**(67)**	**17**	**(71)**
≥ 10%, < 20%	5	(21)	2	(8)	2	(8)
≥ 20%	**8**	**(33)**	**6**	**(25)**	**5**	**(21)**

In this analysis, the Diskus group did not separate statistically from placebo at the 11.5 hour time point, though clearly there is still a favorable trend with more patients being protected (i.e., falling less than 10%) and fewer being unprotected (i.e., falling 20% or more). Again these data are striking for the fact that so few patients consistently fell into the 20% or more category after placebo treatment.

8.4.4.3 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 No deaths or serious AEs were reported in this study, and no patients were withdrawn for an AE. Diskhaler safety data will be discussed,

given the formulation similarities.

8.4.4.3.1 Adverse Event Occurrences

There was only 1 AE reported in a Diskus patient, this patient experienced increase nasal congestion. Two AEs were noted on one DH patient – a patient who experienced a migraine and a rash.

Overall, these data provide little signal of any problems in safety or local tolerability.

8.4.4.3.2 Laboratory Abnormalities / Changes

There were no safety signals detected from the laboratory examinations.

8.4.4.3.3 Vital Signs

Mean values for blood pressure and pulse rate were presented pre and post-exercise by treatment. Looking at the serial data following exercise testing, there is no clear pattern in terms of elevated pulse rate, or changes in blood pressure related to treatment by either the Diskus or the DH.

8.4.4.3.4 ECGs

ECGs were performed pre-dose and 30 minutes post-testing for all three challenges. By both the line listings and by the mean/categorical data for QT intervals, there was no signal of an important effect of salmeterol, particularly at 30 minutes following the first challenge when one might expect the maximum systemic effects (compared to 5.5 and 11.5 hours).

8.4.5 Conclusions

8.4.5.1 Efficacy Conclusions

Study 2003 supports the efficacy of salmeterol Diskus 50 mcg in the prevention of EIB in pediatric asthma patients prone to exercise-related falls in FEV_1. This protection appears to be durable over an 11.5-hour period for many patients, but due to the high placebo response in this trial (the low number of placebo patients showing a 20% decline in FEV_1), it is difficult to confidently state that this is a reasonable proportion of subjects.

8.4.5.2 Overall Safety Conclusions

As in all these studies, the safety data generated were very limited, since the exposures are brief. There does not appear to be any clear signal of a problem with tolerability with the Diskus formulation in children. Despite this dose being the same as that used in the adult trials (50 mcg), no clear signal of more systemic effects was seen.

8.5 STUDY SLGA2014[7]

"A Randomized, Double-blind, Double-Dummy, Single-Dose, Four-Way Crossover Comparison of Salmeterol 25 mcg and 50 mcg Given by the Multi-dose Powder Inhaler (Diskus), Albuterol 180 mcg Given by the Metered-Dose Inhaler for the Prevention of Exercise-Induced Bronchospasm in Pediatric Subjects with Asthma." [sponsor title]

8.5.1 Objectives/Rationale

1. To demonstrate the clinical efficacy of single doses of salmeterol 25 and 50 mcg via the Diskus compared to albuterol MDI and placebo in the prevention of EIB for asthmatic patients 4 - 11 years of age.
2. To characterize the safety and tolerability of single doses of salmeterol 25 and 50 mcg via the Diskus in pediatric patients with asthma and EIB.

8.5.2 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 Feb. 19th and Sept. 12, 1996. Enrollment was planned for 24 evaluable patients 4 - 11 years of age with a diagnosis of asthma and EIB. Each study site was to enroll one 4 year old and one 5 year old (4 total patients).

Note that since many of the design features are shared with the other studies previously reviewed, the summary below will mainly focus on significant differences between this and the latter protocol, preserving the enumeration system.

8.5.3 Summary of the Study Protocol (including amendments)

8.5.3.1 Population

Patients of the appropriate age were recruited if they had a diagnosis of asthma by [redacted] 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 to be able to coordinate and correctly perform with the devices in question (MDIs, the Diskus and PFT equipment). The patients could 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). Also excluded were second generation antihistamines. Environmental tobacco smoke exposure was an exclusion criterion if the exposure was 4 hours of more/day.

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8.5.3.2 Treatment Visits

Random sequence of:

- salmeterol Diskus 25 mcg plus MDI placebo;
- salmeterol Diskus 50 mcg plus MDI placebo.
- Albuterol MDI plus Diskus placebo

There was to be at least 3 days 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.

8.5.3.5 Dosing

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

Table 16

Treatment	Device A	Device B
	MDPI	MDI
MDPI 25	1 blister active	2 inhalations of placebo
MDPI 50	1 blister active	2 inhalations of placebo
Albuterol 180 mcg	1 blister placebo	2 inhalations of albuterol
Placebo	1 blister placebo	2 inhalations of placebo

8.4.3.6 Exercise Testing

The timing of the exercise testing post-dosing was 0.5, 5.5 and 11.5 hours in this study (as amended, as the original protocol alternatively called for 2 tests at 0.5 and 8.5 hours and later 3 tests at 0.5, 5.5 and 12.5 hours). The FEV_1 on the pre-treatment evaluation must have been 80% of baseline for the test to be conducted that day, and FEV_1 must have returned to within 80% of the pre-dose value from that day for the next challenge to take place.

8.5.3.7 Assessments

Efficacy Evaluations

The primary efficacy measure for this study was again 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 and 12-lead ECGs.

8.5.3.9 Endpoints

Efficacy parameters:

The primary variable was essentially the same as the previous studies.

8.5.3.13 Amendments to the protocol

There were 2 protocol amendments. The only one of major consequence to the study was instituted prior to enrollment beginning, and this called for a change from the 0.5 and 8.5 hour testing and 0.5, 5.5, and 12.5 hour testing [sic] in the original protocol to 0.5, 5.5 and 11.5 hours in the final amended protocol.

8.5.4 **Results**

8.5.4.1 Study population characteristics:

Twenty-six subjects between the ages of 4 to 11 years were screened and enrolled into the study, 24 completed the study. The reasons for withdrawal were listed as "other" by the sponsor (i.e., not due to AEs).

Demographics revealed that, as in the other studies, most patients were male and mostly Caucasian (65% and 81% respectively). The mean age was 7.6, with 58% of subjects under the age of 9 and 42% between 9 – 11 years of age. The majority of subjects had a history of asthma of between 1 - 5 years, with the mean screening FEV_1 equal to 1.42 L (85.7% of predicted) with a mean maximal fall post-exercise of 27.4% at screening. (note that African American predicted values were corrected downward 12% from [redacted] criteria).

8.5.4.1.1 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 skin, neurologic and non-site specific categories.

Concurrent medication use was unremarkable. A total of 14 episodes where subjects had an 'exacerbation' during the study (i.e., required Isuprel and/or Ventolin rescue) occurred: 5 at the screening challenge, 4 during placebo treatment, 5 during albuterol treatment and 1 during MDPI 50.

8.5.4.2 Efficacy Analysis

8.5.4.2.1 *Data set analyzed*

All available data from all 26 subjects (the intent-to-treat population) randomized were analyzed.

8.5.4.2.2 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:

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ON ORIGINAL

Table 17

Exercise Challenge	Spirometry assessment	Placebo FEV_1 [SE] (%)	Albuterol FEV_1 [SE] (%)	MDPI 25 FEV_1 [SE] (%)	MDPI 50 FEV_1 [SE] (%)
#1 *Initial*	Pre-exer. Post-exer.	1.48 L 1.28 [2.55] (-13%)	1.60 L 1.54 [1.46] (-4%)	1.52 1.44 [2.10] (-5%)	1.53 1.44 [2.34] (-6%)
#2 *5.5 hr*	Pre-exer. Post-exer.	1.50 L 1.31 [2.59] (-12%)	1.54 L 1.31 [2.58] (-16%)	1.55 1.44 [2.02] (-8%)	1.67 1.53 [2.12] (-7%)
#2 *11.5 hr*	Pre-exer. Post-exer.	1.49 L 1.30 [2.35] (-14%)	1.49 L 1.25 [3.08] (-15%)	1.54 1.44 [1.67] (-7%)	1.57 1.45 [3.06] (-7%)

[For placebo, data came from 24 subjects at the initial testing and the pre-exercise testing for the 5.5 and 11.5 hour time periods, otherwise the number of subjects was 23. For albuterol, there were 25 subjects contributing to all tests except the 11.5 hour time period, where both the pre and post-exercise 'n' was 24. For the MDPI 25, 26 subjects contributed to all the tests except the post-exercise 11.5 hour time point, and for the MDPI 50, 25 subjects contributed to all tests except for the 6 hour time points, where both pre and post-exercise testing was performed on 24 subjects.]

The pairwise testing of the 50 mcg Diskus against placebo was positive at the initial and 11.5 hour challenges (p = 0.002 and 0.002) respectively, but not at the 6 hour time point (p = 0.064). The 25 mcg Diskus was significantly different from placebo at all time points. Albuterol was only superior to placebo initially and trended towards worse responses at subsequent testing (though not significantly). As in the last study, there was a very strong placebo response (i.e., the fall in FEV_1 on placebo was in the range of 12 – 14 percent, when it had been in the range of 27% at screening). A subset analysis of the 9 patients between ages 4 – 8 years yielded numerically similar results to the overall population and support efficacy in that age group.

Comment - it is interesting to note that not only is there no residual protective effect of albuterol seen at 5.5 and 11.5 hours, but there actually is a trend towards the placebo group being worse than placebo at those time points. Although this is not statistically significant, it does lead to a lower p-value for the Serevent-albuterol comparisons than for the Serevent-placebo comparison.

Similar data were also seen from the minimum FEV_1 analysis, although by this analysis, the 50 mcg Diskus beat placebo at the latter two time points, but not initially and the 25 mcg Diskus failed to statistically separate from placebo at any time point.

The categorical analysis provided similar and complimentary data to the analysis of the mean response, although with more clear-cut superiority of the MDPI 50 compared with placebo. These data are summarized in the table below (note that patients unable to conclude an exercise challenge were included in the ≥ 20% category):

Table 18

Challenge % fall	Placebo (N)	Placebo (% total)	Albuterol (N)	Albuterol (% total)	MDPI 25 (N)	MDPI 25 (% total)	MDPI 50 (N)	MDPI 50 (% total)
0.5 hour	26		25		26		25	
< 10%	10	(38)	21	(84)	19	(73)	20	(80)
≥ 10%, < 20%	9	(35)	3	(4)	4	(15)	2	(8)
≥ 20%	7	(27)	1	(4)	3	(12)	3	(12)
5.5 hour								
< 10%	13	(50)	10	(40)	22	(85)	20	(80)
≥ 10%, < 20%	5	(19)	8	(32)	1	(4)	3	(12)
≥ 20%	8	(33)	7	(28)	3	(12)	2	(8)
11.5 hour								
< 10%	9	(35)	10	(40)	17	(65)	19	(76)
≥ 10%, < 20%	9	(35)	9	(36)	5	(19)	4	(16)
≥ 20%	8	(31)	6	(24)	4	(15)	2	(8)

In this analysis, the Diskus group did not separate from placebo at the 11.5 hour time point, though clearly there was still a favorable trend with more patients being protected (i.e., falling less than 10%) and fewer being unprotected (i.e., falling 20% or more). Again these data are striking for the fact that so few patients consistently fell into the 20% or more category after placebo treatment. There is also a clearer dose response relationship at the 11.5 hour time point, with a shift towards better categorical response with the 50 mcg dose compared to the 25 mcg dose.

8.5.4.3 Safety Analysis

The safety analysis included all patients who received any study drug, a total of 26 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. Diskhaler safety data will be discussed, given the formulation similarities.

8.5.4.3.1 Adverse Event Occurrences

There was only 1 AE reported in a Diskus patient, this patient experienced increase nasal congestion. Two AEs were noted on one DH patient – a patient who experienced a migraine and a rash.

Overall, these data provide little signal of any problems in safety or local tolerability.

8.5.4.3.2 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.

8.5.4.3.3 Vital Signs

Mean values for blood pressure and pulse rate were presented pre and post-exercise by treatment. Looking at the serial data following exercise testing,

there is no clear pattern in terms of elevated pulse rate, or changes in blood pressure related to treatment by either the Diskus or the DH.

8.5.4.3.4 ECGs

ECGs were performed predose and 30 minutes post-testing for all three challenges. By either the line listings or by means and categories of QT intervals, there was no signal of an important effect of salmeterol, particularly at 30 minutes following the first challenge when one might expect the maximum systemic effects (compared to 5.5 and 11.5 hours).

8.5.5 Conclusions

8.5.5.1 Efficacy Conclusions

Study 2003 supports the efficacy of salmeterol Diskus 50 mcg in the prevention of EIB in pediatric asthma patients who are known to be prone to an exercise-related fall in FEV_1. This protection appears to be durable over an 11.5-hour period for many patients. However, due to the high placebo response in this trial (the low number of placebo patients showing a stable 20% decline in FEV_1), it is difficult to confidently state that these was a reasonable proportion of subjects who remained protected over and above placebo.

8.5.5.2 Overall Safety Conclusions

As in all these studies, the safety data generated were very limited, since the exposures are brief. There does not appear to be any clear signal of a problem with tolerability with the Diskus formulation in children. Despite this dose being the same as that used in the adult trials (50 mcg), no clear signal of systemic effects was seen.

8.6 **Other Relevant Clinical Data:**

There were several other studies (non-US, +/- placebo controlled) submitted that could be considered as supportive. For the purposes of this review, these studies were primarily reviewed for safety (some of these data were also considered as a part of the ISS of original NDA 20-692 or are in the ISS for SE1-002). However, some of the efficacy data do provide some insights towards this review and therefore are briefly discussed in this section.

8.6.1 Study SLPP01

This was a single center study done in the UK comparing single and chronic dosing (6 weeks) of salmeterol 50 mcg BID via the Diskhaler (DH) vs. sodium cromoglycate 20 mg QID in the prevention of EIB in patients aged 8 to 15 years. No placebo was examined in this trial, which is problematic given the lack of reproducibility of the exercise response seen in the other pediatric trials submitted. Also, since this was a DH trial (not Diskus), the results cannot be considered as directly relevant to the Diskus. Furthermore, the enrollment was only 20 patients, with another 7 patients withdrawn during the run-in period, leaving only 13 patients who were randomized. However, since these data do partially speak to durability of the EIB protection with repeated dosing of salmeterol, they are worth discussion.

The mean percent fall in FEV_1 was approximately 0.82 L or 38% in these patients at screening. Following the 1st dose of Serevent Diskus, there was only a mean overall fall in FEV_1 of 0.27 L at one hour, or approximately 12.5% of the baseline FEV_1. However, this did not diminish over time with regular dosing (in fact, the % fall at the 1-hour time point following 6 weeks of BID dosing of salmeterol was approximately 8%). While this is somewhat reassuring, the ten-hour time point was not examined at six weeks, and therefore there are no data from the time point that might be most sensitive to the effects of tachyphylaxis. The safety data from this trial was largely unremarkable, with fewer AEs with cromoglycate than salmeterol, and no signal of an intolerance or safety issue with the DH formulation.

8.6.2 Study SLPH01

This was a single-center, randomized, placebo-controlled, double-blind cross-over study of salmeterol via the DH and placebo in the prevention of EIB in children, assessing both immediate effects and effects after 4 weeks of regular administration. This study, done in Denmark in 1993-1994, was quite small – enrolling 10 patients of whom 9 were randomized.

The age range of the patients enrolled was 10 – 14 years. The patients were enrolled into two sequences of either placebo or salmeterol 50 mcg via the DH for 4 weeks, with exercise testing at 6 hours and 12 hours after the first and last dose (without any more proximate test). The efficacy results showed that at 6 hours post-exercise, there was a numerical trend towards protection at both the 1st dose and 4 weeks, with the 1st dose results being statistically significant. The 4 weeks analysis is complicated by having few patients who

successfully completed the testing (thereby limiting power), but the numerical separation of active versus placebo at 4 weeks for the 6 hour challenge was less than the 1st dose testing. [19% difference in percent fall in FEV_1 at the 1st dose between active and placebo, 12% difference at the 4 week time point]. At the 12 hour time point, there was even less separation of salmeterol from placebo than found at the 6 hour comparison, with the numerical trend in the data at 4 weeks actually favoring placebo. While this study is flawed and small, it again raises the issue of tachyphylaxis of the EIB protection with regular administration, particularly for exercise more remote from the dosing.

As for safety, the results of this trial were again largely unremarkable. There was one patient – a 14-year-old boy – who 10 days into salmeterol treatment developed URI symptoms and 2 days later needed to be hospitalized for acute asthma. He was withdrawn from the study at that time and recovered uneventfully. However, the investigator rated this as potentially treatment related due to lack of efficacy. Otherwise, the numbers and characteristics of the AEs was similar between the two treatment groups and typical of this population.

8.6.3 Study SLGB4004

This study was conducted with the Diskus device in children to test for any pharmacodynamic (i.e., the bronchoprotective) effects of differing flow rates through this device in children. The patients were trained in the needed inspiratory maneuvers, and the flow rates were monitored during the dosing via a pneumotachometer to assure that the mean flow rate for the first 500 cc of breath was within 20% of the targets. The low flow rate target was 30 L/min and the high flow rate target was 90 L/min.

This was a small, double-blind, placebo-controlled cross-over study of Serevent Diskus 50 mcg in children with documented EIB. It was performed at a single site (Copenhagen). There were 18 patients enrolled, 13 of whom were males. The age range studied was between 8 and 15 with a mean age of 12. This study supported the fact that the effects of salmeterol (both in terms of bronchodilation as assessed by pre-exercise FEV_1 and bronchoprotection) were very similar despite a three-fold difference in flow-rate. Essentially, this study gives some supportive evidence of the 12-hour duration of efficacy in pediatric patients, and also offers some reassurance that over an approximate 30 – 90 L/min flow-rate, the device's delivery characteristics clinically are relatively insensitive to inspiratory flow rates.

Table 19

% fall in FEV_1	Placebo	Diskus – 30 L/m	Diskus – 90 L/min
1 hour	*N = 18*	*N = 18*	*N = 18*
Rise in FEV_1 – no change	0	5	5
Fall of > 0 – 10%	3	6	6
>10 – 20%	4	3	6
> 20 – 30%	6	2	0
> 30%	5	2	1
12 hours	*N = 18*	*N = 17*	*N = 18*
Rise in FEV_1 – no change	1	0	1
Fall of > 0 – 10%	4	11	7
>10 – 20%	6	4	6
> 20 – 30%	3	1	2
>30%	4	1	2

9.0 INTEGRATED SUMMARY OF EFFICACY (ISE)

Since this application is relatively concise and the main evidence of efficacy arises from the five, small single-dose US studies, the reporting of the ISE review will be relatively brief.

9.1 Onset of Efficacy

The onset of efficacy was not examined in these trials. Based on prior experience with salmeterol (which is somewhat slower in onset than albuterol), the sponsor consistently conducted the first exercise challenge at 30 minute post-dosing. These data reproducibly support the proposed instructions to dose *at least* 30 minutes prior to exercise, as the efficacy of the 50 mcg dose was seen at this time point in all the US pivotal trials.

9.2 Duration of Efficacy

Unlike the data from bronchodilation, efficacy data provided by the sponsor for the Serevent Diskus in preventing EIB for patients ages 12 and above do not support a 12-hour duration of protection. In fact, the sponsor's proposed labeling for adults only supports a duration of 9-hours in *most* patients. This is in contradistinction to the EIB labeling of the MDI where a claim of up to 12-hours of protection is made. This likely is a reflection of differing dose delivery characteristics of the two formulations.

There are now data in both the original Diskus NDA 20-692 and in this efficacy supplement which strongly suggest that the MDI and the Diskus are not equivalent in terms of efficacy. The studies in this supplement - 2013 and 2017 - show a trend towards greater protection for the MDI than the Diskus at almost all comparisons. Though some of the MDI – MDPI comparisons were "statistically significant" in favor of the MDI, this was not uniform and these *p*-values were not corrected for multiple comparisons. Nonetheless, these trends imply more effective dose delivery with the MDI reflected by more

complete and more durable EIB protection with the MDI. That said, the Diskus device is clearly effective compared to placebo when used in a single dose and maintains that efficacy for many adolescent and adult patients out to 8.5 hours post-dosing (but likely not out to 12 hours, as documented in study 2002). Below is the combined categorization of percent fall in FEV_1 data from studies 2013 and 2017:

Table 20

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	52		52		52		53	
< 10%	**15**	**(29)**	**36**	**(69)**	**31**	**(60)**	**36**	**(68)**
≥ 10%, < 20%	3	(6)	12	(23)	11	(21)	8	(15)
≥ 20%	**34**	**(65)**	**4**	**(8)**	**10**	**(19)**	**9**	**(17)**
8.5 hour								
< 10%	**12**	**(23)**	**31**	**(60)**	**26**	**(50)**	**23**	**(43)**
≥ 10%, < 20%	7	(13)	12	(23)	12	(23)	16	(30)
≥ 20%	**33**	**(63)**	**9**	**(17)**	**14**	**(27)**	**14**	**(26)**

When assessed by these categorical presentations, it appears that the proposed dose of the Diskus is fully protective (fall in FEV_1 < 10%) in many patients and offers relative protection (fall of >10% but less than 20%) in many more patients out to 8.5 hours, when compared to placebo.

For adolescents and adults, therefore, it appears the data presented in this supplement appear adequate for a claim of 8.5 hours duration for the protective effect when the Diskus is used episodically, with the caveat that this will not be experienced by all patients who initially responded.

For the 4 – 11 year old population, the two pivotal studies examined an 11.5 hour time point (referred to by the sponsor as 12 hours in the ISE). The categorical data for these studies are represented separately below:

Table 21

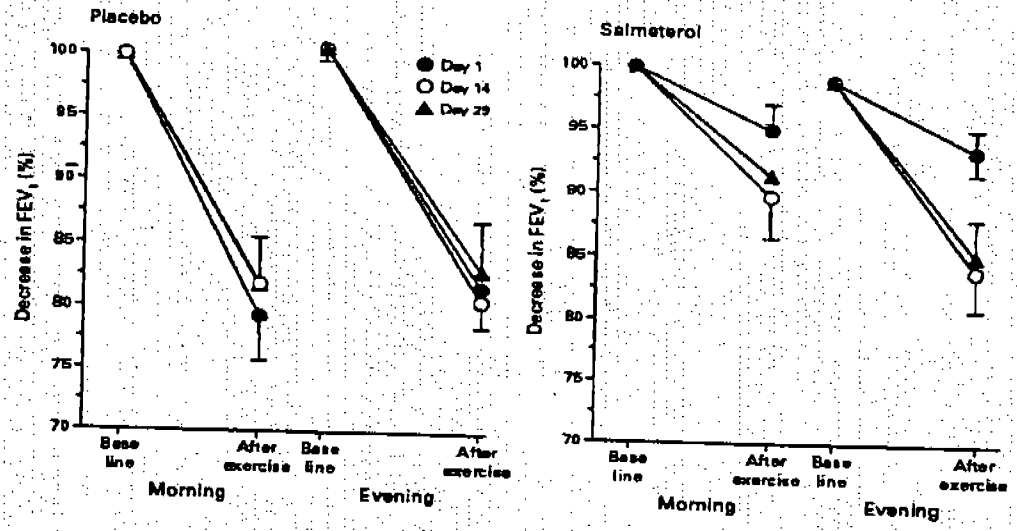
Study	2014				2003			
Challenge	Placebo		MDPI 50		Placebo		MDPI 50	
% fall	(N)	(% total)	(N)	(% total)	(N)	(% total)	(N)	(% total)
0.5 hour	26		25		24		24	
< 10%	**10**	**(38)**	**20**	**(80)**	**13**	**(54)**	**22**	**(88)**
≥ 10%, < 20%	9	(35)	2	(8)	7	(29)	0	(0)
≥ 20%	**7**	**(27)**	**3**	**(12)**	**4**	**(17)**	**2**	**(13)**
11.5 hour								
< 10%	**9**	**(35)**	**19**	**(76)**	**11**	**(46)**	**16**	**(71)**
≥ 10%, < 20%	9	(35)	4	(16)	5	(21)	2	(8)
≥ 20%	**8**	**(31)**	**2**	**(8)**	**8**	**(33)**	**6**	**(21)**

These results are quite consistent across the two studies. As previously mentioned, these children did not display good reproducibility of the fall in FEV_1 response to exercise, since there were between 35 – 54% of subjects did not drop their FEV_1 by 10% during subsequent placebo testing. This

might be expected to hamper the ability to show a treatment response that statistically separates from placebo (and to some degree, did). However, if one focuses on the < 10% and the ≥ 20% categories, it is clear that both studies show a smaller percentage of subjects who had a clear lack of protection and a higher percentage of subjects who were more fully protected in the Diskus group compared to the control groups' response. Although not represented here, this was true at the 5.5-hour challenge as well. Therefore, it appears that the sponsor's claim of up to 12 hours protection in 4 – 11 year olds is warranted, again with the caveat that not all patients who initially respond can expect protection out to that time period.

Another aspect of duration of response is how regular dosing of Serevent (i.e., BID on a daily basis) effects the protection against EIB. There are a few articles in the literature suggesting that tachyphylaxis to the EIB protection may occur with Serevent in the setting of regular dosing (as well as tolerance to other bronchoprovocations). A recent article in the New England Journal of Medicine [*N Engl J Med* 1998; 339:141-6] utilizing the MDI help to confirm this finding that became apparent from the original NDA for Serevent Inhalation Aerosol (and as represented in that labeling). The NEJM article suggests that tachyphylaxis most affects the duration of EIB protection. Below is a figure reproduced from the NEJM article depicting the relative effects of salmeterol in protecting against exercise over a 29 day study (all data are related to a 100% baseline). The evening exercise challenge was performed approximately 9 hours post-dosing.

Figure 2



The above figures show that although even the early protective effects of salmeterol lessen over time with continual dosing, this is even more apparent at the 9 hour challenge or 'evening' time point. This decrease in protective

effect is apparent at 14 days and does not appear to further change out to 29 days.

This issue of a lessening of the EIB protection with regular dosing was only partly addressed in the original Diskus NDA, since this NDA did not claim EIB as an indication. Unfortunately, the studies available to examine this issue (either from the NDA itself or this supplement) are not of sufficient quality in terms of the device used, population enrolled, and in other aspects of their design to sufficiently answer whether this tachyphylaxis clearly occurs with Serevent Diskus. However, it does appear from studies SLPH01 and SLPP01 that it is quite possible that regular dosing with Serevent Diskus would lead to a diminished EIB protection, particularly if the exercise is more remote from dosing (that is, beyond 6 hours). It seems reasonable based on existing data to assume tachyphylaxis would occur with the Diskus device when dosed regularly, until the sponsor provides data to answer the question.

9.3 **Dose - Response Characteristics**

While there are were dose ranging comparisons in this application (50 and 100 mcg for the 12 and above population, 25 and 50 mcg for the 4 – 11 year olds), there is surprisingly little in the way of dose-effect seen. For the Diskus used in adolescents and above, it appears that the 50 and 100 mcg give quite comparable results in terms of efficacy, and both appear to offer somewhat less protection against EIB than the MDI formulation. For the younger pediatric population, there was at most a marginal signal of more patients being in the <10% category of fall in FEV_1 at 11.5 hours and fewer in the ≥ 20% category for the 50 mcg over the 25 mcg. Fortunately, in neither population did there appear to be dose-response safety concerns for the range and duration of exposure studied. Therefore, the 50 mcg dose from the Diskus does appear to be reasonably supported in both populations.

9.4 **Efficacy in Subgroups**

9.4.1 Gender Subgroups

The sponsor pooled the two adult / adolescent trials (2013, 2017) to allow for gender subset analysis. These data show that there were 22 females and 31 males enrolled into these studies (although data from only 21 females is available for the relevant treatments). The overall results support efficacy in both genders subsets at both the 30 minute and 8.5 hour challenges. However, the results for the 8.5-hour challenge were more statistically convincing in males than females. This appears to be partly due to less of a fall in FEV_1 during placebo treatment in females. Below is a depiction of the categorical analysis by gender for the comparison of placebo and MDPI 50:

Table 22

Study	Female				Male			
Challenge	Placebo		MDPI 50		Placebo		MDPI 50	
% fall	(N)	(% total)	(N)	(% total)	(N)	(% total)	(N)	(% total)
0.5 hour	21		21		31		31	
< 10%	9	(43)	15	(71)	6	(19)	16	(52)
≥ 10%, < 20%	2	(10)	4	(19)	1	(3)	7	(23)
≥ 20%	10	(48)	2	(10)	24	(77)	8	(26)
11.5 hour								
< 10%	7	(33)	12	(57)	5	(16)	14	(45)
≥ 10%, < 20%	4	(19)	4	(19)	3	(10)	8	(26)
≥ 20%	10	(48)	5	(24)	23	(74)	9	(29)

9.4.2 Age Subgroups

One important age-related issue that comes out of these data is the lack of support for 11.5 hours of protection in patients age 12 and above, compared to the younger age group where two studies showed efficacy for many patients out to 11.5 hours. Because of the failure in SLGA2002 to show efficacy out to 11.5 hours, the pivotal US adult / adolescent studies were only done at 0.5 and 8.5 hours, and therefore one can only conclude from the data available that there is support for a claim of 12 hour duration for this subgroup of patients, where there are such data for the 4 – 11 year olds.

9.4.3 Race / Ethnic Subgroups

The large majority of the patients enrolled in these trials were Caucasian. There were not sufficient numbers of Blacks, Asians or Hispanics to make any meaningful inferences.

9.5 Overall Efficacy Conclusions

The sponsor has provided sufficiently compelling data to support the EIB claim for Serevent Diskus in both adults and pediatrics (down to age 4). However, this protection is most apparent shortly after dosing (i.e., at approximately 30 minutes) and is not durable in all responding patients out to the proposed time frames (9 hours in adults / adolescents, 12 hours in patients ages 4 – 11 years). This needs to be reflected in labeling. Furthermore, data with salmeterol, including some data with the DPI formulations, suggest that with regular dosing, the EIB protection wanes – particularly when the exercise is more remote from dosing. This also needs to be captured in the labeling so that affected individuals will continue to carry a relieving medication with them for such circumstances. Finally, these data suggest that the EIB protection with the Diskus is not as complete nor as durable as that afforded by the MDI. In part, this is already implicit in the proposed duration of 9 hours for the Diskus versus 12 hours for the MDI. However, the labeling should be changed to reflect that this potential clinical disparity was seen not only with bronchodilation trials (as is included in the approved and proposed labeling), but also bronchoprotection trials.

10.0 Integrated Summary of Safety

Due to the limited exposures resulting from small (approximately 24 subjects per study), single dose trials, the ISS presentation for the EIB indication is included with the SE1-002 Serevent Diskus supplement for the pediatric maintenance. This approach was previously agreed upon with the division. Collectively, there is a small signal of some product-related pharyngeal irritation and there were some patients who appeared to have a systemic beta-adrenergic response to salmeterol administered at 50 mcg from the Diskus. However, there appeared to be no unexpected level of systemic action and the potential for systemic reactions is well discussed in the approved labeling for the Serevent Diskus Inhalation Powder.

The safety data from these trials, combined with the previous finding of sufficient safety for the Serevent Diskus for patients ages 12 and above, are sufficient for approval of the EIB indication. This conclusion is also contingent on there being no safety concerns found during the review of SE1-002 for the maintenance treatment of asthma in patients ages 4 – 11 years.

11.0 Comments on Proposed Labeling[8]

The proposed labeling revises the recently approved Serevent Diskus labeling and incorporates proposed revisions based both on SE1-001 and 002. This review will comment only on those proposed revisions pertinent to the EIB indication. Comments will be given in sequential order below:

- In the *clinical trials* subsection, lines 130 – 139, there is a discussion of the clinical disparity between the MDI and the Diskus. Since a clear trend towards a difference was also seen in the EIB studies, this section should be amended. The following sentence should be added to line 137 following "...better results."

  Similar findings were noted in two randomized single dose crossover comparisons of salmeterol powder and salmeterol aerosol for the prevention of exercise-induced bronchospasm.

- In the *clinical trials* subsection, lines 152-154, there is a brief reference made to the two US EIB studies in adolescents and adults, claiming protection for at least 9 hours. Taking into account the fact that a proper correction for multiple endpoints would have rendered the 8.5 hour time point as insignificant in one of these two trials, this statement should be revised to read (and should include a table similar to that below):

  In two randomized single dose crossover studies in adolescents and adults with exercise-induced bronchospasm (EIB), 50 mcg of salmeterol powder significantly prevented EIB when dosed 30 minutes prior to exercise. For most patients, this protective effect against EIB was still apparent up to 8.5 hours following a single dose.

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8 **Proposed revisions to the package insert are found on page 11-29 in volume revised volume 1.001. Note that line numbers refer to enumerated lines in the proposed labeling.**

		Placebo (N = 52)		Serevent Diskus (N = 52)	
0.5 hour post-dose exercise challenge	% fall in FEV_1	(N)	(% total)	(N)	(% total)
	< 10%	15	(29)	31	(60)
	≥ 10%, < 20%	3	(6)	11	(21)
	≥ 20%	34	(65)	10	(19)
8.5 hour post-dose exercise challenge	% fall in FEV_1				
	< 10%	12	(23)	26	(50)
	≥ 10%, < 20%	7	(13)	12	(23)
	≥ 20%	33	(63)	14	(27)

- Lines 155 – 156 carry wording related to the pediatric EIB studies. This statement should be reworded as follows:

  In two randomized studies in children 4 – 11 years old with asthma and EIB, a single 50 mcg dose of salmeterol powder significantly attenuated EIB when dosed 30 minutes prior to exercise, with protection lasting up to 11.5 hours in repeat testing following this single-dose. [redacted]

- Lines 158 – 163 relate to the **Indications and Usage** section. This needs to be reworded not only to be more consistent with the MDI labeling, but also to separate the EIB indication from the regular dosing discussion. The following wording should be used:

  SEREVENT DISKUS inhalation powder is indicated for long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma in patients **[4 – if SE1-002 is approvable]** *years of age and older with reversible airway disease, including patients with nocturnal asthma, who require regular treatment with inhaled, short-acting beta$_2$-agonists. It is not indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting beta$_2$-agonists.*

  SEREVENT DISKUS is also indicated for prevention of exercise-induced bronchospasm in patients 4 years of age and older.

  SEREVENT DISKUS may be used with or without concurrent inhaled or systemic corticosteroid therapy.

- Although the rewrite of enumerated warning #2 related to 'Metabolic Effects of Serevent' is generally acceptable, as currently proposed, the words "*in serum potassium*" need to be added following the word "decrease..." in line 277.

- Lines 419 – 420 of the Pediatric Use subsection should be revised similarly to lines 156-157 to clarify that not all patients initially respond and not all patients who do respond initially are protected out to 11.5 hours.

- Lines 537-540 contain the EIB dosage and administration information. This statement needs to be revised to both incorporate some of the MDI labeling cautions on EIB use, and to incorporate concerns over tachyphylaxis:

  Prevention of Exercise-Induced Bronchospasm (EIB): *One inhalation of SEREVENT DISKUS inhalation powder at least 30 minutes before exercise has been shown to protect patients against EIB. When used as needed for prevention of EIB, this protection may*

last up to 9 hours in adolescents and adults, and up to 12 hours in patients 4 – 11 years of age. ADDITIONAL DOSES OF SEREVENT SHOULD NOT BE USED FOR 12 HOURS AFTER THE ADMINISTRATION OF THIS DRUG.

PATIENTS WHO ARE RECEIVING SEREVENT DISKUS INHALATION POWDER TWICE DAILY SHOULD NOT USE ADDITIONAL SEREVENT FOR PREVENTION OF EXERCISE-INDUCED BRONCHOSPASM.

12.0 OVERALL CONCLUSIONS

This supplement is approvable, provided that the labeling comments above as well as any deemed necessary by the other review teams are satisfactorily addressed. If the sponsor wishes to remove the caveats about regular administration and its deleterious effect on EIB protection, they will need to conduct studies to support such a revision. Since this phenomenon is reasonably well documented in the sponsor's original Serevent Inhalation Aerosol NDA and in the clinical literature, a specific phase 4 commitment to study its occurrence with the Serevent Diskus Inhalation Powder does not appear otherwise warranted, since its occurrence may be assumed.

APPEARS THIS WAY
ON ORIGINAL

cc:

NDA 20-692
HFD-570/Div. file/NDA 20-692
HFD-570/Medical Officer/Johnson
HFD-570/Chemistry Reviewer/Koble
HFD-570/Pharm - Tox Reviewer/Sancilio
HFD-570/Project Manger/Jani
HFD-570/Medical Officer/Meyer