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RESEARCH**

APPLICATION NUMBER:

21-949

MEDICAL REVIEW

MEDICAL OFFICER REVIEW			
Application:	NDA 21-949	Trade Name:	Pulmicort
Applicant/Sponsor:	AstraZeneca	USAN Name:	Budesonide
Medical Officer:	James Kaiser, M.D.	Indication:	asthma
Team Leader:	Peter Starke M.D.	Category:	corticosteroid
Review completed:	22 June 2006	Route:	inhalation
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date:	CDER Stamp Date:	Submission:	Comments:
11 May 2006	12 May 2006	Clinical trial cortisol data	See below
In addition to the review of the cortisol data, in this document I correct two transcription errors I made in the review of the NDA.			
REVIEW SUMMARY			
<p>In the original NDA submission, AstraZeneca presented summaries of cortisol testing during clinical development of the Pulmicort Turbuhaler M3 prior to the newly submitted placebo-controlled trials (urinary cortisol was measured in a small subset of subjects in the newly-submitted pediatric trial; see original NDA review). The trials included trials 0210, 0667, 0668, 0673, and 0600. Upon request, AstraZeneca submitted plasma cortisol values for each subject in these clinical trials. I conducted a review of these tabulations in order to look for large suppressive effects not detectable from the summary information. Other than in trial 0210, in which there were two dose levels, there was no control in these studies, making it difficult to detect anything other than gross effects.</p> <p>Among subjects with values below-reference value in trials 0668 and 0673 (where subjects were treated with the M3 at 360 µg BID) there were larger numbers of subjects with decreases from baseline in morning plasma cortisol than with increases, but large suppressive effects were not apparent. In trial 0210, where two dose levels of the M3 were tested (540 µg BID and 90 µg BID), there were too few subjects with abnormally low values (6 subjects) for a dose trend to be apparent. I did not detect a clear increased safety signal from listings of ACTH testing in trials where this was performed (trials 0668 and 0673).</p> <p>Pharmacokinetic information indicates that systemic exposure associated with the M3 product is no more than that associated with the current marketed product. My review does not indicate that current labeling needs to be revised.</p> <p>The submitted data do not indicate the need to change the labeling with respect to the systemic cortisol response to Pulmicort.</p> <p>Errata:</p> <p>Table 30 on page 42 of my review of the NDA contains two errors. The post-baseline time point for determination of cortisol should read "month 6" instead of "week 12" and the range of morning plasma cortisol values at month 6 should read "10-1110" instead of "10-110."</p>			

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this page is the manifestation of the electronic signature.**

/s/

James Kaiser
6/23/2006 04:23:43 PM
MEDICAL OFFICER

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CLINICAL TEAM LEADER MEMORANDUM

Date: May 31, 2006
To: NDA 21-949
From: Peter Starke, MD
Medical Team Leader
Division of Pulmonary and Allergy Products (DPAP), HFD-570
Product: Pulmicort Turbuhaler® (budesonide inhalation powder)
Applicant: AstraZeneca LP
Submission date: September 12, 2005
PDUFA date: July 12, 2006

Administrative and Introduction

This is a clinical team leader memorandum for a 505(b)(1) application (NDA 21-949) submitted by AstraZeneca LP for the **M3** presentation of Pulmicort Turbuhaler® (budesonide inhalation powder). The application is in Common Technical Document (CTD) format and includes information in Modules 1, 2, 3, and 5. It was filed electronically, although it is not an eCTD application.

The application proposes no changes to the INDICATION, although changes and additions are proposed to the CLINICAL TRIALS and DOSING AND ADMINISTRATION sections. Two new 12-week clinical trials are submitted to support a device switch from the current **M0-ESP** to the new **M3** presentation, which represents both a new formulation and modifications to the device, as discussed below. The application includes two dosage strengths of the M3 drug product, **90** and **180** mcg budesonide per inhalation (metered), which deliver **80** and **160** mcg, respectively. While the 180 mcg dosage strength is meant to replace the current 200 mcg M0-ESP dosage strength, the 90 mcg dosage strength is new. Reference is made to clinical studies submitted to previous marketing applications for Pulmicort Turbuhaler to support the 90 mcg dosage strength. Because this represents a new formulation, AZ has submitted a new NDA for this drug product; the stated plan is to discontinue production of and withdraw the NDA for the previous formulation (NDA 20-441) once the new NDA is approved.

Background

Pulmicort Turbuhaler is an inhalation-driven, multidose, dry powder inhaler containing the corticosteroid budesonide. It was approved in June, 1997, for the maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients six years of age and older (NDA 20-441). It is marketed in one dosage strength, 200 mcg budesonide per inhalation (metered), which delivers 160 mcg. The original NDA application included three dosage strengths, 100, 200 and 400 mcg, which deliver 80, 160 and 320 mcg, respectively. However, this application resulted in a refusal to file. There were significant problems with dose content uniformity of the lowest [100 mcg] dosage strength, such that when AZ

resubmitted the application, the 100 mcg dosage strength was omitted. The primary basis of approval was clinical data from 4 multicenter, randomized, double-blind, placebo-controlled, 12-20-week studies in subjects 6 years and older with asthma whose symptoms had been managed with and without inhaled or oral corticosteroids. Since the clinical program included all three dosage strengths, the reviews commented upon efficacy, but the labeling that resulted from the application never considered the 100 mcg dosage. While the 400 mcg dosage was approved and labeled, AZ chose not to market this product. AZ identified the originally approved product as **Pulmicort Turbuhaler M0**. [Note: The labeling does not and has never stated the product version.]

Because of the poor dose content uniformity of the approved dosage strengths, the approval for Pulmicort included a Phase 4 commitment to “conduct an ongoing development program for Turbuhaler which includes modifications of Turbuhaler, the process of controlled aggregation of micronized budesonide, the powder composition, and possible clinical testing.” The first change in the product made to honor the Phase 4 commitment was implementation of an enhanced spherization process (ESP) and the resultant drug product was **Pulmicort Turbuhaler M0-ESP**, approved in December, 2000 (NDA 20-441, S-009). The M0-ESP presentation generated more uniform spheres and reduced batch-to-batch variability of the product. The switch from M0 to M0-ESP was based on CMC data with support from one relative bioavailability study, SD-004-0708. Clinical studies were not required. Pulmicort Turbuhaler M0-ESP is the product currently marketed in the United States, available only in the 200 mcg metered/160 mcg delivered dosage strength.

This application is a new NDA for the newest presentation, **Pulmicort Turbuhaler M3**, which is intended to replace the M0-ESP device. It differs from the previous products in several notable ways [p1-2; qualsum.pdf]:

- The currently approved product meters 200 mcg per puff (160 mcg delivered); AZ proposes to market 90 mcg and 180 mcg metered dosage strengths, which deliver 80 and 160 mcg, respectively. (package sizes were developed for each dosage strength, 120 inhalations, but only the 120 size is intended for approval.)
- The formulation now includes a new excipient, micronized lactose, “to improve dosing accuracy.” Whereas previous M0 and M0-ESP presentations metered only budesonide, each M3 inhalation now meters mcg total per inhalation, including micronized lactose plus either budesonide per gram of lactose [160 and 80 mcg dosage strengths, respectively].
- The process of spherization has been modified.
- The mouthpiece has been redesigned with a new cleaning feature and new outer design.
- The device includes a new dose indicator.

Figure 1 shows a picture of the new Pulmicort Turbuhaler M3 device, which does not differ substantially in look from the previous device.

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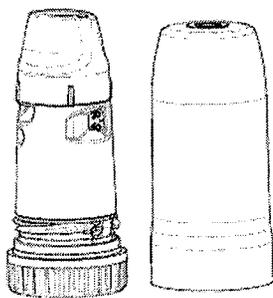


Figure 1. Pulmicort Turbuhaler M3

Source: F1, p7; qualsum.pdf

Since a comparable dosage strength to the 90 mcg is not approved, with this application AstraZeneca is seeking approval for the 90 mcg dosage strength with a starting dose of 90 mcg BID in children and adults with mild asthma. Approval of the lower dosage strength relies in part on previous Agency findings of efficacy and safety from the two pivotal M0 studies (04-3020A and 04-3023A) submitted to and reviewed with the original application, with bridging to M3, as noted above. These studies are re-submitted with this application.

The clinical development program for this NDA was performed under IND 63,762, and discussed at multiple meetings with the FDA, including EOP2 and pre-NDA meetings. The need for clinical studies and other aspects of the development program were discussed at a meeting dated July 20, 2000. Several issues discussed are notable. Clinical studies were needed because the addition of micronized lactose represents a major change to the formulation. A pediatric study was requested specifically because of concerns that children may have lower inspiratory flow rates (see discussion in CMC section below). The M3 drug product appears to be quite sensitive to decreases in flow rate below 60 L/min, with *in vitro* data showing a drop-off in mean particle and fine particle distribution by about one-half at flow rates of 30 L/min. For that reason, both PK and efficacy was requested in children in addition to adults. Also discussed was how the Agency would label the product if two dosage strengths were to be approved rather than the current single dosage strength. With two dosage strengths, a dose of 180 mcg BID might be achieved by 2 inhalations of the 90 mcg dosage strength

~~_____~~ AstraZeneca agreed that labeling might state that the 180 mcg dose has to be via 2 inhalations of the 90 mcg ~~_____~~

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One consultation was made during the course of this review as of the time of finalization of this Team Leader memo. The Division of Drug marketing, Advertising, and Communications provided labeling comments. Since no financial, ethical, or other issues of concern were uncovered during the reviews, a DSI audit was not requested or performed.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

The product review was performed by Dr. Craig Bertha. As of the completion of this review, there were two remaining CMC issues. The first is that there is the potential for changes in the composition of the ~~_____~~ component of the device. AstraZeneca has been requested to either attain a ~~_____~~ composition or to supply data to verify similar drug product performance regardless of the ~~_____~~ formulation composition ~~_____~~ As of the time of

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completion of this review, a recommendation from the Office of Compliance with regard to the site inspections is still pending.

With the addition of micronized lactose, the M3 device represents a new formulation as well as a slightly redesigned device. It was noted in submissions during the development program that there is a progressive drop-off in the measured *in vitro* fine particle dose (FPD, i.e. respirable dose) below an inspiratory flow rate (IFR) of 60 L/min, such that FPD and midstack particle dose (MPD) are less than half at an IFR of 30 L/min than at IFR of 60 L/min (Figure 2). [Note: FPD = Fine particle dose; ~~MPD = Midstack particle dose,~~ ~~_____~~ Inspiratory flow is quite effort-specific. While low flow rates may occur in adults, it is more likely that this would be an issue for a pediatric population. For these reasons, a pediatric study was requested in addition to an adult study as part of the clinical development program. It should also be noted that in the M3 clinical development program inspiratory flow was measured *in vivo* only within the pediatric study, not the adult study, resulting in proposed labeling to the DESCRIPTION (CMC) section that is more limited for the M3 than for previous version labeling.

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During the review process the Division requested information regarding how the previous and the new devices match for the *in vitro* aerodynamic particle size distribution (APSD) at various flow rates. These results are shown in Figure 3 for the beginning and end of product life. Both the FPD (shown) and the MPD (not shown) are *lower* (less fine particle delivery) at all flow rates for the M3 version as compared to the M0 and M0-ESP. Nevertheless, the drop-off in fine particle dose with decreasing inspiratory flow rates, as measured by *in vitro* testing, is not substantially different for the new product compared to the old products. In addition, there is at least one other marketed corticosteroid DPI product with similar *in vitro* inspiratory flow characteristics. The data and information regarding the flow rate dependency of the product should be captured in the DESCRIPTION section ~~_____~~

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In addition, the Division requested information on typical inspiratory flow rates in children down to 6 years of age. Little published data is available for children, but in one study the flow rate was 118 (N=35) for children 6-7 years of age, 140 (N=71) in 8-9 year olds, 173 (N=60) in 10-11 year olds, but only 78 (N=36) in 4-5 year olds.¹ Based on this information, it is reasonable to accept use down to 6 years of age, but labeling should include clear instructions on inspiring with sufficient force to maximize the respirable dose.

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¹ Vogelberg C., Kremer H. -J., et al. Clinical evaluation of the peak inspiratory flow generalized by asthmatic children through the Novolizer. *Respiratory Medicine* (2004) 98, 924-931.

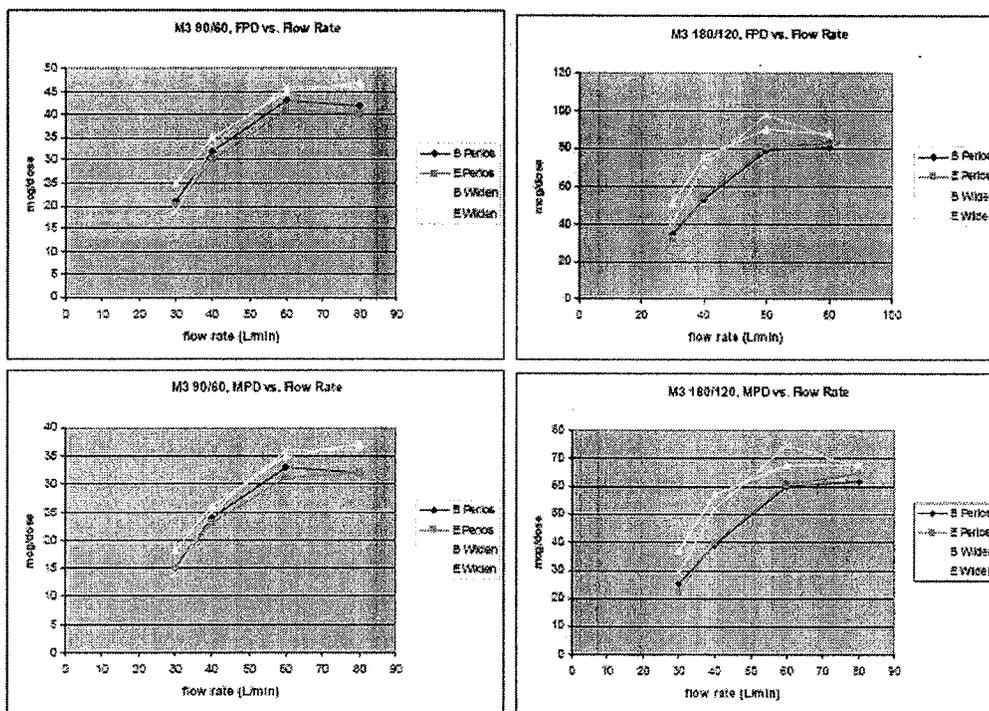


Figure 2. Particle delivery vs Inspiratory flow rate, M3 device, 90 and 180 mcg dosage strengths

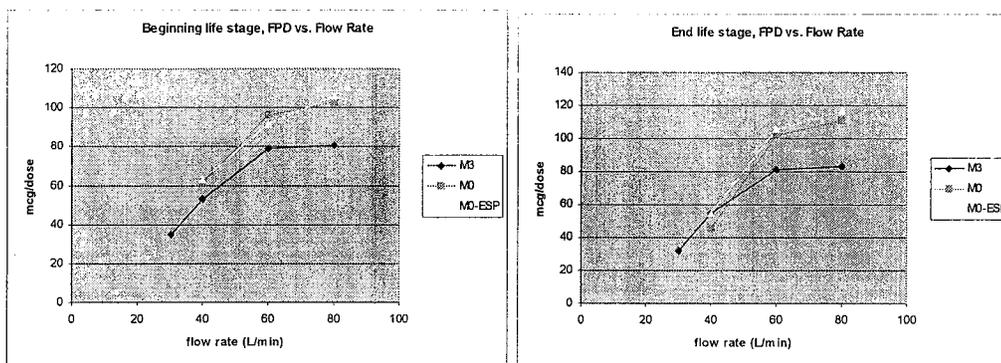


Figure 3. FPD vs Inspiratory flow rate; M0, M0-ESP, and M3 devices; beginning and end of life

Pharmacology and Toxicology

No new preclinical toxicology or pharmacology studies were performed for this NDA. References were provided to the applicant's NDAs for the budesonide drug products. Dr. Sancilio performed the Pharmacology and Toxicology review and recommends an Approval. There were no major Pharm/Tox issues with this application.

Clinical Pharmacology and Biopharmaceutics

Dr. Sayed Al Habet reviewed the Clinical Pharmacology and Biopharmaceutics data submitted with the application and recommends an Approval. One new and one old clinical pharmacology / biopharmaceutics study were submitted to support this application. Study

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SD-004-0708 (previously submitted to support the M0 to M0-ESP switch) compared the relative bioavailability of the **M0** versus the **M0-ESP** device, whereas study SD-004-CR-0601 (new) compared the relative bioavailability of the **M0** versus the **M3** device. No relative bioavailability studies compared the current M0-ESP with the M3 device, with the exception that systemic exposure was evaluated in a subset of patients in the two clinical studies. Please refer to the clinical studies for details.

Study SD-004-0708

This was an open, randomized, single-dose, 3-way crossover, relative systemic bioavailability study in 36 adult healthy volunteers comparing 4 inhalations of the original approved M0 200 mcg with 4 inhalations of the M0-ESP 200 mcg Pulmicort Turbuhaler (2 replications). The primary variables were the area under the curve (AUC_{0-12}) and the maximum concentration (C_{max}). The 90% confidence interval for both AUC_{0-12} and C_{max} fell between 80 and 125% for comparison of the two products.

Study SD-004-CR-0601

This was an open, randomized, single-dose, 3-way crossover, relative systemic bioavailability study in 36 adult well-controlled asthmatics comparing 4 inhalations of the original approved M0 200 mcg Pulmicort Turbuhaler [Batch BC199] with 4 inhalations of the M3 180 mcg [Batch BL12] and 8 inhalations of the M3 90 mcg [Batch BL11] formulation/device, with a washout period of at least 5 days. The primary aim was to compare the M3 180 with the M0 200, with the secondary aim to compare the two dosage strengths of the M3 formulation/device. The primary variables were $AUC_{0-\infty}$ and C_{max} .

The PK parameters (not shown) and the plasma concentration-time profiles (Figure 4) for the three treatments were comparable. The 90% confidence interval for both $AUC_{0-\infty}$ and C_{max} fell between 80 and 125% for both the primary comparison between Pulmicort Turbuhaler M0 4 x 200 mcg and Pulmicort Turbuhaler M3 4 x 180 mcg and the secondary comparison between the two strengths of the Pulmicort Turbuhaler M3 (Table 1).

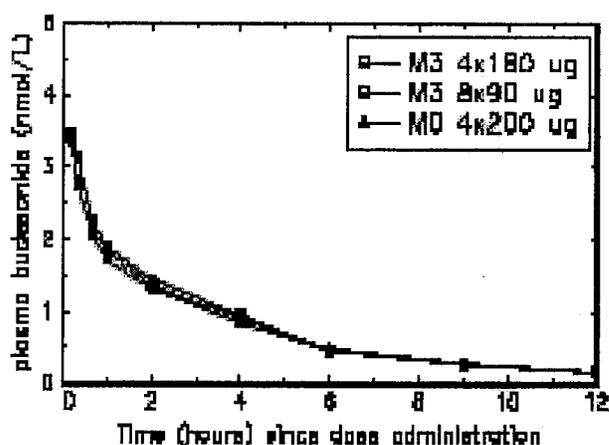


Figure 4. SD-004-CR-0601, Mean budesonide plasma concentration-time profiles

Source: F3, p34; SD-004-0601.pdf

Table 1. SD-004-CR-0601, Bioequivalence of plasma budesonide

Treatment Ratios	Ratio (%)	90% CI
AUC_{0-∞}		
M3 4x180 / M0 4x200	96.3	90.9, 102.1
M3 4x180 / M3 8x90	92.2	87.0, 97.7
C_{max}		
M3 4x180 / M0 4x200	100.4	92.1, 109.4
M3 4x180 / M3 8x90	94.4	86.6, 102.9

Source: T1, T2, p269; clinsum.pdf

Clinical and Statistical

Dr. James Kaiser performed the clinical review and recommends Approval. I also recommend Approval. However, we both conclude that the two drug products are not comparable; I therefore recommend severely limiting the efficacy and dosing labeling to information based on only the new clinical studies.

Clinical support for a switch from the M0-ESP to the M3 presentation rests with two new clinical studies, SD-004-0620 and SD-004-0726, and PK study SD-004-0601, which seek to link the old with the new product presentations (Table 2). Since this represents an abbreviated program rather than a full clinical development program, approval also rests with the findings of efficacy and safety from the original NDA application (Table 3). In particular, approval of lower dosing recommendations that accompany the M3 90 mcg strength depends on the Agency's previous findings of efficacy of studies 04-3020A and 04-3023A submitted and reviewed as part of the original NDA. Studies 3020A and 3023A support the efficacy and safety of the lower dosage (i.e. 80 mcg delivered dose) administered BID, whereas 620 and 726 support the switch from the old to the new presentation of the drug product. The results of studies 3020A and 3023A are briefly discussed in this review for two reasons. As noted above, the M3 clinical program builds upon the original studies. In addition, in light of the conclusions and recommendations outlined in this document, these studies provide a contextual frame of reference with which to interpret the new studies submitted to this application.

Dose selection for the switch program was based on several factors. AstraZeneca states that the high dose was selected based on the highest approved starting dose in patients previously treated with inhaled corticosteroids, 400 mcg BID for the M0-ESP, with a comparable dose of 360 mcg BID for the M3. This is a reasonable approach. AstraZeneca states that the choice of the once-daily low dose "was based on the unavailability of a lower dose strength of Pulmicort Turbuhaler M0-ESP in the US (e.g., the 100 mcg bid dose, which is approved in the Rest of World)." [p58; clinsum.pdf] Note that this created a situation in which the clinical studies provided data with a not-currently labeled once-daily starting dose, since once daily dosing is currently approved for some patients during the maintenance treatment phase but not as a starting dose. To explore the reasoning for why this dose was acceptable to the Agency, we reviewed all minutes from various meetings with the applicant, and were unable to find a specifically stated reason. However, it is my understanding that this dose was acceptable as an intentionally low (and unapproved) dose hoping that would fall on the rising slope of the dose response curve and therefore better elucidate any differences between the two products (see the discussion of lack of dose response in the Original NDA Clinical Studies section below). Since this is not a dose expected to be efficacious, each study

included only one dose to allow comparability of the M3 to an approved starting dose of the M0-ESP.

One possible concern in this switch program was that the to-be-marketed formulation was not used over the full course of both 12-week studies. To account for a loss of budesonide content of about 5% during blending, the budesonide content was increased during the course of the clinical development program. The metered dose content of the M3 180 device presentation was increased by 5% from _____ and the M3 90 device presentation was also increased by 5% to _____. The intent of the changes was that the M3 more closely match the delivered dose from the 200 mcg M0-ESP device. Only the US sites in study 620 were affected, the Asian sites all using the higher dose content formulation. As a result, in study 620 approximately two-thirds of the patients received the 178 mg/g formulation/device, representing patients enrolled after July 3, 2003 in the US (and all Asian patients). For the M3 90 device presentation, the change was implemented near the end of the clinical study, with the result that NONE of the patients in study 726 received the _____ formulation/device. Various sensitivity analyses were performed as part of the review of study 620, and it was determined that this small dose content change would not be expected to, nor did it reflect in any clinically apparent differences in efficacy. It was therefore treated as a CMC issue rather than an issue of clinical concern for either study.

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Dr. Kaiser's review revealed no new clinical safety concerns about budesonide. Since the M3 device has not been approved in any country, no postmarketing data are available for the proposed new device.

Table 2. Clinical Studies with Pulmicort M3

Study / Location	Design / Population	Product	Dose / Dosage strength	N
SD-004-0620 U.S., SE Asia	<ul style="list-style-type: none"> ▪ 525 Adults ≥18 yrs with asthma currently treated with inhaled steroids ▪ Double-blind, randomized, placebo-controlled, multicenter ▪ Placebo run-in, 12-week treatment ▪ Subset of pts for PK measurements ▪ 1° endpoint: mean change from baseline in FEV₁ (L) 	M3 180	180 mcg QD (180 x 1)	123
		M0-ESP 200	360 mcg BID (180 x 2)	130
		M0-ESP 200	200 mcg QD (200 x 1)	114
		M0-ESP 200	400 mcg BID (200 x 2)	130
		Placebo to match		124
SD-004-0726 U.S., SE Asia	<ul style="list-style-type: none"> ▪ 460 Children and adolescents 6-17 yrs with asthma currently treated with inhaled steroids ▪ Double-blind, randomized, placebo-controlled, multicenter ▪ Placebo run-in, 12-week treatment ▪ Subset of pts for PK measurements ▪ Subset of pts for PD urinary cortisol ▪ 1° endpoint: mean change from baseline in FEV₁ (% predicted) 	M3 90	180 mcg QD (90 x 2)	108
		M3 90	360 mcg BID (90 x 4)	96
		M0-ESP 200	200 mcg QD (200 x 1)	104
		M0-ESP 200	400 mcg BID (200 x 2)	102
		Placebo to match		106

Study / Location	Design / Population	Product	Dose / Dosage strength	N
SD-004-0601 Sweden	<ul style="list-style-type: none"> ▪ 37 "Well-controlled adult asthmatics" ▪ Open, randomized, crossover ▪ Three separate treatment days separated by 5-day washouts ▪ Endpoints: AUC, C_{max} 	M3 90 mcg M3 180 mcg M0 200 mcg	720 mcg (90 x 8) 720 mcg (180 x 4) 800 mcg (200 x 4)	
T1, p57; Clinsum.pdf				

Table 3. Other Pulmicort Clinical Studies (Including Original Efficacy and Safety Studies)

Study	Design	Treatments	N
04-3020 (GHBA-165) A: 12-wk double-blind B: 52-wk open-label extension C: 5-yr open-label extension Submitted in NDA 20-441	<ul style="list-style-type: none"> ▪ 473 Adults with chronic steroid-dependent asthma ▪ Double-blind, randomized, placebo-controlled, multicenter ▪ Run-in, 12-week treatment ▪ 1° endpoint: 2-week average morning PEF and average FEV₁ for each 2-week period and over 12-week study 	M0 100 mcg BID M0 200 mcg BID M0 400 mcg BID M0 800 mcg BID Placebo	91 92
04-3023 (GHBA-168) A: 12-wk double-blind B: 52-wk open-label extension C: 5-yr open-label extension Submitted in NDA 20-441	<ul style="list-style-type: none"> ▪ 404 Children and adolescents 6-18 yrs with chronic steroid-dependent asthma ▪ Double-blind, randomized, placebo-controlled, multicenter ▪ Run-in, 12-week treatment ▪ 1° endpoint: 2-week average morning PEF and average FEV₁ for each 2-week period and over 12-week study 	M0 100 mcg BID M0 200 mcg BID M0 400 mcg BID M0 800 mcg BID Placebo	102 103
Study	Description		
850-CR-0280	1-year open-label extension of 04-3020A		
D5254C00007	3-5 year open-label extension of 04-3020A		
SD-004-0708	PK study in healthy adults comparing M0 to M0-ESP		
SD-004-0600	BA of budesonide in M2 vs. M3		
SD-004-0210	Efficacy of M2 vs. M3		
SD-039-0667	Efficacy of Pulmicort M3 + terbutaline vs. Symbicort		
SD-039-0668	Efficacy of Pulmicort M3 + terbutaline vs. Symbicort		
SD-039-0673	Various combinations of Pulmicort, terbutaline, and Symbicort		

Original NDA Clinical Studies

The original NDA studies were intended to support 3 dosage strengths of the original M0 device, 100, 200, and 400 mcg metered (80, 160 and 320 delivered) doses. The 400 mcg dosage strength was never marketed, and the 100 mcg dosage strength suffered from such severe dose content variability that it could not be approved. The Division Director supervisory review of Jun 2 14, 1996, written by Dr. Jenkins, stated that the clinical program supported approval of the 100 mcg dosage strength from a clinical perspective. It also noted that "as is typical of clinical trials with inhaled corticosteroids, little evidence of a dose response trend was demonstrated, although in some trials 800 mcg BID was statistically superior to 100 mcg BID on some clinical endpoints." The memo also noted that the trials

submitted in support of a once-daily (QD) dosing recommendation were not adequate to support such a dosing regimen.

Studies 3020A (GHBA-165) and 3023A (GHBA-168) were both 12-week, randomized, double-blind, placebo-controlled, multicenter efficacy and safety studies that evaluated of 100, 200, 400 (and, in Study 3020A only, 800) mcg of Pulmicort M0 or placebo administered BID in adult or pediatric patients with inhaled corticosteroid-dependent asthma. Study 3020A evaluated patients ≥ 18 to 70 years, while Study 3023A evaluated patients ages 6 to 18 years. The studies had a 1-week screening period, 2-week baseline period, and a 12-week treatment period. In Study 3020A, the 473 randomized patients were stratified based on their daily dose of beclomethasone dipropionate (BDP) at baseline (6 to 10 vs 11 to 20 inhalations), whereas in 3023A the 404 randomized patients were stratified based on age (6 to 12 vs 13 to 18 years). The co-primary efficacy variables in Study 3020A were change from baseline in average morning PEF and change from baseline in FEV₁. The co-primary efficacy variables in Study 3023A were change from baseline in average morning PEF and change from baseline in FEV₁, both expressed as % of predicted normal. Both studies had 1- and 5-year open-label safety extensions, labeled with the suffixes B and C, respectively.

While the Division Director supervisory review noted that there was little evidence of a dose response between the 100 and 800 mcg BID doses, in study 3020A there is a small separation between doses apparent visually (but not statistically), with dose-ordering seen particularly for the 100 mcg BID dose (shown graphically in Figure 5 and Figure 6). Of particular note, the change from baseline in FEV₁ (Table 4) over the study was in the range of 220-270 mL for the 200-800 mcg BID dosages, but only 141 mL for the 100 mcg BID dosage, whereas placebo lost 167 mL. In study 3023A, dose ordering was less apparent in % predicted PEF, but still apparent in % predicted FEV₁ (Figure 7, Figure 8, and Table 5).

Although cross-study comparison is of limited value, the pros and cons of which will not be discussed here, it should also be noted that the placebo arms declined in both of the original studies, whereas in studies 620 and 726 placebo arms improved over the course treatment. Therefore, both change from baseline and difference from placebo should be taken into consideration.

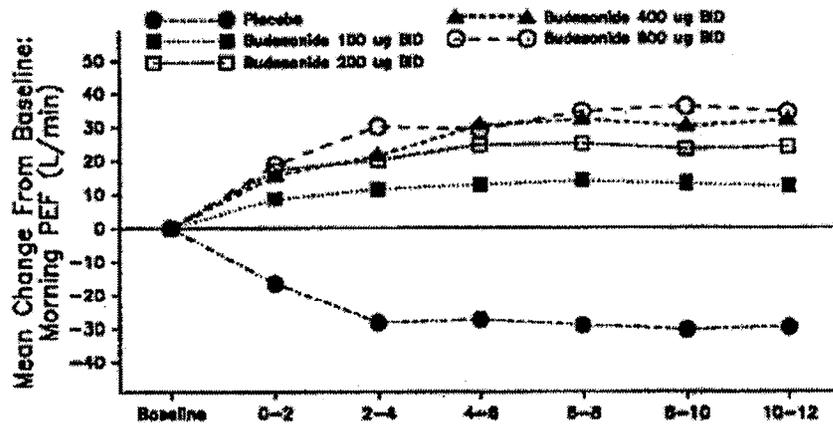


Figure 5. 3020A, Mean change from baseline in PEF (L/min)

Source: F8, p102; clinsum.pdf

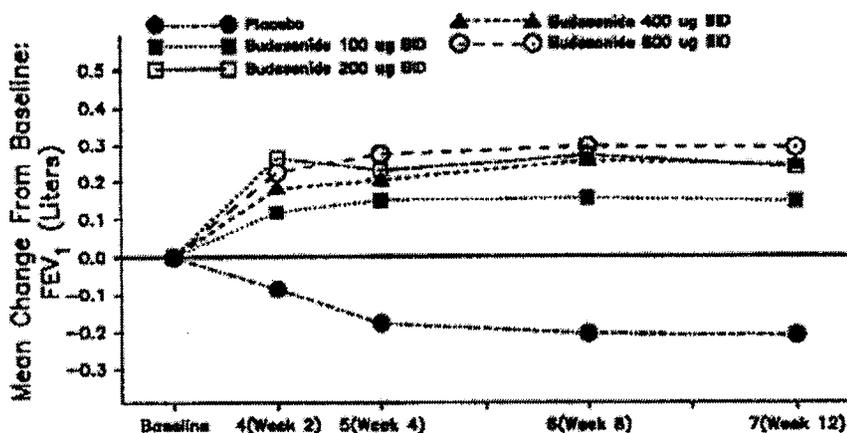


Figure 6. 3020A, Mean change from baseline in FEV₁ (L)

Source: F3, p97; errata 04-3020a part1.pdf; F9, p103; clinsum.pdf

Table 4. 3020A, Mean change in from baseline in FEV₁ (L)

		Placebo	Budesonide			
			100	200	400	800
N		82	91	92	97	97
Baseline		2.08	2.05	2.06	2.06	1.97
Change at Visit	Week 2	-0.09	0.12	0.26	0.18	0.22
	Week 4	-0.18	0.15	0.23	0.20	0.27
	Week 8	-0.21	0.15	0.27	0.26	0.29
	Week 12	-0.21	0.15	0.24	0.24	0.29
	Week 0-12	-0.17	0.14	0.25	0.22	0.27
Difference from placebo			0.31 (0.19, 0.43)	0.42 (0.30, 0.54)	0.39 (0.27, 0.50)	0.44 (0.32, 0.56)
p-value			<0.001	<0.001	<0.001	<0.001

Source: Table G, p97 and T3.3, p909; errata 04-3020a part1.pdf

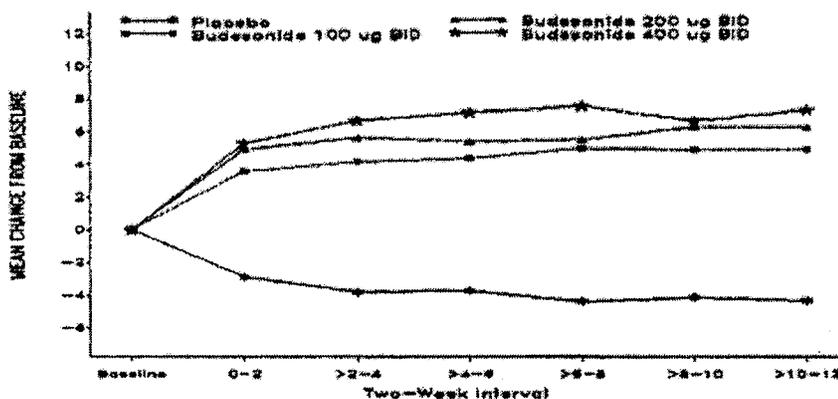


Figure 7. 3023A, Mean change from baseline in % predicted PEF (L/min)

Source: F10, p105; clinsum.pdf

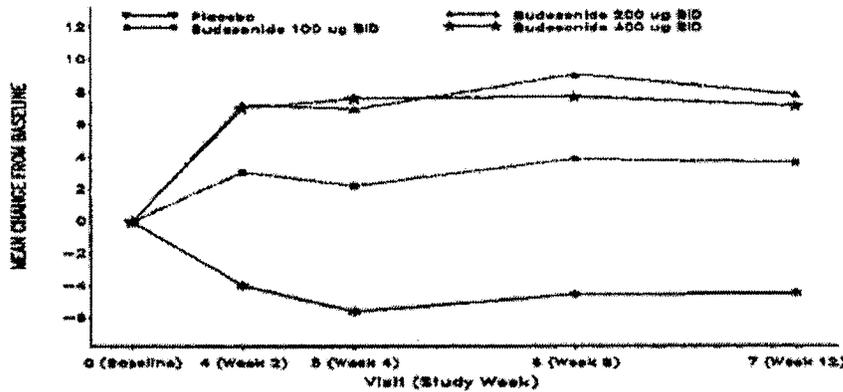


Figure 8. 3023A, Mean change from baseline in % predicted FEV₁ (L)

Source: F11, p106; clinsum.pdf

Table 5. 3023A, Mean change in from baseline in percent predicted FEV₁ (L)

		Placebo	Budesonide		
			100	200	400
N		98	99	99	99
Baseline		73.8	75.7	74.6	74.8
Change at Visit	Week 2	-4.0	3.0	7.2	7.0
	Week 4	-5.6	2.1	6.9	7.6
	Week 8	-4.6	3.8	9.0	7.6
	Week 12	-4.5	3.6	7.7	7.0
	Week 0-12	-4.6	3.1	7.7	7.3
Difference from placebo			7.9 (4.7, 11.0)	12.3 (9.1, 15.4)	11.8 (8.6, 14.9)
p-value			<0.001	<0.001	<0.001

Source: Table LG, p103 and T3.3, p622; errata 04-3023a.pdf

Study SD-004-0620

This was a randomized, double-blind, placebo-controlled, 12-week efficacy switch and safety study conducted at 90 centers in the US and Asia in 621 mild-to-moderate asthmatics (FEV₁ ≥60% and ≤90% predicted, FEV₁ reversibility ≥12% and ≥0.20 L, and recent use of orally inhaled corticosteroids for at least 3 months) ≥18 years of age. After a 5- to 40-day single-blind, placebo run-in period patients were randomized to one of 2 doses of the M3 180 mcg (1 inhalation QAM, 2 inhalations BID) or M0-ESP 200 mcg (1 inhalation QAM, 2 inhalations BID), or placebo (2 arms: 1 inhalation QAM or 2 inhalations BID) inhalers for 12 weeks of treatment. The primary endpoint was the change from baseline to average over the treatment period in pre-dose (trough) FEV₁, with baseline defined as pre-dose FEV₁ on the day of randomization. Secondary endpoints included change from baseline to each visit in FEV₁, FVC, and FEF₂₅₋₇₅; change from baseline in FVC, FEF₂₅₋₇₅, morning and evening PEF, day and night asthma symptom scores, daytime and nighttime beta-agonist use; and number of patients who met pre-defined asthma-related discontinuation criteria. PK (AUC_{0-t}, C_{max} and time to C_{max}) was performed in a subset of 24 patients from each treatment arm at the end of treatment. Safety was evaluated by AEs (AEs, SAEs, DAEs, OAEs, causality), laboratory tests, vital signs, and physical examinations including mouth and throat findings.

The study report states that 2027 patients were screened, but does not state how many patients were entered into the run-in period and subsequently not randomized. The study randomized 621 patients (450 or 72.5% US, 171 or 27.5% Asian) at 74 US and 16 Asian centers, 404 (65.1%) women, 217 (34.9%) men, 400 (64.4%) Caucasian, 38 (6.1%) Black, 180 (29.0%) Oriental, 3 (0.51%) Other, with a mean age of 40 years (range 18-80, 20 (3.2%) ≥ 65 years), and a history of asthma for approximately 20 years. The mean FEV₁ was 74.0% predicted at screening and 65.0% predicted at randomization (i.e. post placebo run-in). Treatment groups were relatively similar in baseline characteristics, including FEV₁, other pulmonary function measurements, and symptom scores.

The applicant's primary and certain secondary analyses were confirmed by the FDA statistician, Dr. Gebert. In addition, various exploratory analyses were conducted by the review team. Results of the treatment arms (not considering differences in dose content) are shown in Table 6, with results of the primary analysis shown in Table 7. The results are shown graphically in Figure 9. There appeared to be both dose-ordering (as expected) and device-ordering (not expected) with the M0-ESP showing greater numerical improvement from baseline than the M3. The M0-ESP device consistently exhibited a greater treatment effect than the M3 comparator at all study time points; however, the high-dose regimen using the M3 device, like the high-dose regimen using the M0-ESP device, showed statistically significant differences from placebo. The low-dose (180 mcg QD) regimen was not statistically different from placebo on the primary endpoint, and in numerous comparisons of effect it exhibited less effect than the low-dose comparator, the currently used M0-ESP device.

b(4)

However, at the end of 12 weeks, the M3 180 BID and the M0-ESP 200 QD treatment arms had quite similar results for % change from baseline in FEV₁. While there appeared to be a gender effect (Table 8), with treatment differences for BID dosing driven by differences in males but not females, a significant gender effect is generally not seen with corticosteroids; therefore, this finding was not considered meaningful. Secondary endpoints were generally similar to the primary endpoints, lending support for the primary results.

As noted previously, a change in dose content of about 5% was done during this study. Based on the small relative difference in dose content between the M3  and M3  devices, one would not expect to detect differences in treatment results based on changes in dose content during the study. Nevertheless, an attempt was made to evaluate whether this assessment was accurate. Results for the various treatment arms are shown in Table 9. Note that the change in dose content applied only to US patients. No consistent pattern could be elucidated. Interpretation of any differences between treatment groups was complicated by concomitant improvement in the placebo treatment sub-groups.

b(4)

Consideration was given to the effect of the relatively large number of dropouts in the study as well as the improvement in the placebo arm over the treatment period. The effect of dropouts on baseline FEV₁ was evaluated (Table 10); no meaningful changes were noted, implying that dropouts did not bias the results. The improvement in placebo would have served to make treatment differences from placebo smaller, thereby reducing the effect size. However, change from baseline for each treatment arm and relative change for each active treatment was unaffected, thereby allowing meaningful comparison of active treatments.

Overall PK findings (Figure 10) were consistent with the PD findings, with relative device- and dose-ordering noted. Interpretation is limited based on the small N and the variability of individual results. The study report did not note whether the results reflect the M3 or M3 mcg/g formulations, or a combination thereof. Nevertheless, these findings are consistent with the PK found in pediatric study 726, but not with those of the more definitive bioequivalence study 601, and support the clinical findings of dose- and device-ordering.

b(4)

There were no major safety issues found during the review of this study. There were no deaths. Two patients had serious adverse events, both on the approved device. Discontinuations due to “asthma” occurred almost as frequently in subjects in the low-dose M3 treatment arm as in the combined placebo arms. There were no particular trends of note with regard to AEs except for a higher incidence of asthma in the lower dose and placebo groups.

At US centers, M3 inhalers were collected at the last two visits and sent for functionality and performance assessments. No major issues were identified. Excerpts from the study report follow:

“The average delivered dose level was slightly lower, and the average relative standard deviation was higher, for the clinical returns compared to the release data. The batch average-delivered dose ranged from 88% to 103% for the returned inhalers. The corresponding range at release was 93% to 104%.” “The batch average of the fine-particle dose for the used inhalers ranged from 96% to 111%, with an average of 107% when compared to the values obtained at release testing.” “The amounts of moisture in the spheronized powder were generally slightly higher compared to the release data. This was to be expected since the inhalers had been subjected to moisture during use.”

Table 6. SD-004-0620, Predose FEV₁ (L), Treatment Means (ITT, LOCF)

Treatment	N	Baseline	Treatment period*			
			Observed value	Change from baseline	From ANCOVA	
		Mean	Mean	Mean	LS Mean (SE)	95% CI
M3 360 BID	128	2.14	2.44	0.30	0.29 (0.03)	0.22 to 0.34
M0-ESP 400 BID	128	2.15	2.52	0.36	0.34 (0.03)	0.29 to 0.40
M3 180 QD	119	2.09	2.29	0.19	0.18 (0.03)	0.12 to 0.24
M0-ESP 200 QD	110	2.19	2.46	0.27	0.25 (0.03)	0.29 to 0.31
Placebo	114	2.14	2.26	0.12	0.10 (0.03)	0.04 to 0.16

*Mean of all predose FEV₁ values obtained during the double-blind treatment period
 Source: T16, p98; SD-004-0620.pdf

Table 7. SD-004-0620, Treatment differences from pooled placebo (FEV₁), ITT

Treatment	LS mean difference	SE	95% CI	p-value
M3 360 BID	0.18	0.041	0.10 to 0.26	<0.001
M0-ESP 400 BID	0.24	0.041	0.16 to 0.32	<0.001
M3 180 QD	0.07	0.042	-0.01 to 0.16	0.078
M0-ESP 200 QD	0.15	0.043	0.06 to 0.23	<0.001

Source: T17, p99; SD-004-0620.pdf

Table 8. SD-004-0620, Change from baseline in FEV₁ by gender, ITT

Treatment	Females			Males		
	N	Mean	Change	N	Mean	Change
M3 360 BID	75	2.11	0.27	53	2.91	0.34
M0-ESP 400 BID	84	2.14	0.27	44	3.24	0.54
M3 180 QD	83	2.05	0.17	36	2.83	0.25
M0-ESP 200 QD	71	2.12	0.27	39	3.07	0.28
Placebo	75	2.01	0.12	39	2.75	0.13

Source: T11.2.1.1.4, p404; SD-004-0620.pdf

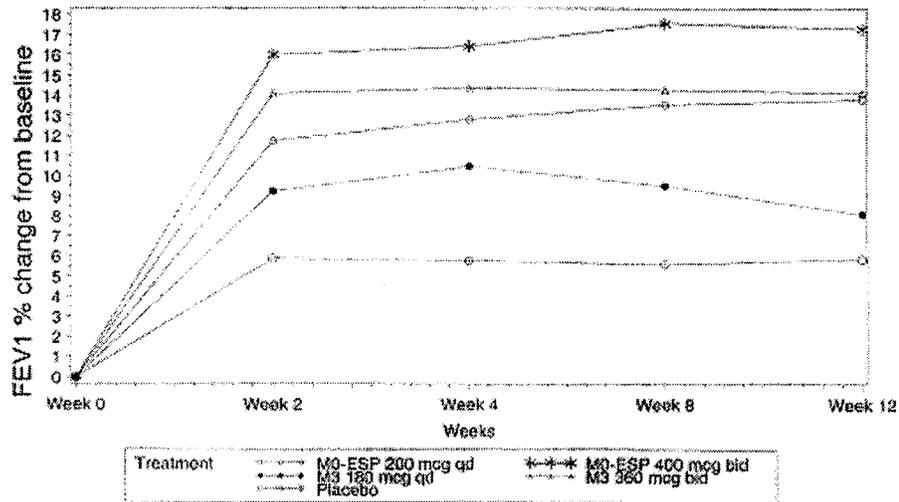


Figure 9. SD-004-0620, Percent change from baseline in FEV₁ by week, LOCF, ITT

Source: F5, p101; SD-004-0620.pdf

Table 9. SD-004-0620, FEV₁ by dose content, Efficacy analysis set, LOCF, All patients/US patients*

Treatment	Dose Content	Location	N	Baseline	Treatment	Change
M3 360 BID	mcg/g	All (US only)	54	2.26	2.56	0.30
		All (US + Asia)	74	2.04	2.35	0.30
		US only	39	2.25	2.63	0.38
M3 180 QD	mcg/g	All (US only)	51	2.18	2.32	0.14
		All (US + Asia)	68	2.03	2.26	0.23
		US only	39	2.22	2.63	0.38
Placebo	0	All (US only)	42	2.24	2.40	0.10
Placebo	0	All (US + Asia)	72	2.05	2.19	0.13
		US only	39	2.12	2.31	0.19

*All patients in Asia received the mcg/g formulation. US patients received one or the other formulation, but No patients received both.

Source: T11.2.1.1.6, p410-1; T11.2.1.1.7, p420-1; SD-004-0620.pdf

b(4)

Table 10. SD-004-0620, Baseline FEV₁ (L), over the treatment period, observed data

Visit	Placebo N=124		Budesonide							
			BID dosing				QD dosing			
			M3 360 N=130		M0-ESP 400 N=130		M3 180 N=123		M0-ESP 200 N=114	
N	FEV ₁	N	FEV ₁	N	FEV ₁	N	FEV ₁	N	FEV ₁	
Randomization visit	119	2.12	130	2.13	129	2.16	121	2.10	113	2.19
Week 2	113	2.14	127	2.14	124	2.16	116	2.11	108	2.18
Week 4	86	2.14	115	2.16	122	2.16	106	2.10	94	2.23
Week 8	78	2.16	111	2.17	118	2.17	92	2.11	88	2.19
Week 12	57	2.19	95	2.16	98	2.20	82	2.13	83	2.25
Weeks 0-12	114	2.14	128	2.14	128	2.15	119	2.09	110	2.19

Source: T13, p90; T11.2.1.2.2, p430; SD-004-0620.pdf

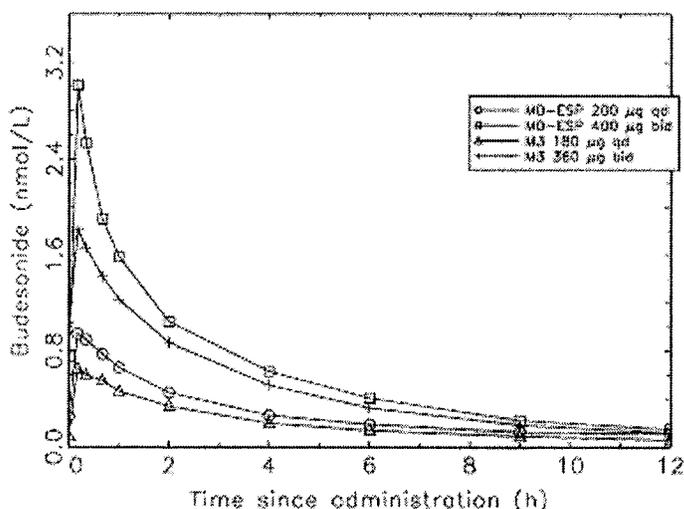


Figure 10. SD-004-0620, Mean plasma concentration curves

Source: F3, p3560; SD-004-0620.pdf

Study SD-004-0726

The design for this study was quite similar to that for study 620, except that it was conducted in a pediatric population 6-17 years of age. Other major differences included: FEV₁ eligibility criteria (6-11 yrs old: 75-90% predicted; 12-17 yrs old: 60-90% predicted; FEV₁ could be 90-95% predicted if FEV₁/FVC were <80%), the duration of asthma requirement was shorter (≥3 months), and patients could be enrolled if they were not taking inhaled corticosteroids, or were on a stable dose of inhaled corticosteroids for a shorter period of time (≤1 month) than in trial 0620. During the 14-day run-in period patients were continued on or off previous ICS while qualifying for randomization (most patients were not on ICS).

In this study the Pulmicort Turbuhaler M3 90 mcg device was tested (Batch numbers CL13, EB18, EF21, EK22, and EF20). Patients were randomized to one of 2 doses of the M3 90 mcg (2 inhalations QAM, 4 inhalations BID) or M0-ESP 200 mcg (1 inhalation QAM, 2 inhalations BID), or placebo (4 arms: 1 and 2 inhalation QAM or 2 and 4 inhalations BID)

inhalers for 12 weeks of treatment. The primary endpoint was the change from baseline to average over the treatment period in pre-dose (trough) percent predicted FEV₁, with baseline defined as pre-dose FEV₁ on the day of randomization. Secondary and safety endpoints were the same as in study 620.

The study randomized 516 patients (347 or 67.2% US, 169 or 32.8% Asian) at 69 US and 15 Asian centers, 179 (34.7%) female, 337 (65.3%) male, 269 (52.1%) Caucasian, 64 (12.4%) Black, 172 (33.3%) Oriental, 11 (0.51%) Other, with a mean age of 11.6 years (range 6-17), and a history of asthma for approximately 7 years. Most (96%) patients were not on ICS during the run-in period. The mean FEV₁ was 81.7% predicted at screening and 85.1% predicted at randomization. Treatment groups were relatively similar in demographic and baseline characteristics, including FEV₁, other pulmonary function measurements, and symptom scores.

The applicant's primary and certain secondary analyses were confirmed by the FDA statistician. Results of the treatment arms are shown in Table 11, with results of the primary analysis shown in Table 12. All four treatment arms showed statistically significant differences from placebo. Secondary analyses were consistent with and supportive of the primary results. The results are shown graphically in Figure 11. Just as for the adult study, there appeared to be dose-ordering (as expected). However, in results that were opposite those for study 620, there was device-ordering at the high dose with the M3 device showing greater numerical improvement from baseline than the M0-ESP device, although the size of this difference was numerically small. There was no device ordering at the low dose, and in fact in this study the M0-ESP 400 mcg BID dose did not substantially outperform either QD dosage. The overall effect size seen in this study was quite small probably due to the fact that most patients were not on (and may not have needed) ICS therapy based on the previous history and their mean randomization FEV₁ % predicted of 85%. For secondary endpoints, while AM and PM PEF and FEF₂₅₋₇₅ results followed the percent predicted FEV₁ measure, no effect was noted for any treatment on FVC, asthma scores, number or percent of patients meeting asthma discontinuation criteria, or albuterol use.

A subset of 15 patients/arm had PK performed. However, the study did not use the to-be-marketed M3 formulation, but rather a formulation with about 5% less budesonide. This may best explain the results of the PK analysis, which appeared to show both dose- and device-ordering (Figure 12), with the M0-ESP showing higher plasma concentrations than the M3 device at both doses. This is not consistent with the PK results of study 601 or the PD results in this study, but it is consistent with both the PK and PD results in study 627.

There were no major safety issues found during the review of this study. There were no deaths. There were 3 SAEs: 1 gastric pain (M0-ESP), 1 food poisoning (placebo), 1 asthma (placebo). There were 10 DAEs, 8 of which were due to an asthma exacerbation. Discontinuations due to "asthma" occurred more often in the combined placebo arms than in the active treatment arms. Cough, nasal congestion, and pharyngitis were more frequent in the high dose groups than either lower dose or placebo groups. There were no unusual trends in ECG, laboratory, vital signs, or physical exam findings. The 24-hour urinary cortisol results in the subset of patients who had baseline and end-of treatment sampling showed substantial variation in mean results, making interpretation problematic. Although trends to lower cortisol levels were seen in both high-dose treatment groups, all that one can say is that there was no new safety signal evident with the M3 when compared with the M0-ESP.

At US centers, M3 inhalers were collected at the last two visits and sent for functionality and performance assessments. No major issues were identified. Excerpts from the study report follow:

“The average delivered dose level was slightly lower, and the average relative standard deviation was higher, for the clinical returns compared to the release data. The batch average-delivered dose ranged from 88% to 103% for the returned inhalers. The corresponding range at release was 93% to 104%.” “The batch average of the fine-particle dose for the used inhalers ranged from 96% to 111%, with an average of 107% when compared to the values obtained at release testing.” “The amounts of moisture in the spheronized powder were generally slightly higher compared to the release data. This was to be expected since the inhalers had been subjected to moisture during use.” [p134]

Table 11. SD-004-0726, Predose percent predicted FEV₁ (L), Treatment means (ITT, LOCF)

Treatment	N	Baseline	Treatment period*			
			Treatment	Change	From ANCOVA	
					LS Mean (SE)	95% CI
M3 360 BID	90	84.2	99.0	5.8	5.57 (0.8)	3.94 to 7.20
M0-ESP 400 BID	98	86.6	90.7	4.1	4.44 (0.8)	2.88 to 6.01
M3 180 QD	103	84.7	87.3	2.7	2.55 (0.8)	1.03 to 4.08
M0-ESP 200 QD	101	84.4	87.3	2.9	2.69 (0.8)	1.10 to 4.24
Placebo	101	84.4	84.8	0.4	0.19 (0.8)	-1.36 to 1.73

*Mean of all predose FEV₁ values obtained during the double-blind treatment period
 Source: T16, p978; SD-004-0726.pdf

Table 12. SD-004-0726, Treatment differences from pooled placebo (FEV₁), ITT

Treatment	LS mean difference	SE	95% CI	p-value
M3 360 BID	5.4	1.1	3.2 to 7.6	<0.001
M0-ESP 400 BID	4.3	1.1	2.1 to 6.4	<0.001
M3 180 QD	2.4	1.1	0.2 to 4.5	0.030
M0-ESP 200 QD	2.5	1.1	0.4 to 4.7	0.022

Source: T17, p98; SD-004-07260.pdf

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from the original drug product provide the underpinnings for the switch program from the M0-ESP to the new M3 formulation/device as well as the proposed addition of new dosing information to the labeling. The proposed label therefore retains much of the safety and efficacy data, while adding the results of the two new studies. This typically is a reasonable approach, as long as the switch program verifies comparability of the old and new drug products.

The PK study 601 demonstrated comparability as well as bioequivalence of systemic exposure between the M0 and M3 drug products after a single 800 or 720 mcg dose, supporting the switch. However, PK from the two clinical studies do not exactly match the PK found in this study, as discussed below.

The two clinical studies support approval, but do not support carry-over of efficacy from the original drug product. The main reason for the studies was to assure that the new product would perform comparably to the old product with regard to both efficacy [and safety]. To support this, the primary statistical analysis was against placebo, with the expectation that a visual overlay of the primary results would show substantial comparability but not bioequivalence. Study 620, performed in a population of adults previously on ICS with a mean % predicted FEV₁ of 64% at baseline, showed both PD and PK device- and dose-ordering, with the M0-ESP device outperforming the M3. At the end of 12 weeks, the M0-ESP 200 BID outperformed all other treatment arms for % change from baseline in FEV₁, whereas the M3 180 BID and the M0-ESP 200 once-daily treatment arms had somewhat comparable results. The difference between the M0 and M3 twice daily regimens appears meaningful, and is noted despite the clinical backdrop of no difference between doses of 200 to 800 mcg BID in the original clinical program. About two-thirds of patients received the final formulation; as expected, there were no meaningful differences in results for the various subgroups that did or did not receive the final drug product. The once-daily M3 dose was not statistically significant from placebo, but lack of statistical significance using a low-dose once-daily dosing regimen is not surprising, given the fact that these were patients who previously required ICS and were being re-started on Pulmicort after a placebo run-in period. Lack of comparability is supported by the limited PK data available from this study, which points to the same dose- and device-ordering seen clinically. In summary, this study does not support comparability. No safety issues were identified.

In study 726, the results were less clear, and did not distinguish any differences between the products. However this study has some major drawbacks limiting interpretability. The study was performed in a very mild set of asthmatics previously not on ICS and with a baseline % predicted FEV₁ of 85%, in whom there was little room for clinical improvement. In this setting, all active treatments showed statistical significance compared to placebo and the M3 appeared to numerically outperform the M0-ESP; however the difference between the two products was numerically small and clinically not meaningful. Just as for study 620, this study in showed PK device- and dose-ordering, implying that in clinical practice there may be less systemic exposure with the M3 device than with the M0-ESP device. Based on the results, this study is equivocal in support of comparability. No safety issues were identified.

Because the PD effects do not match up for adults, the clinical program does not support a switch. However, efficacy with BID dosing was demonstrated in the two studies at a dose of 360 mcg BID. Therefore, the program is sufficient to support approval this drug product, although the M3 must stand on its own with regard to efficacy. Information from the 100

mcg dosage strength in the original NDA cannot be accepted, since the only dose supported by the clinical program is 360 mcg BID, achieved by either 180 mcg 1 inhalation BID or 90 mcg 2 inhalations BID.

Since the PK results demonstrate similar (study 0601) or less (studies 620 and 726) systemic exposure with no differences in systemic safety or local toxicity, safety may be extrapolated from the previous labeling.

Product Name

The proposed product name is the same as the previous versions of this drug product: PULMICORT TURBUHALER® 180 mcg (budesonide inhalation powder) and PULMICORT TURBUHALER® 90 mcg (budesonide inhalation powder). This is of concern, since the product name will not distinguish between the old M0-ESP Pulmicort Turbuhaler and the new M3 drug product. With introduction of the M3, there may be a time period where both drug products are available in pharmacies. Pharmacists may interchange the two, and physicians may continue to prescribe based on previous labeling rather than on new labeling. Since there will be differences in the labeling and dosing of the two products, the name should distinguish between them to prevent dosing and administration errors.

Preliminary Labeling Review

Labeling was submitted, reviewed, and compared with the last approved package insert for the Pulmicort Turbuhaler. The labeling seeks to port much of the information from the previous label, while describing the links between the old and new products. The DESCRIPTION section therefore starts out with the following statement:

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This is not acceptable.

The INDICATION section remains unchanged, with the indication being “for the maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients six years of age or older. It is also indicated for patients requiring oral corticosteroid therapy for asthma. Many of those patients may be able to reduce or eliminate their requirement for oral corticosteroids over time.” This is acceptable.

The CLINICAL STUDIES section seeks to include information from the original efficacy and safety studies, and add information from the two new studies linking the current M0-ESP to each dosage strength of the proposed M3 product at two different doses in adults and children. This is not acceptable. Labeling in this section will need to be based on the two clinical studies submitted to this NDA.

The DOSAGE AND ADMINISTRATION section seeks to retain much of the same dosing information as before, although reference is to the metered dose of the new M3 device rather than the metered dose of the M0/M0-ESP device, and a new starting dose of 90 to 180 mcg BID is now recommended in children. This starting dose extends the dosing range in children lower based on the previously-submitted safety and efficacy studies with the M0 device submitted to the original application. The old and new dosing instructions are shown in Table 13.

The only dose supported by the clinical program is 360 mcg BID, although based on the safety data and a dose of 720- mcg BID is also supported.

With approval of two dosage strengths, a dose (for example) of 180 mcg BID might be achieved by 2 inhalations of the 90 mcg drug product.

Previously, AstraZeneca agreed that labeling might state that the 180 mcg dose has to be via 2 inhalations of the 90 mcg. I recommend that we provide this information in the labeling. Now that the dosing will be 360 mcg BID for all ages, this is somewhat moot, although the dosing for the 90 mcg dosage strength would be 4 inhalations BID.

b(4)

Table 13: Current and Proposed Dosing for Pulmicort Turbuhaler

Current D&A Table			
	Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Adult	Bronchodilators alone	200 to 400 mcg twice daily	400 mcg twice daily
	Inhaled corticosteroids*	200 to 400 mcg twice daily	800 mcg twice daily
	Oral corticosteroids	400 to 800 mcg twice daily	800 mcg twice daily
Children	Bronchodilators alone	200 mcg twice daily	400 mcg twice daily
	Inhaled corticosteroids*	200 mcg twice daily	400 mcg twice daily
	Oral corticosteroids	The highest recommended dose in children is 400 mcg twice daily	

b(4)

Proposed D&A Table			
	Previous Therapy	Recommended Starting Dose	Highest Recommended Dose

Pediatric Considerations

PREA is triggered by this application. AstraZeneca has requested a partial pediatric waiver for children under the age of 6 years on the grounds that Pulmicort Respules® is already approved for treatment for this age group, that the Pulmicort Turbuhaler M3 does not represent a therapeutic benefit over existing treatments, and that this product is not likely to be used in a substantial number of patients in that age group. For a DPI formulation, the Division has previously made the decision that studies in patients less than 6 years of age is

unreasonable. I agree with the applicant's reasoning and recommend a waiver of pediatrics studies below 6 years of age for this drug product.

Growth data is included in two sections of the labeling: in the CLINICAL PHARMACOLOGY: Pharmacodynamics subsection as well in the PRECAUTIONS: Pediatric Use subsection. No new information is submitted on growth in the current submission. The PRECAUTIONS: Pediatric Use subsection presents data from an unreviewed published NIH-sponsored ("CAMP") study.² These data must be reviewed prior to inclusion in the label. Growth data is also presented in CLINICAL PHARMACOLOGY: Pharmacodynamics subsection. Documentation of where these data originate was not included in this application, as this information is in the current Pulmicort Turbuhaler label.

Recommendation

I recommend Approval of this NDA, although labeling for this product will be limited because of the limited clinical program submitted to the NDA.

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² Szeffler S et al. Long-Term Effects Of Budesonide Or Nedocromil In Children With Asthma. New Engl. J. Med. (2000) 343 (15): 1054-1063

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/s/

Peter Starke
6/1/2006 11:28:12 AM
MEDICAL OFFICER

Badrul Chowdhury
6/1/2006 11:33:41 AM
MEDICAL OFFICER
I concur

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CLINICAL REVIEW

Application Type New Drug Application
Submission Number 0
Submission Code NDA 21-949

Letter Date 12 September 2005
Stamp Date 12/14 September 2005
PDUFA Goal Date 12 July 2006

Reviewer Name James Kaiser
Review Completion Date 17 May 2006

Established Name Budesonide
(Proposed) Trade Name Pulmicort Turbuhaler
Therapeutic Class Glucocorticoid
Applicant AstraZeneca LP

Priority Designation Standard

Formulation Dry Powder Inhaler
Dosing Regimen Adults: 180 mcg-720 mcg twice
daily
Children: 90 mcg-360 mcg twice
daily
(age not specified) 180-360 once
daily

Indication Asthma
Intended Population Patients down to the age of 6

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This NDA submission is intended to provide evidence to support a change in a currently marketed product, the "M0-ESP" version of the Pulmicort Turbuhaler, to an "M3" version. Currently the product is labeled for use at doses of 200-800 µg twice daily, and lower doses once daily in patients whose asthma is well-controlled on inhaled corticosteroids. It is the intent of the applicant to continue this labeling paradigm and to add a low-dose dosing regimen based on the strength of clinical trials that were limited in scope, on previously submitted information using the original, "M0" device, at a low dose, and on pharmacokinetic information. Approval would also be contingent on adequate device characteristics.

The new clinical trials showed equivocal results with regards to comparability on their primary endpoints using a twice-daily dosing regimen. In a critical trial in adults, the M3 device produced less effect on treatment period mean FEV₁ than the M0-ESP device at 360 µg twice daily; in a critical pediatric trial, the M3 device produced more effect on FEV₁ % predicted.

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pharmacokinetic study at a single high dose showed equivalent systemic exposure produced by the two devices; the pharmacokinetic substudies in the clinical trials, while not as well-controlled, did not show higher systemic exposure. These three pharmacokinetic studies produce no concern over higher systemic exposure.

The submission supports approval of the M3 at a twice-daily dose of 360 µg or 720 µg (equivalent to the currently labeled upper limit of recommended dosing). I base this primarily on the showing of a statistically significant difference from placebo of approximately 10% of baseline FEV₁ in the new adult trial and on the finding of slightly better effect on FEV₁ % predicted compared to the M0-ESP version in a pediatric trial.

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The Pulmicort Turbuhaler M3, like the M0-ESP, exhibits notable drops in delivery of fine particles at inspiratory flow rates below 60 l/min.

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1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Because of the safety profile of Pulmicort, postmarketing risk management is not required for approval of the current application.

1.2.2 Required Phase 4 Commitments

1.2.3 Other Phase 4 Requests

I have no additional recommendations for Phase 4 activity.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Note on nomenclature: This clinical review denotes the dose “metered” as the primary identifier for the content of the product. This is the quantity of drug that escapes the device’s reservoir. The “delivered” dose is the quantity of the drug that escapes the device as measured by in vitro testing. For the Pulmicort Turbuhaler M3, two dose strengths are proposed, one that meters 180 mcg and another that meters 90 mcg. These devices deliver 160 mcg and 80 mcg, respectively. For comparison, the prior version of the product, the M0-ESP, meters 200 mcg and delivers the same amount as the higher dose strength (160 µg) M3 device. In referring to the newly submitted efficacy trials, the higher dose arms were either (M3) 360 µg BID or (M0-ESP) 400 µg BID, occasionally referred to as the twice-daily dosing arms or the higher dose dosing arms. The trials also studied a dose of (M3) 180 µg QD or M0-ESP 200 µg QD, occasionally referred to as the once-daily dosing arms or the lower dose arms.

NDA 21-949 contains a proposal to market a new, “M3” version of the Pulmicort Turbuhaler, which is a marketed dry-powder inhaler for the delivery of the glucocorticoid budesonide. Twice-daily dosing with the Pulmicort Turbuhaler was approved in June 1997 based on the original marketing application for the Pulmicort Turbuhaler (the M0 version). The primary basis of approval was clinical data from 4 multicenter, randomized, double-blind, placebo-controlled, 12-20-week trials in subjects 6 years and older with asthma whose symptoms had been managed with and without inhaled or oral corticosteroids. In October 1998 AstraZeneca received approval for once daily dosing at two specified dose levels (200 and 400 mcg) in adults with mild to moderate asthma stabilized on inhaled corticosteroids based primarily on a single pivotal trial in adults. AstraZeneca decided not to market the 400 mcg version. AstraZeneca’s next submitted version of the device (M0-ESP) was approved on 8 December 2000 on the basis of nonclinical information alone.

The M3 device is considered sufficiently different from the M0-ESP that an approval requires adequate support from additional clinical information. The M3 device still delivers budesonide, but now with lactose as an excipient. The formulation involves a change to the “spheronization” process. In addition, the inhaler device itself has been modified in several ways

including a new cleaning feature to reduce retention of powder, a new dose indicator, and a new outer design.

The current application makes no changes to the indicated populations. The application contains two new 12-week clinical trials testing the M3 device in subjects down to the age of 6 years with asthma controlled either on inhaled corticosteroids (adolescents or adults) or on bronchodilators alone. A device metering 180 mcg/puff was studied in adolescents and adults; a device metering 90 mcg/puff was studied in children. A total of 457 subjects were treated with the M3 device, of whom 204 were between 6-17 years old. The marketing application for the original device contained clinical trial data on the 90 mcg BID dosing regimen, but the 90 mcg dose strength could not be approved due to inadequate dose content uniformity. Two clinical trials are resubmitted with a total of 193 subjects treated at 90 mcg twice a day, for consideration of the approvability of this dose regimen.

No postmarketing data are available for the proposed new device.

1.3.2 Efficacy

The current application is submitted to establish the clinical equivalence of a new version of the Pulmicort Turbuhaler to the currently-marketed device. The fact that other glucocorticoid preparations are available for the treatment of asthma is not an issue for the approvability of the currently proposed device.

Two new clinical trials are submitted:

- Trial SD-004-0620 treated 621 subjects aged 18 or older whose symptoms were managed with inhaled corticosteroids for 12 weeks with either the new proposed M3 device, the currently marketed M0-ESP device, or placebo as a control. Subjects received either a single puff once daily or 2 puffs twice a day of either the M3 device or M0-ESP devices, metering 180 mcg/puff. Thus the total doses of active product administered were 180 mcg once daily and 360 mcg twice a day. The primary endpoint measurement was the difference between baseline and the mean of the treatment period FEV₁. The primary endpoint was a comparison of the M3 device to placebo; comparisons were also made between the M3 and M0 devices.
- Trial SD-004-0726 treated 516 subjects for the same duration with placebo, M3, or M0-ESP devices. The most notable differences from the 0626 trial group were that
 - The trial population was aged 6-12 years
 - Subjects were primarily on inhaled bronchodilators only, not requiring inhaled corticosteroids.
 - The M3 devices metered 90 mcg/puff. Total doses for all treatment arms were the same as trial 0620.
 - The primary endpoint was expressed as FEV₁ % predicted.

In addition, two previous clinical trials are resubmitted for consideration of the approvability of modification of dosing recommendation to include a low dose.

The new clinical trials studied only one dosing regimen, 360 µg BID, currently labeled for initial treatment (as opposed to maintenance treatment) using the precedent device. Subjects did not include all levels of severity for which the current product is labeled. However, the clinical trials were intended to demonstrate clinical equivalence of the M3 to the precedent

device. Regulatory approval does not require a full repetition of the clinical program. The endpoints were consistent with the previous trials accepted as bases for licensure of the product.

The clinical trials were adequately designed. The major conduct issue in the trials was an approximately 5% increase in dose content that occurred during the adult/adolescent trial. This change in dose content had no effect on efficacy or safety.

While the higher dose tested (360 µg BID) would be expected to have show a notable effect on FEV₁ based on prior data, the 180 µg once-daily dose (for the M0-ESP this is the 200 µg once-daily dose) was included to establish a dose response. The clinical trials showed that treatment with the M3 device at 360 mcg twice a day in the adult trial produced improvements in FEV₁ that were less than those produced by the M0-ESP device; in the pediatric trial, improvements in FEV₁ % predicted were slightly higher using the M3 device.

~~_____~~
~~_____~~ In addition, in the adolescent/adult trial the effect on FEV₁ at the low, daily dose was not statistically different from placebo using the M3. Neither a notable clinical effect nor a statistical separation from placebo would be required for this dosing regimen.

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The pediatric trial was not designed to discern differences in effect with respect to peak inspiratory flow. ~~_____~~

b(5)

1.3.3 Safety

The clinical data base consists of

- 1137 subjects with asthma (457 on the M3 device) in placebo-controlled efficacy trials
- 2503 subjects in noncontrolled trials of asthma subjects using the M3 product
- 60 subjects in M3 pharmacokinetic trials
- 193 subjects in placebo-controlled efficacy trials on M0 at 100 µg BID (similar dose to the proposed low BID dose)
- 1133 subjects with asthma in a 1-year open-label, single-arm trial using the M0 device
- 171 subjects with asthma in a 5-year open-label, single-arm trial using the M0 device

Evaluations were adequate, including clinical events and laboratory evaluations. Deaths and serious adverse events were few and did not have any pattern of concern. No new safety concerns emerged from the clinical trials.

The pediatric trial included a substudy of the effects of the M3 and the approved device on the hypothalamic-pituitary-adrenal (HPA) axis by measuring urinary cortisol. This substudy was inadequate to determine differences between the M3 and the currently approved device.

Pharmacokinetic analyses show that the M3 produces similar or less systemic exposure than similarly metered doses of the M0 or M0-ESP devices. Systemic safety is not an increased concern with the M3 device.

1.3.4 Dosing Regimen and Administration

The applicant recommends revising current dosing recommendations to change the labeled dose ranges consistent with the change in the metered dose of the new device. In addition, a new dose of 90 mcg twice a day is included.

I recommend that the M3 be approved at a dose of 360 and 720 µg BID _____

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1.3.5 Drug-Drug Interactions

Because of the proposed device contains only lactose in addition to budesonide, further information on drug-drug interactions beyond that already known about budesonide is not required.

1.3.6 Special Populations

The Pulmicort Turbuhaler was adequately tested in the pediatric range for which it is to be marketed (down to the age of 6 years old). Further clinical data would be necessary to support use of the device in a lower age range.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

AstraZeneca proposes to a market a new version of a dry-powder inhaler (DPI) under the current name, "Pulmicort Turbuhaler." The Turbuhaler is a plastic handheld device; the operator uses it to deliver the product to the airways upon inhalation through the device.

The established name for the product is Budesonide. Its chemical class is "glucocorticoid" and its pharmacologic class is "anti-inflammatory."

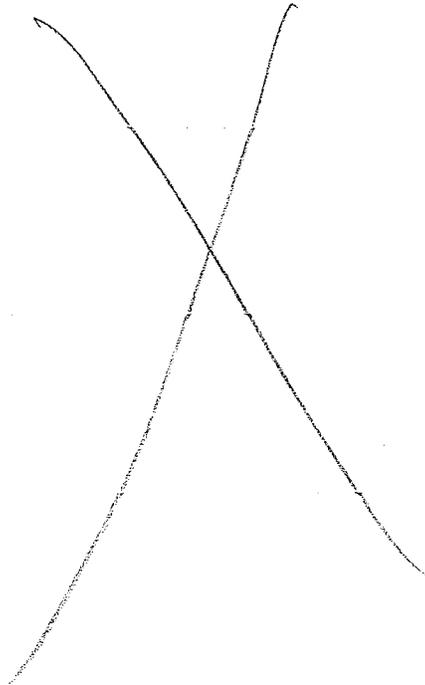
This NDA represents the third proposed version of the Pulmicort Turbuhaler. The original and second versions of the device, termed "M0" and "M0-ESP" by the applicant respectively (designations do not appear in labeling) delivered a dry powder of budesonide alone. The current proposed version of the device, "M3", delivers a dry powder containing the glucocorticoid budesonide and lactose, an excipient. The M3 device also incorporates changes to the formulation method (spheronization), mouthpiece, dose indicator, numbers of doses/device, and dose content.

The M3 device proposed for marketing will be provided in two strengths designated by the metered dose, 90 mcg and 180 mcg. During the clinical trials two versions of the 180 mcg device were tested, one that delivers 60 doses and one that delivers 120 doses. Only the 120-dose device is intended to be marketed. AstraZeneca intends to discontinue marketing the M0-ESP if the M3 is approved.

The applicant proposes to retain the indicated asthma subgroups and age ranges for which the product is currently labeled. Proposed dosing modifications reflect the difference in metered

dose between the current and the proposed devices and the addition of the 90 µg twice daily dosing regimen. Changes to labeled doses are summarized in Table 1.

Table 1. Proposed dose modifications



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2.2 Currently Available Treatment for Indications

The current product is a variation on an available marketed product. There are many alternatives available to treat asthma. Long-term controller medications include other corticosteroid preparations, β-agonists, leukotriene antagonists, 5-lipoxygenase enzyme inhibitors, cromolyn sodium and nedocromil; theophylline; short term controller medications include β-agonists and ipratropium bromide.

2.3 Availability of Proposed Active Ingredient in the United States

Budesonide is marketed by AstraZeneca to treat asthma in patients from 12 months of age to 8 years old as Pulmicort Respules, which is delivered by nebulizer. Budesonide is also available for non-asthma indications: Entocort EC capsules (Prometheus Laboratories) for the treatment of Crohn's disease, and Rhinocort nasal spray (AstraZeneca) for perennial and seasonal allergic rhinitis.

2.4 Important Issues With Pharmacologically-Related Products

Glucocorticoids have numerous systemic side effects when adequate levels are present for a period of time. However, inhaled glucocorticoids have been associated with fewer of these toxicities, at least in the asthma population, which is the primary population for which these drugs have been prescribed. The major toxicities of high doses of inhaled glucocorticoids include: ocular hypertension; lens opacities, early growth retardation; osteoporosis, and suppression of the hypothalamic-pituitary-adrenal axis. Other, more local toxicities, include dysphonia, oral candidiasis, perioral dermatitis, tongue hypertrophy, and increased thirst (reference 1).

2.5 Presubmission Regulatory Activity

AstraZeneca submitted the original NDA application on 22 February 1994, with information on a previous version of the inhaler, called the M0 device, which metered 200 mcg, 400, or 800 mcg of budesonide. Approval was granted to market the 200 and 400 mcg devices, for twice-daily dosing regimens only, on 24 June 1997. The 100 mcg device exhibited unacceptable dose-content uniformity. AstraZeneca decided to market the 200 mcg device only.

AstraZeneca submitted a supplement to the NDA on 6 October 1997 for once-daily dosing. It was amended, then approved on 8 October 1998 for patients with mild to moderate asthma well-controlled on inhaled glucocorticoids.

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In response to this commitment, AstraZeneca developed and obtained approval in 2000 to market a modified device called the "M0-ESP," which is the currently marketed product. This product change included changes to the processing of the budesonide ("spheronization") and changes to the device. No additional clinical information was supplied for that approval.

The current submission is a further response to postmarketing commitment 4.

2.6 Other Relevant Background Information

The proposed device is not marketed anywhere.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The following is a list of important issues identified by the product review, paraphrased in the interest of brevity:

- The dose uniformity acceptance criterion is based on data collected from batches of the drug product made before a small increase in the budesonide concentration in the formulation, tending to widen the acceptance criterion.
- The allowed limit for dosing outliers by should be justified with data.
- It is unclear whether the dose delivery data have been obtained with the device in the upright position, as recommended in the labeling.
- Robustness to dropping the device or simulations of shipping have not been fully characterized.
- The effect of increased humidity on dose delivery has not been fully characterized.
- Deficient Drug Master Files were identified; component composition was inconsistent with respect to the device suppliers and the applicant.
- Sampling for APSD is inadequate; the mass balance acceptance criterion should be revised to account for the formulation concentration increase.
- Key dimensional tolerance limits for components responsible for metering should be tightened.

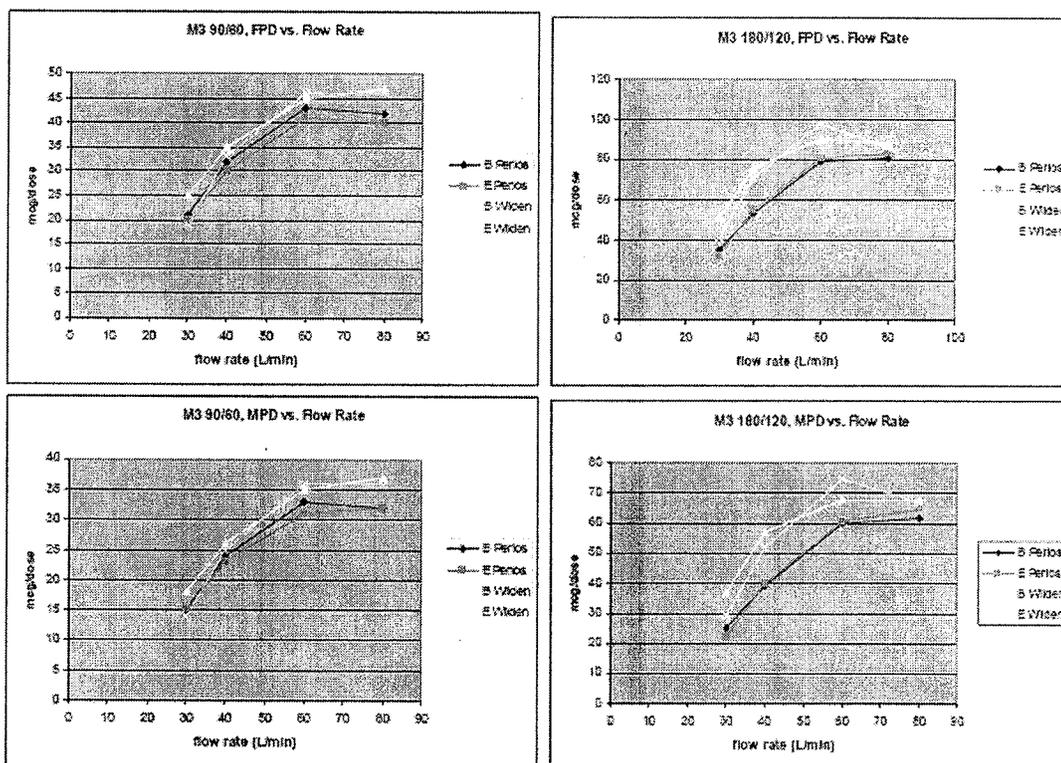
A letter was issued regarding these items. The review of AstraZeneca's responses is beyond the scope of this review.

In addition, the following issue is discussed in the product review that has great relevance to the clinical program.

As detailed in the product review, the amount of drug delivered as a fine or midstack particle dose decreases at flow rates below 60 l/min (Table 2). As stated in the product review, "In general, the FPD [fine particle dose] or MPD [midstack particle dose] is less than half at 30 L/min when compared to these at 60 L/min... The submicron particle dose (SPD) deposited on the filter.. is also halved when comparing 30 to 60 L/min flow data, but the amounts collected are all relatively small."

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Table 2. Dependency of particle delivery on flow rate



* FPD= fine particle dose; MPD=midstack particle dose

This review discusses the impact that this characteristic of the M3 device has on the results of the pediatric clinical trial, where peak inspiratory flow was measured.

AstraZeneca responded to a request for a comparison of the M3 to the M0-ESP in terms of fine particle delivery. The review of these data is beyond the scope of this review.

3.2 Animal Pharmacology/Toxicology

AstraZeneca did not submit new animal studies. No new animal studies were required.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The NDA includes three new clinical trials, two of which (trials SD-004-0620 and SD-004-0726) contain new efficacy information and are reviewed extensively in this document (see Section 10, Appendices). The additional clinical trial (trial SD-005-0601) was conducted to examine pharmacokinetics; see the pharmacologist's review of that trial. The NDA also includes information from two efficacy trials that were reviewed with the original NDA submission, 04-

CR-3020A (GHBA-165) and 04-CR-3023A (GHBA-168). These clinical trials are submitted for further consideration of the safety and efficacy of the 90 mcg dose strength.

The clinical trials submitted provide new clinical information about the effects of 180 mcg once daily or 360 mcg twice daily, delivered by either the low- or high-dose device, in adults who are taking inhaled corticosteroids or children whose asthma is largely controlled without the use of inhaled corticosteroids.

Approval of the new devices is a judgment based on the clinical information in conjunction with pharmacokinetics for consideration of safety, in conjunction with acceptability from a product point of view.

4.2 Tables of Clinical Studies

Table 3 shows the critical trials discussed in this document (further clinical trials are discussed in the integrated summary of safety). The efficacy trials were all randomized, double-blinded, placebo-controlled trials, 12-week trials. The intent of the review of the trials that studied M0 is to compare the safety and efficacy of the currently proposed device that meters 90 mcg to previous data from subjects who received a similar dose.

Table 3. Designs of critical trials submitted

Efficacy trials				
Active device	Trial	Primary endpoint	Subjects randomized / treatment arm	Population (all asthma)
Newly submitted trials				
M3 180 µg/puff M0-ESP 200 µg/puff	SD-004- 0620	FEV ₁ mean treatment period change from baseline, compared between M3 and placebo	M3 360 µg BID: 130 M0-ESP 400 µg BID: 130 M3 180 µg QD: 123 M0-ESP 200 µg QD: 114 Pooled placebo: 124	Ages 18-80; taking inhaled corticosteroids only
M3 90 µg/puff M0-ESP 100 µg/puff	SD-004- 0726	FEV ₁ % predicted mean treatment period change from baseline, compared between M3 and placebo	M3 360 µg BID: 96 M0-ESP 400 µg BID: 102 M3 180 µg QD: 108 M0-ESP 200 µg QD: 104 Pooled placebo: 106	Ages 6-17; primarily on bronchodilators
Previously submitted trials				
M0-ESP 100, 200, 400, and 800 µg/puff	GHBA-165 (04-CR- 3020A)	FEV ₁ and morning peak flow mean treatment period change from baseline, compared between M0 and placebo	100 µg BID: 91 200 µg BID: 93 400 µg BID: 99 800 µg BID: 98 Placebo: 92	Ages 18-70; on inhaled corticosteroids, minority on oral corticosteroid also
M0-ESP 100, 200, and 400 µg/puff	GHBA-168 (04-CR- 3023A)	FEV ₁ % predicted and morning peak flow mean treatment period change from baseline, compared between M0-ESP and placebo	100 µg BID: 102 200 µg BID: 100 400 µg BID: 99 Placebo: 103	Ages 6-18, on inhaled corticosteroids, minority on oral corticosteroid also
Pharmacokinetic trial				
M3, 90 and 180 µg/puff M0 200 µg/puff	SD-004- 0601	Pharmacokinetic parameters AUC _{0 - infinity} and C _{max}	M3 180 µg x 4 M3 90 µg x 8 M0 200 µg x 4	Ages 18-65, no glucocorticoid use

Other, noncontrolled clinical trials were performed using the M3 device (Table 11 and Table 17). These are unsuitable for the evaluation of efficacy, but are considered for their safety information.

4.3 Review Strategy

Substantial information has been previously submitted on clinical efficacy of the M0 version of the Turbuhaler. The clinical approvability of the M3 device rests on the demonstration of clinical equivalence to the approved product, the M0-ESP. This equivalence was assessed by evaluation of the new clinical data. The clinical safety of the M3 was assessed through evaluation of the total human experience generated in the new placebo-controlled trials as well as noncontrolled trials including pharmacology studies. Pharmacokinetic data were evaluated to assess the potential for an increased safety risk in case of increased exposure.

4.4 Data Quality and Integrity

The data were not audited by the Division of Scientific Investigations, nor were case report forms audited. During my review of the submission, I noted no issues with data integrity.

4.5 Compliance with Good Clinical Practices

AstraZeneca states that for both newly submitted efficacy trials “All involved IRBs approved the final study protocol and written informed consent form before any subject was enrolled in the study.” The description of trial procedures states that consent (and assent if applicable) was obtained prior to admission to the trial, and that parents and guardians received a copy of the consent form. AstraZeneca states that both clinical trials were conducted in accordance with Good Clinical Practice.

AstraZeneca identifies one investigator (for trial ~~██████████~~ ██████████) as potentially problematic. AstraZeneca was notified during the course of the trial that his name appeared on an FDA Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE). This investigator’s data were included in analyses, as only ~~██████████~~ subjects in the trial were randomized at his site.

b(6)

4.6 Financial Disclosures

One investigator ██████████ disclosed a financial equity interest in AstraZeneca. Given that this investigator randomized only ~~██████████~~ subjects into trial ~~██████████~~ (into ~~██████████~~ active treatment arms, including the comparator device) and no subjects into trial ~~██████████~~ the impact of his financial involvement is expected to be minimal.

b(6)

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The newly submitted clinical trials included pharmacokinetic substudies and one pharmacokinetic trial to test the two drug products. A summary of the findings of the substudies is included in the review of these trials.

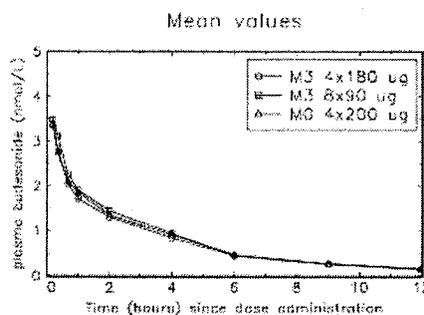
AstraZeneca conducted a 3-way crossover study of pharmacokinetics in 37 subjects with asthma (Study SD-004-0601), comparing the M3 to the original, M0 device. In each arm the total delivered dose was 640 mcg. The treatments were:

- M3 180 mcg x 4 inhalation
- M3 90 mcg x 8 inhalation
- M0 200 mcg x 4 inhalation

The results are shown in Figure 1.

**Appears This Way
On Original**

Figure 1. Pharmacokinetic study SD-004-0601: Budesonide concentration vs. time, individual and geometric means



This study shows similar levels produced by the M0 and the M3 under these conditions. As the M0-ESP is considered comparable to the M0, these results can be used to infer the M3 would have produced comparable levels to those produced by the M0-ESP if it had been tested in this study.

The newly submitted clinical trials contained pharmacokinetic substudies that are reviewed with the clinical trials (see sections 10.1.15 and 10.1.29). These substudies were not adequate to establish reasonable certainty with regards to systemic levels produced in the clinical trials. However, they produce no concern that the use of the M3 results in increased systemic levels compared to the M0-ESP.

AstraZeneca submitted results of a population pharmacokinetic analysis using data from subjects in 11 trials exposed to an M0, M0-ESP, or M3 Pulmicort Turbuhaler. The analysis was performed to discern any differences that may be due to age, race, or other factors. AstraZeneca concludes, "Many of the demographic covariates (age, gender, body weight, height, BMI, race, Clcr and disease state) were determined to have a statistically significant effect on either extravascular clearance and/or volume of distributions, however, the magnitude of these effects were small." For full review of this report, see the review of the pharmacokinetics reviewer.

5.2 Pharmacodynamics

Glucocorticoids have numerous physiological consequences. One of these, suppression of the hypothalamic-pituitary-adrenal axis may be measured fairly readily by means of serum or plasma cortisol, either basal or stimulated. Material related to the suppression of the HPA axis is reviewed in section 7.1.7.5, "Special assessments."

Suppression of growth is another potential issue with the administration of glucocorticoids to growing persons. AstraZeneca did not measure the effect of Pulmicort on growth in the newly submitted trials.

5.3 Exposure-Response Relationships

The original marketing submission for Pulmicort (section 10.1.32, "Review of Pertinent Results from Previously Submitted Trials") showed that doses as low as 100 µg BID administered through the M0 device produced mean changes in on-treatment FEV₁ or FEV₁% predicted (12-week treatment period) that were statistically different from placebo. The difference from placebo was greater at 200 µg BID, a difference that did not increase notably at higher doses.

_____ } b(4)

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The marketing application does not propose to change the current indication:

PULMICORT TURBUHALER is indicated for the maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients six years of age or older. It is also indicated for patients requiring oral corticosteroid therapy for asthma.

6.1.1 Methods

Although the current label contains recommendations for several levels of dosing, AstraZeneca proposes to support the clinical efficacy of the M3 device for the indication primarily with data from two newly submitted clinical trials that tested one dose expected to be clinically effective. The submission also includes the resubmission of data relative to one dosing regimen (90 µg BID) from two other efficacy trials in which the original version of the device was tested (see Table 3). The latter trials are resubmitted as the newly submitted clinical trials did not test the 90 µg BID dosing regimen. The determination of approvability is based not only on the demonstration of efficacy in the limited populations tested, but also on equivalence of systemic drug levels (as a safety measure) and acceptability of the device.

6.1.2 General Discussion of Endpoints

The controlled clinical trials were designed to test the effect of the product on FEV₁ (adolescents and adults) or FEV₁ % predicted (pediatric trials) integrated over time in the trial. Specifically, they compared active to placebo treatment in the difference between a baseline

measurement and a mean of pre-dose morning values over the entire treatment period. This is an appropriate means to determine the effect of an asthma controller medication such as budesonide, which is not expected to have an acute bronchodilating effect, but rather an effect with chronic use.

Secondary endpoints also included measures of pulmonary function other than FEV₁, use of β -agonist rescue treatment, and rates of discontinuation of blinded treatment for asthma worsening. These secondary endpoints were of sufficient breadth to provide potential support for the primary endpoint.

6.1.3 Study Design

The newly submitted trials (0620 and 0726) tested the M3 and M0-ESP devices at two dose levels. For trial 0620, the high dose was the upper dose recommended as a starting dose in patients on inhaled corticosteroids (similar to the trial population) or bronchodilators alone. For trial 0726, the high dose was twice the highest recommended starting dose for patients on inhaled corticosteroids or bronchodilators (Table 1). The low dose was used to establish a dose range, and would not be expected to show a difference from placebo. Single daily doses have been approved, but as a step-down regimen for patients who are well-controlled on inhaled corticosteroids. All the trials, previously submitted and newly submitted, had a treatment period of 12 weeks after a run-in period. This is an adequate time during which to assess the chronic effect of the corticosteroid treatment.

The newly submitted trials were randomized and placebo-controlled. These are features that improve the ability of a trial to detect a true treatment difference. The trials were adequately blinded. One group of subjects was given active reference (M0-ESP) devices or placebo devices that resembled the M0-ESP device (these placebo devices contained lactose); the other group was given active M3 devices or placebo devices that resembled them. It is possible that the subjects given the M3 device or the M0-ESP placebo devices could taste the lactose in the formulation. However, the lack of a systematic effect in the behavior of the placebo arms (see the review of the individual trials) is evidence that the results are relatively free of bias.

The resubmitted trials (3020A and 3023A) for consideration of the 90 mcg twice-daily dose were double-blind, randomized trials comparing several doses of the M0 product to placebo using the primary endpoints tested in the newly submitted trials. Results from these trials were important for the original U.S. approval of the Pulmicort Turbuhaler.

6.1.4 Efficacy Findings

Trial SD-004-0620 was a randomized, double-blind trial designed to test the efficacy of the M3 and the M0-ESP devices against placebo, with FEV₁ as the primary endpoint, over a 12-week treatment period in adults and adolescents. Treatment arms were balance demographically, and the trial was adequately conducted to address the question of the effect of two dosing regimens using the 180 mcg/dose M3 device. The trial population consisted of subjects with asthma on inhaled corticosteroids, from 18 to 80 years of age, mostly Caucasian and "Oriental" (65% and 30%), with a baseline FEV₁ of about 2.1 (FEV₁ % predicted of about 64). An increase in dose content of the device during the trial was the principal issue of concern over the conduct of the trial. However, this dose change did not have a clinical impact. Dosing arms were: M3 at

180 µg QD or 360 µg BID, M0-ESP at 200 µg QD or 400 µg BID, or matching placebo. Table 4 shows the primary endpoint results of the trial.

Table 4. Trial 0620: Primary endpoint results (morning predose FEV₁ (L))

	n	Baseline	Treatment period	Change	LS mean Change (SE)	Difference from placebo (SE)	p-value of Difference from Placebo
M3 360 µg bid	128	2.14 (0.05)	2.44 (0.06)	0.30 (0.02)	0.28 (0.03)	0.18 (0.04)	<0.001
M0-ESP 400 µg bid	128	2.15 (0.05)	2.52 (0.06)	0.36 (0.03)	0.34 (0.03)	0.24 (0.04)	<0.001
M3 180 µg qd	119	2.09 (0.05)	2.29 (0.06)	0.19 (0.02)	0.18 (0.03)	0.07 (0.04)	0.078
M0-ESP 200 µg qd	110	2.19 (0.06)	2.46 (0.07)	0.27 (0.03)	0.25 (0.03)	0.15 (0.04)	<0.001
Placebo (pooled)	114	2.14 (0.05)	2.26 (0.06)	0.12 (0.03)	0.10 (0.03)	-	-

- The M0-ESP device produced a greater treatment effect than the M3 comparator at each of two dose levels on the primary endpoint.
- **b(4)**
- The subgroup analyses should be viewed with some caution, based on the sample sizes and lack of randomization. The increase in effect size for the M0-ESP device in the twice-daily dosing arms was not seen in the subgroup of females. It was seen primarily in the U.S. and in the highest quartile of FEV₁. Racial subgroups of Caucasians and “Orientals,” the majority of the population, showed no meaningful differences. Little information is available for “Blacks” and the trials enrolled very few subjects over the age of 65.
- Most secondary endpoints (FVC, FEF₂₅₋₇₅, PEF, symptom scores, albuterol use) showed that the high-dose M0-ESP treatment arm produced a somewhat greater effect than the M3 device.
- Discontinuations due to asthma worsening were lowered to a greater extent in both high-dose groups than in the lower dose groups, and all were lowered compared to placebo.
- A pharmacokinetic substudy produced no concern over higher drug levels due to the M3 device.
- There was no new safety concern with the use of either the M0-ESP or the M3 device.

In summary, the trial showed that effect was less with the M3 device. The M3 failed to separate from placebo statistically.

AstraZeneca proposes that labeling include the statement, “Pulmonary function improved with all doses of Pulmicort Turbuhaler compared with placebo.” **b(4)**

The design of pediatric trial SD-004-0726 was very similar to that of the adolescent/adult trial SD-004-0620, but was conducted in a population of subjects whose asthma symptoms were

reasonably controlled on bronchodilators alone. Demographics were balanced, the trial population consisting of subjects from 6 to 17 years of age, mostly Caucasian and “Oriental” (50-57% and 32-25%), with a baseline FEV₁ % predicted of about 81-83. The conduct of the trial was adequate to permit a reasonable confidence in the analysis of the results. In this patient population, efficacy was seen in the primary endpoint but not in several secondary endpoints. This is not unexpected, given the relatively well population of subjects with asthma who were enrolled. Doses tested were the same as in the adult trial. Table 5 shows the primary endpoint results of the trial.

Table 5. Trial 0726: Primary endpoint results (morning predose FEV₁ % predicted)

	n	Baseline	Treatment period	Change	LS mean Change (SE)	Difference from placebo (SE)	p-value of Difference from Placebo
M3 360 µg bid	90	84.2 (1.0)	90.0 (1.1)	5.8 (1.0)	5.6 (0.8)	5.4 (1.1)	<0.001
M0-ESP 400 µg bid	98	86.6 (0.7)	90.7 (0.8)	4.1 (0.7)	4.4 (0.8)	4.3 (1.1)	<0.001
M3 180 µg qd	103	84.7(1.0)	87.3 (1.2)	2.7 (0.8)	2.6 (0.8)	2.4 (1.1)	0.03
M0-ESP 200 µg qd	101	84.4 (0.9)	87.3 (1.0)	2.9 (0.8)	2.7 (0.8)	2.5 (1.1)	0.022
Placebo (pooled)	101	84.5 (0.9)	84.8 (1.0)	0.4 (0.8)	0.2 (0.8)	-	-

- All treatment arms separated from placebo statistically on the primary endpoint, FEV₁ % predicted. The M3 device arm showed a larger treatment effect in the twice-daily dosing arm. Differences from placebo in the once-daily arms were not clinically notable.
- b(5)
- The subgroup analyses should be viewed with some caution, based on the sample sizes and lack of randomization. The increase in effect size for the M3 device was not seen in the subgroups of younger age groups or females. It was seen across regions and across racial groups of Caucasians and “Orientals,” the majority of the population. Very little information was available for “Blacks.”
- There was no effect of any treatment on FVC, asthma scores, meeting discontinuation criteria, or albuterol use.
- FEV₁, FEF₂₅₋₇₅, trended in the same direction as the primary endpoint. The FEV₁ is highly correlated with the primary endpoint and offers negligible additional information.
- A pharmacokinetic substudy produced no concern over higher drug levels due to the M3 device.
- There was no new safety concern with the use of either device.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The integrated summary of safety was conducted to discern safety issues with use of the M3 product. AstraZeneca conducted several trials with the M3 device prior to the conduct of the placebo-controlled trials submitted as efficacy trials. In addition, a brief overview of the safety of the M0 product is helpful to put the efficacy of the M0, 90 mcg BID dosing arm, in perspective.

Summary of data and the findings

The M3 product was studied in placebo-controlled, noncontrolled, and pharmacokinetics studies. The placebo-controlled trials were 12 weeks in duration. The important noncontrolled experience with the M3 device was in trials of 12 weeks to 12 months duration. Clinical data regarding the M0 product are reviewed for comparison to the M3 product.

No new toxicities were uncovered related to use of the new device. Serious and severe toxicities were rare and of no convincing relationship to use of the product.

AstraZeneca provided information regarding potential suppression of the hypothalamic-pituitary-adrenal axis in clinical trials testing the M3. FDA requested further information, which will be reviewed in an addendum. Urinary cortisol results from the pediatric trial, newly submitted, were inconclusive.

Clinical data base and safety assessments

Controlled trials

Table 6 shows the important placebo-controlled trials clinical trials in which subjects were treated with the M3 (or M0 product at 90 µg BID). The designs of these trials are discussed with review of the trial results (section 10, Appendices).

Table 6. Placebo-controlled clinical trials with safety information on the M3, M0-ESP, and M0*

Study number/ location	Duration of randomized treatment	Age category of subjects (yrs)	M0- ESP 200 µg QD	M0- ESP 400 µg BID	M3 180 µg QD	M3 360 µg BID	M0 100 µg BID	Placebo
0620/US/Asia ¹	12 weeks	≥18	114	130	123	130	NA	124
0726/US/Asia ¹	12 weeks	6 to 17	104	102	108	96	NA	106
3020A/US ²	12 weeks	≥18 ≤70	NA	NA	NA	NA	91	92
3023A/US ²	12 weeks	6 to 18	NA	NA	NA	NA	102	103

* M0 trials with information about the 90 µg BID dose

¹ newly submitted; ² previously submitted

Source: Applicant table 1, safety summary

Demographics in controlled trials

Table 7 shows the demographic information for subjects in the placebo-controlled trials of the M3, trials 0620 and 0726.

Table 7. Placebo-controlled trials with M3 device: Demographics of subjects

	M0-ESP 200 µg QD (N=218)	M0-ESP 400 µg BID (N=232)	M3 180 µg QD (N=231)	M3 360 µg BID (N=226)	Placebo (N=230)
Sex					
Female	119 (54.6)	123 (53.0)	118 (51.1)	106 (46.9)	117 (50.9)
Male	99 (45.4)	109 (47.0)	113 (48.9)	120 (53.1)	113 (49.1)
Race					
Caucasian	124 (56.9)	133 (57.3)	134 (58.0)	135 (59.7)	143 (62.2)
Oriental	69 (31.7)	73 (31.5)	71 (30.7)	71 (31.4)	68 (29.6)
Black	24 (11.0)	23 (9.9)	18 (7.8)	20 (8.8)	17 (7.4)
Other	1 (0.5)	3 (1.3)	8 (3.5)	0	2 (0.9)
Age group (yrs)					
6 to <12	47 (21.6)	51 (22.0)	43 (18.6)	45 (19.9)	46 (20.0)
12 to ≤17	57 (26.1)	51 (22.0)	65 (28.1)	51 (22.6)	60 (26.1)
18 to ≤65	112 (51.4)	128 (55.2)	121 (52.4)	125 (55.3)	115 (50.0)
>65	2 (0.9)	2 (0.9)	2 (0.9)	5 (2.2)	9 (3.9)

*ns=not summarized

Source: Applicant's table 16, summary of safety. Racial terms as used by applicant.

Subjects in the M3 clinical trials had a mean duration of asthma of 12.7-15 years (range 0.1 to 65 years).

Table 8 shows that the sex and age characteristics of the M0 treatment groups were similar to those of the M3 trials. Race characteristics were somewhat different between the clinical programs, but the percents of "Blacks" is small in both. Importantly, it should be remembered that these tabulations do not consider important aspects of the prior treatment of asthma such as the use of corticosteroids.

Table 8. Placebo-controlled trials with M0 device: Demographics of subjects

	M0 100 µg bid (N=193)	M0 200 µg bid (N=193)	M0 400 µg bid (N=198)	M0 800 µg bid (N=988)	Placebo (N=195)
Sex					
Female	76 (39.4)	78 (40.4)	65 (32.8)	55 (56.1)	72 (36.9)
Male	117 (60.6)	115 (59.6)	133 (67.2)	43 (43.9)	123 (63.1)
Race					
Caucasian	167 (86.5)	168 (87.0)	173 (87.4)	82 (83.7)	173 (88.7)
Black	15 (7.8)	16 (8.3)	16 (8.1)	11 (11.2)	14 (7.2)
Hispanic	8 (4.1)	3 (1.6)	6 (3.0)	4 (4.1)	4 (2.1)
Other	3 (1.6)	6 (3.1)	3 (1.5)	1 (1.0)	4 (2.1)
Age group (yrs)					
6 to <12 (y)	41 (21.2)	46 (23.8)	45 (22.7)	0	47 (24.1)
12 to ≤17 (y)	58 (30.1)	45 (23.3)	47 (23.7)	0	45 (23.1)
18 to ≤65 (y)	90 (46.6)	97 (50.3)	100 (50.5)	91 (92.9)	99 (50.8)
>65 (y)	4 (2.1)	5 (2.6)	6 (3.0)	7 (7.1)	4 (2.1)

Source: Applicant's table 17, summary of safety. Racial terms as used by applicant

Exposure in controlled trials

Table 9 shows an overview of exposure in placebo-controlled experience for the proposed product.

Table 9. M3 placebo-controlled trials: Duration of exposure

	M0-ESP 200 µg qd (N=218)	M0-ESP 400 µg bid (N=232)	M3 180 µg qd (N=231)	M3 360 µg bid (N=226)	Placebo (N=230)
≤2 weeks	11 (5.0)	5 (2.2)	11 (4.8)	7 (3.1)	10 (4.3)
>2 weeks to ≤4 weeks	18 (8.3)	9 (3.9)	18 (7.8)	13 (5.8)	34 (14.8)
>4 weeks to ≤8 weeks	12 (5.5)	11 (4.7)	20 (8.7)	12 (5.3)	15 (6.5)
>8 weeks to <12 weeks	39 (17.9)	38 (16.4)	36 (15.6)	42 (18.6)	40 (17.4)
≥12 weeks	138 (63.3)	169 (72.8)	146 (63.2)	152 (67.3)	131 (57.0)
Mean (SD) (days)	73.0 (25.9)	78.6 (19.6)	72.7 (25.7)	76.2 (22.7)	68.2 (29.0)
Median	85.0	85.0	85.0	85.0	84.5
Min, max	1, 112	5, 123	1, 121	8, 121	1, 122

Source: Applicant's table 10, clinical summary of safety

Table 10 shows that the exposure in the M0 efficacy trials was very similar.

Table 10. M0 placebo-controlled trials: Duration of exposure

	M0 100 µg bid (N=193)	M0 200 µg bid (N=193)	M0 400 µg bid (N=198)	M0 800 µg bid (N=988)	Placebo (N=195)
≤2 weeks	7 (3.6)	5 (2.6)	5 (2.5)	2 (2.0)	38 (19.5)
>2 weeks to ≤4 weeks	11 (5.7)	6 (3.1)	9 (4.5)	3 (3.1)	35 (17.9)
>4 weeks to ≤8 weeks	11 (5.7)	10 (5.2)	9 (4.5)	2 (2.0)	28 (14.4)
>8 weeks to <12 weeks	41 (21.2)	43 (22.3)	44 (22.2)	24 (24.5)	35 (17.9)
≥12 weeks	123 (63.7)	129 (66.8)	129 (65.2)	67 (68.4)	59 (30.3)
Missing	0	0	2 (1.0)	0	0
Mean (SD) (days)	76.3 (22.0)	77.8 (18.8)	78.7 (19.2)	79.7 (17.5)	52.1 (31.8)
Median	84	84	84	84	55
Min, max	1, 110	1, 124	10, 130	1, 104	2, 95

Source: Applicant's table 12, clinical summary of safety

Variables collected in placebo-controlled trials

- All the trials collected adverse events, hematology, clinical chemistry, urinalyses, vital signs, physical examination data, mouth and throat examinations
- Plasma cortisol was collected in 3020a and 3023a
- 24-hr urinary cortisol was collected only in trial 0726
- Visual acuity was measured in 3020a and 3023a

Noncontrolled trials with the M3 device

Table 11 shows the noncontrolled clinical trials in which subjects were treated with the M3 product.

Table 11. Noncontrolled clinical trials with safety information on the M3 device

Study number/ location	Duration of randomized treatment	Age category of subjects (yrs)	M3 90 µg bid	M3 540 µg bid	M3 360 µg qd	M3 360 µg bid
SD-004-0210/Non-US	12 weeks	≥18 to ≤70	148	145	NA	NA
SD-039-0667/Non-US	6 months	≥12 to ≤80	NA	NA	342	NA
SD-039-0668/Non-US	12 months	≥12 to ≤80	NA	NA	NA	943
SD-039-0673/Non-US	12 months	≥4 to ≤80	NA	NA	106*	820

*Subjects 4-11 years old

Source: Applicant's table 2 and S1, clinical summary of safety

Trial 0210 was a double-dummy, double-blind, randomized, parallel-group, multicenter trial in inhaled corticosteroid-treated adult patients with moderate to severe asthma. Subjects were randomized into treatment with M3 at either 90 or 540 µg BID or an “M2” device not marketed in the U.S.

Trial 0667 was a double-blind, randomized, parallel-group, multicenter trial in adults and adolescents (12 to 80 years) with mild to moderate asthma. Subjects were treated for 6 months with the M3 180 µg/inhalation, 2 inhalations once daily (360 µg qd) plus terbutaline sulfate as-needed, or with a budesonide/formoterol device.

Trial 0668 was a double-blind, double-dummy, randomized, parallel-group, multicenter trial in adults and adolescents (12 to 80 years) with moderate to severe asthma. Subjects were treated for 6 months with the M3 180 µg/inhalation, 2 inhalations once daily (360 µg qd) plus terbutaline sulfate as-needed, or with a budesonide/formoterol device.

Trial 0673 was a double-blind, randomized, parallel-group, multicenter trial in subjects with mild to moderate asthma. Subjects were treated for 12 months with M3 360 µg/inhalation, 1 inhalation twice daily (360 µg bid) plus Bricanyl (terbutaline sulfate) Turbuhaler 0.4 mg/inhalation as-needed or with a budesonide/formoterol device. For the subject group 4-11 years half the regular dose was given, administered once daily in the evening; for M3 subjects the dose was 360 µg qd.

Demographics in noncontrolled trials

Table 12 shows demographics of subjects who participated in noncontrolled trials with the M3 device. Most of these trials were predominantly Caucasian.

Table 12. Noncontrolled clinical trials with the M3 device: Demographics of subjects

	Trial 0210		Trial 0667	Trial 0668	Trial 0673
	M3 90 µg bid (N=148)	M3 540 µg bid (N=145)	M3 360 µg qd (N=342)	M3 360 µg bid (N=943)	M3 360 µg bid* (N=148)
Sex	93 (62.8)	88 (60.7)	219 (64.0)	538 (57.1)	510 (55.1)
Female	55 (37.2)	57 (39.3)	123 (36.0)	405 (42.9)	416 (44.9)
Male					
Race					
Caucasian	144 (97.3)	143 (98.6)	173 (50.6)	874 (92.7)	711 (76.9)
Oriental	2 (1.4)	0	167 (48.8)	7 (0.7)	158 (17.1)
Black	1 (0.7)	0	2 (0.6)	5 (0.5)	13 (1.4)
Other	1 (0.7)	2 (1.4)	0	57 (6.0)	44 (4.8)
Age group (yrs)					
≤11 (y)	0	0	1 (0.3)	1 (0.1)	106 (11.5)
12 to ≤17 (y)	0	0	52 (15.2)	64 (6.8)	107 (11.6)
18 to ≤64 (y)	142 (95.9)	135 (93.1)	269 (78.7)	806 (85.5)	652 (70.5)
≥65 (y)	6 (4.1)	10 (6.9)	20 (5.8)	72 (7.6)	61 (6.6)
Min, max	19, 68	18, 74	11, 78	11, 80	4, 79
Baseline ICS use (µg/d)					
Mean	885.3	887.9	343	748	620
Range	500 to 1600	400 to 1500	200 to 500	400 to 2000	100 to 100
Asthma history (yrs)					
Mean	8.48	10.45	10 (Median)	12	9
Min, max	1.0, 47.7	1.1, 57.8	1, 61	1, 71	0, 69

*Includes 106 subjects 4-11 years old who received 360 mcg QD

Source: Applicant's table 19, clinical summary of safety. Racial terms as used by applicant.

Exposure

Table 13 shows exposure in noncontrolled trials using the M3 device.

Table 13. Noncontrolled M3 clinical trials: Duration of exposure

	Trial 0210		Trial 0667	Trial 0668	Trial 0673
	M3 90 µg bid (N=148)	M3 540 µg bid (N=145)	M3 360 µg qd (N=342)	M3 360 µg bid (N=943)	M3 360 µg bid* (N=925)
Mean (days)	79.4	80.1	172.8	319.8	327.6
Median	84	84	182	364	365
Min, max	1, 94	5, 97	2, 224	1, 405	1, 415

*Includes 106 subjects 4-11 years old who received 360 mcg QD
 Source: Applicant's table 15, clinical summary of safety

Variables collected in noncontrolled trial

The clinical summary of safety includes adverse events and basal and ACTH-stimulated plasma cortisol measurements from these trials.

Noncontrolled trials (extension trials) with the M0 device

Table 14 is a summary of clinical trials (open-label extension trials) in which subjects were treated with the M0 product at the dose comparable to the low proposed dose. In trial 850 subjects received treatment following two weeks to five months of double-blind treatment in 4 prior trials (two of which were GHBA-165 (04-CR-3020A) and GHBA-168(04-CR-3023A)). In trial D525400007 subjects were originally treated in 3 of the 4 double-blind trials (including the two aforementioned trials) that served as the root trials for 850-CR-0280. Subjects were to be dependent on inhaled or oral corticosteroids.

Table 14. Extension trials with safety information on M0 use

Trial	Duration of treatment	Age category of subjects (yrs)	Number of subjects	Total daily dosage (BID dosing)
850-CR-0280	1 year extension open-label	6 to 70	1133	200-1600
D525400007	5 year extension open-label	6 to 70	171	200-1600

Source: Applicant table 1, Clinical Overview

Subjects in these experiences were allowed to switch dose levels.

Demographics in extension trials with M0 device

Table 15 shows that the bulk of subjects who entered into the extension trials was Caucasian. There were slightly more males in the 1-year extension, but the sexes were evenly balanced at the outset of the 5-year extension.

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Table 15. Open-label extensions using M0 device: Demographics of subjects

	850-CR-0280 (N=1133)	D525400007 (N=171)
Sex		
Female	478 (42.2)	87 (50.9)
Male	655 (57.8)	84 (49.1)
Race		
Caucasian	1000 (88.3)	158 (92.4)
Black	82 (7.2)	7 (4.1)
Hispanic	32 (2.8)	4 (2.3)
Other	19 (1.7)	2 (1.2)
Age		
Mean (SD)	33.4 (18.4)	45.3 (16.7)
Min, max	6.0, 70.0	6.0, 70.0

Source: Applicant table 18, clinical summary of safety
 Racial terms as used by applicant.

Exposure

Table 16 shows an overview of exposure in the M0 extension trials.

Table 16. M0 extension trials: Exposure

	850-CR-0280 (N=1133)	D525400007 (N=171)
Mean (SD) (days)	366 (12)	1432 (595)
Median	364	1683
Min, max	216, 457	1, 2057

Source: Applicant's table 14, clinical summary of safety

Variables collected

The following variables were collected during these trials:

- Both trials collected adverse events, vital signs, and physical examination data.
- Trial 850-CR-0280 collected clinical chemistry and urinalysis laboratory tests, plasma cortisol, mouth and throat fungal cultures and ophthalmic examination.
- Trial D525400007: hematology, clinical chemistry, urinalysis laboratory tests, and mouth and throat fungal cultures were done if clinically indicated.

Subjects were allowed to switch dose levels in these extension trials; in trial D525400007 many evaluations were optional. For these reasons, because of the open-label nature of treatment, and because of dropouts, the data from these trials is useful primarily to find large safety signals.

Pharmacokinetics trials with the M3 device

Table 17 shows the data base for subjects who were treated with the M3 product in pharmacokinetic trials. Trial 0600 was an open-label, randomized, crossover trial in healthy subjects 18-55 years old (the comparator treatment was the M2 device (not marketed in the U.S.)). Trial 0601 was an open-label, randomized, crossover trial in subjects with asthma 18-65 years old.

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Table 17. Summary of pharmacokinetic trials with safety information on the M3 device

Study number/ location	Duration of randomized treatment	Age category of subjects (yrs)	M3 4X180 µg	M3 8X90 µg	M3 4X180 µg	M0 4X200 µg
SD-004 0600/ Non-US	single dose x 2	≥18 to ≤55	24	NA	NA	NA
SD-004-0601/ Non-US	single dose x 3	≥18 to ≤65	NA	36	36	37

Source: Applicant table 3, safety summary

Demographics

In trial 0600, 15 men and 9 women were enrolled whose age ranged from 20-47; 23 were Caucasians and 1 was “Black.” In trial 0601, 22 men and 15 women were enrolled whose age ranged from 19-61; all were Caucasian.

Exposure

Twenty-three of 24 subjects completed 0600 (1 withdrew due to pregnancy); 37 completed trial 0601 (1 withdrew due to an aggravation of asthma).

Variables collected

The clinical summary of safety includes adverse events, hematology and clinical chemistry laboratory measurements, plasma cortisol (Study 0600 only), vital signs, and physical examinations.

Miscellaneous methodological issues

- Safety analyses included all subjects who received at least one dose of randomized treatment.
- The definition of a serious adverse event was revised as of April 1, 1998, so that cancer and overdoses themselves were not serious adverse events unless the other criteria for a serious adverse event were fulfilled (i.e., resulting in death, immediately life-threatening, requiring hospitalization or prolonging a hospitalization, resulting in persistent or significant disability or incapacity, resulting in a congenital abnormality or defect, or required an intervention). Trials 3020a, 3023a, 850-CR-0280, and D5254C00007 used the definition prior to April 1, 1998.
- Adverse events occurring after the beginning of treatment are separately considered for the controlled trials and their extensions. For trials 0600, 09601, 0210, 0667, 0668, and 0673, adverse events include those at any phase of the trial.

7.1.1 Deaths

The few deaths that have occurred in the clinical program have not pointed to a life-threatening toxicity of the product.

Four deaths occurred during the 1- and 5-year extension trials.

850-CR-0280

- 36 year-old woman who died as the result of an automobile accident. She had been treated at M0 100 µg BID, then M0 200 µg BID

D525400007

- 56 year-old woman who died as the result of an automobile accident. She had been treated with M0 800 µg BID.

- 69 year-old man who died with multiple myeloma, an myocardial infarction, and dissection of the aorta. He had been treated with M0 200-800 µg BID.
- 46 year-old man who died of a myocardial infarction. He had been treated with M0 400-800 µg BID.

Four deaths occurred in subjects on the M3 product in other noncontrolled trials (all M3 360 µg BID with concomitant terbutaline sulfate as needed):

Trial 0668:

- 55 year-old man died of a myocardial infarction after about 3 months of treatment
- 47 year-old woman who died after about a year of treatment of hypertrophic cardiomyopathy
- (discontinued subject) 23 year-old man who discontinued treatment due to severe asthma and died of acute cardiac failure and cerebral edema 2 weeks later

Trial 0673:

- 67 year-old man who died after about 10 months of treatment with cyanosis and coma; further data not provided.

7.1.2 Other Serious Adverse Events

Nonfatal serious adverse events occurring during treatment did not fall into any concerning pattern.

M3 placebo-controlled trials

- Nonfatal serious adverse events in the placebo-controlled M3 trials did not fall into a pattern when considered either as preferred terms or system organ classes. No event (preferred term) occurred in more than a single subject, and none occurred in a subject treated with the M3 device. These events were: upper abdominal pain, anal fistula, acute bronchitis, perirectal abscess, asthma, and acute myocardial infarction.

M0 placebo-controlled trials

- Two nonfatal serious adverse events, anaphylactoid reaction and myopathy, occurred in subjects treated with the M0 at 100 µg BID. Among M0 device-treated subjects at higher doses, asthma occurred as a nonfatal serious adverse event in 2 subjects; all other events occurred in single subjects without a concerning pattern, and in no apparent dose relation organ class.

850-CR-0280

- AstraZeneca provided a tabulation of all serious adverse events. Review of these data show no adverse event occurring at a notable frequency.

D525400007

- Several subjects experienced a neoplasm (basal cell carcinoma, malignant hair matrix tumor, skin carcinoma, bleeding colonic polyps, breast nodule, and breast cancer). Given the noncontrolled nature of this trial, its 5-year duration, and the experience with inhaled corticosteroids generally, these events are probably sporadic and do not point to a significant safety concern.

Other noncontrolled trials

- Trial 0210: Single subjects experienced the following: aggravation of asthma, cerebrovascular disorder, gastroenteritis, aggravation of hypertension, ventricular tachycardia, and tracheitis

- Trial 0667: Single subjects (all at M3 360 QD) experienced accident or injury, aggravation of asthma, cerebrovascular disorder, fracture, gastroenteritis, hypertension, or sexual dysfunction
- Trial 0668: The most frequent events were aggravated asthma (11 subjects, 1%) and pneumonia (7 subjects, 1%). Other events occurred in less than 0.5% of subjects and exhibited no clear pattern.
- Trial 0673: The most frequent event was aggravated asthma (occurring in 10 (1% of the M3 360 BID treatment arm) and 2 (2% of the M3 360 QD treatment arm). Other events occurred in less than 0.5% of subjects and exhibited no clear pattern.
- Pharmacokinetic trials: no serious adverse events were reported.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The important trials for the licensure of the M0 device and for the proposed licensure of the M3 device included a provision for dropping out due to worsened asthma symptoms. Most of the dropouts were due to worsened asthma. Other causes were of diverse nature (see section 10, Appendices, for details of discontinuations).

7.1.3.2 Adverse events associated with dropouts

Discontinuations of treatment due to asthma worsening occurred more frequently in the placebo and lower-dose arms of the adult/adolescent trial 0626 (for details, see the section 10.1 of this review). Discontinuations for other events during treatment in the placebo-controlled efficacy trials for M3 did not occur in a discernible pattern (3 discontinuations due to upper respiratory tract infection in 3 active treatment arms; 1 discontinuation due to bronchitis in an M0-ESP 200 µg QD subject and one in placebo).

There were no discontinuations due to adverse events in the 800 µg BID arm of the M0 placebo-controlled trials. The most common adverse event associated with discontinuation overall was asthma, which occurred in 7 (3.6%) placebo-treated subjects, 3 (1.6%) of subjects treated at 200 µg BID, and 1 (0.5%) in each of the 400 and 100 µg BID treatment arms. Single subjects experienced respiratory infection, anaphylactoid reaction, and cataract (each at 100 µg BID), hyperthyroidism (400 µg BID), and urticaria (200 µg BID). Overall, these results do not show a pattern of toxicity of the M0 device.

In the 1-year extension, 33 subjects (0.7%) discontinued. The most common reason was asthma.

In the 5-yr extension, 7 subjects (4%) discontinued due to an adverse event. Causes were diverse (cataract, breast carcinoma, oral moniliasis, injury, angina pectoris, cardiovascular disorder (dissection of aorta), neoplasm (multiple myeloma), myocardial infarction, and asthma.

7.1.3.3 Other significant adverse events

AstraZeneca identified particular adverse events associated with corticosteroid administration or with asthma (Table 18). The events of interest were further categorized by MedDRA preferred terms.

Table 18. AstraZeneca categorization of adverse events of interest

Class effect	Event of interest	Class effect	Event of interest
Asthma events	Asthma	Systemic effects of ICS	Adrenal suppression
Disease under study (DUS) events	Breathlessness		Diabetes control
	Chest tightness		Fractures
	Cough		Growth retardation
	Phlegm		Metabolic bone effects
	Wheezing		Ocular effects
Local effects of ICS	Candidiasis		Psychiatric effects
	Voice effects		Skin effects
	-		Taste effects
	-		Weight gain

Source: Applicant Table 1.2.11.1, Appendix 2.7.4.7

Table 19 shows the events from the pre-selected adverse events of interest for the important efficacy trials 0620 and 0726.

Table 19. Placebo-controlled trials of M3 device: Pre-selected adverse events (related to inhaled corticosteroid or asthma)

Category of event		M3 360 µg bid (n=226)	M0-ESP 400 µg bid (n=232)	M3 180 µg qd (n=231)	M0-ESP 200 µg qd (n=218)	Placebo (n=230)
Local	Subjects with 1 or more AEs representing local effects of ICS	7 (3.1)	1 (0.4)	0	2 (0.9)	3 (1.3)
	Oral candidiasis	5 (2.2)	1 (0.4)	0	2 (0.9)	2 (0.9)
	Voice effects	2 (0.9)	0	0	0	1 (0.4)
Systemic	Subjects with 1 or more AEs representing systemic effects of ICS	1 (0.4)	2 (0.9)	2 (0.9)	2 (0.9)	2 (0.9)
	Fractures	1 (0.4)	1 (0.4)	2 (0.9)	1 (0.5)	1 (0.4)
	Skin effects	0	1 (0.4)	0	1 (0.5)	1 (0.4)
Asthma	Subjects with 1 or more AEs representing asthma or potentially asthma-related AEs	12 (5.3)	14 (6.0)	24 (10.4)	15 (6.9)	30 (13.0)
	Asthma	5 (2.2)	4 (1.7)	15 (6.5)	11 (5.0)	23 (10.0)
	Subjects with potentially asthma-related AEs (Disease under study events)	7 (3.1)	10 (4.3)	9 (3.9)	5 (2.3)	8 (3.5)
	Cough	7 (3.1)	9 (3.9)	9 (3.9)	4 (1.8)	8 (3.5)
	Increased upper airway secretion	0	1 (0.4)	0	1 (0.5)	0

Sources: Applicant's tables 37, 38, 39, and 41; clinical summary of safety

There were slightly more subjects with oral candidiasis among the high-dose M3 subjects than among the high-dose M0-ESP subjects. However, there is no pattern of concern for the M3 device among these preselected events. For comparison, Table 20 shows the incidences of the preselected events in the M0 placebo-controlled trials. Overall, there was an increase among actively-dosed groups in local and systemic effects of corticosteroids. The differences in event rates between the two devices is small and may represent differences in the populations, trial procedures, the devices, or other effects.

Table 20. M0 placebo-controlled trials: Pre-selected adverse events (related to inhaled corticosteroid or asthma)

Category of event		M0 100 µg bid (N=193)	M0 200 µg bid (N=193)	M0 400 µg bid (N=198)	M0 800 µg bid (N=988)	Placebo (N=195)
Local	Subjects with 1 or more AEs representing local effects of ICS	4 (2.1)	5 (2.6)	10 (5.1)	10 (10.2)	2 (1.0)
	Oral candidiasis	3 (1.6)	4 (2.1)	8 (4.0)	4 (4.1)	2 (1.0)
	Voice effects	1 (0.5)	1 (0.5)	2 (1.0)	6 (6.1)	0
Systemic	Subjects with 1 or more AEs representing systemic effects of ICS	6 (3.1)	9 (4.7)	7 (3.5)	3 (3.1)	2 (1.0)
	Bone effects	2 (1.0)	3 (1.6)	3 (1.5)	0	0
	Ocular effects	3 (1.6)	1 (0.5)	1 (0.5)	2 (2.0)	1 (0.5)
	Skin effects	0	2 (1.0)	2 (1.0)	0	1 (0.5)
	Taste effects	1 (0.5)	1 (0.5)	0	1 (1.0)	0
	Weight gain	0	2 (1.0)	1 (0.5)	0	0
Asthma	Subjects with 1 or more AEs representing asthma or potentially asthma-related AEs	7 (3.6)	12 (6.2)	10 (5.1)	2 (2.0)	18 (9.2)
	Asthma	1 (0.5)	3 (1.6)	2 (1.0)	0	7 (3.6)
	Subjects with potentially asthma-related AEs (Disease under study events)	6 (3.1)	9 (4.7)	8 (4.0)	2 (2.0)	11 (5.6)
	Cough	6 (3.1)	9 (4.7)	6 (3.0)	2 (2.0)	10 (5.1)
	Dyspnea	0	0	2 (1.0)	0	3 (1.5)

Sources: Applicant's tables 39, 40, 42, clinical summary of safety

7.1.4 Other Search Strategies

I did not use any additional search strategies to discover toxicities of treatment with Pulmicort Turbuhaler.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Trials 0620 and 0726 used the Medical Dictionary for Regulatory Activities (MedDRA); the other M3 trials used an AstraZeneca event dictionary (AAED). The M0 trials and their extensions used Coding Symbols for the Thesaurus of Adverse Reaction Terms (COSTART). The first coding system has five levels of hierarchy; the last two have three.

For trials 04-3020A and the extension trials, AstraZeneca states, “The subjects were asked in a general manner regarding possible adverse [*sic*] that occurred since their last visit.” For the other trials, AstraZeneca supplies quotations. A typical question was: “Have you had [or “Have you/has the child had”] any health problems since the previous visit?” Adverse events were recorded from the time of enrollment.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Review of adverse event terms from the new clinical trials indicates no significant gaps or inappropriately coded items that would complicate the understanding of the events.

7.1.5.3 Incidence of common adverse events

The review of common adverse events is most profitably done by means of comparison to control. This section will review placebo-controlled data first, but will also show the incidences of common events occurring in the noncontrolled trials with the M3 product.

Placebo-controlled trials

Table 21 shows the incidences of adverse events that occurred in any treatment group at an incidence of $\geq 3\%$. There was no pattern of toxicity compared to placebo.

Table 21. M3 placebo-controlled trials: Adverse events occurring at $\geq 3\%$ in any treatment arm

MedDRA preferred term	M0-ESP 200 μg QD (n=218)	M0-ESP 400 μg BID (n=232)	M3 180 μg QD (n=231)	M3 360 μg BID (n=226)	Placebo (n=230)
Total	113 (51.8)	120 (51.7)	115 (49.8)	99 (43.8)	121 (52.6)
Headache	20 (9.2)	24 (10.3)	18 (7.8)	16 (7.1)	18 (7.8)
Nasopharyngitis	18 (8.3)	21 (9.1)	13 (5.6)	21 (9.3)	19 (8.3)
Upper respiratory tract infection	15 (6.9)	13 (5.6)	15 (6.5)	11 (4.9)	12 (5.2)
Asthma	11 (5.0)	4 (1.7)	15 (6.5)	5 (2.2)	23 (10.0)
Pharyngolaryngeal pain	9 (4.1)	10 (4.3)	11 (4.8)	10 (4.4)	14 (6.1)
Pyrexia	5 (2.3)	8 (3.4)	8 (3.5)	7 (3.1)	10 (4.3)
Cough	4 (1.8)	9 (3.9)	9 (3.9)	7 (3.1)	8 (3.5)

Source: Applicant table 22, clinical summary of safety

For comparison’s sake, Table 22 shows the most common adverse events that occurred in the pivotal trials for the M0 device. Note that the reporting method was COSTART, not MedDRA. Events were generally similar.

Table 22. M0 placebo-controlled trials: Subjects with adverse events occurring at $\geq 3\%$

COSTART Preferred term	M0 100 μg bid (N=193)	M0 200 μg bid (N=193)	M0 400 μg bid (N=198)	M0 800 μg bid (N=98)	Placebo (N=195)
Total	116 (60.1)	118 (61.1)	133 (67.2)	61 (62.2)	96 (49.2)
Respiratory infection	34 (17.6)	26 (13.5)	47 (23.7)	19 (19.4)	25 (12.8)
Headache	20 (10.4)	31 (16.1)	30 (15.2)	14 (14.3)	13 (6.7)
Pharyngitis	21 (10.9)	20 (10.4)	18 (9.1)	5 (5.1)	16 (8.2)
Sinusitis	15 (7.8)	23 (11.9)	17 (8.6)	2 (2.0)	11 (5.6)
Flu syndrome	13 (6.7)	10 (5.2)	11 (5.6)	14 (14.3)	9 (4.6)
Rhinitis	7 (3.6)	10 (5.2)	10 (5.1)	3 (3.1)	8 (4.1)
Cough increased	6 (3.1)	9 (4.7)	6 (3.0)	2 (2.0)	10 (5.1)
Pain	5 (2.6)	8 (4.1)	6 (3.0)	5 (5.1)	4 (2.1)
Infection	13 (6.7)	7 (3.6)	4 (2.0)	1 (1.0)	1 (0.5)

Source: Applicant's table 26, clinical summary of safety

Table 23 contains preferred terms that occurred at an incidence of $\geq 1\%$ in the M3 360 μg BID group.

Table 23. M3 controlled trials: Subjects with adverse events occurring at $\geq 1\%$ in the M3 360 μg BID treatment arm

MedDRA preferred term	M3 360 μg bid (N=226)	M3 180 μg bid (N=231)	Placebo (N=230)
Nasopharyngitis	21 (9.3%)	13 (5.6%)	19 (8.3%)
Nasal congestion	6 (2.7%)	4 (1.7%)	1 (0.4%)
Pharyngitis	6 (2.7%)	1 (0.4%)	4 (1.7%)
Rhinitis allergic	5 (2.2%)	2 (0.9%)	3 (1.3%)
Gastroenteritis viral	4 (1.8%)	2 (0.9%)	1 (0.4%)
Viral upper respiratory tract infection	5 (2.2%)	2 (0.9%)	3 (1.3%)
Nausea	4 (1.8%)	0	2 (0.9%)
Otitis media	3 (1.3%)	2 (0.4%)	2 (0.9%)
Oral candidiasis	3 (1.3%)	0	1 (0.4%)

Source: Applicant's table 1.2.3.2.1, clinical summary of safety

The small increases in adverse events noted in the M3 360 μg BID groups are not a significant safety concern for use of the product.

Noncontrolled trials with the M3 device

Table 24 shows events that occurred in two or more subjects per treatment arm in trial 0210. There was no clear evidence of a dose relationship, and unusual events were not seen with notable frequency.

Table 24. Trial 0210: Subjects reporting adverse events (≥2 for either treatment arm)

Preferred Term (AstraZeneca definition)	M3 90 µg bid n=148	M3 540 µg bid n= 145
Respiratory Infection	16 (10.8)	14 (9.7)
Rhinitis	10 (6.8)	9 (6.2)
Bronchitis	6 (4.1)	6 (4.1)
Tracheitis	0	4 (2.8)
Headache	1 (0.7)	3 (2.1)
Pharyngitis	8 (5.4)	3 (2.1)
Sinusitis	7 (4.7)	3 (2.1)
Arthralgia	0	2 (1.4)
Fracture	1 (0.7)	2 (1.4)
Gastroenteritis	1 (0.7)	2 (1.4)
Hypertension Aggravated	0	2 (1.4)
Coughing	1 (0.7)	2 (1.4)
Fever	0	2 (1.4)
Accident And/Or Injury	1 (0.7)	2 (1.4)
Asthma Aggravated	9 (6.1)	1 (0.7)
Infection Viral	3 (2.0)	1 (0.7)
Dysphonia	3 (2.0)	0
Laryngitis	2 (1.4)	0

Source: Applicant's table 5.2.3.2, clinical summary of safety

Table 26,

Table 27, and

Table 27 show events experienced by ≥1% of subjects in trial 0667, 0668, and 0673 (exposure was considerably longer than in 0210). Events not seen in the shorter placebo-controlled trials were not seen with concerning frequency.

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Table 25. Trial 0667: Subjects reporting adverse events in clinical at $\geq 1\%$ incidence

Preferred Term (AstraZeneca definition)	M3 360 µg bid n= 342
Respiratory Infection	54 (15.8)
Pharyngitis	21 (6.1)
Headache	18 (5.3)
Rhinitis	13 (3.8)
Eczema	9 (2.6)
Infection Viral	9 (2.6)
Sinusitis	7 (2.0)
Bronchitis	7 (2.0)
Urinary Tract Infection	6 (1.8)
Dizziness	5 (1.5)
Asthma Aggravated	5 (1.5)
Myalgia	4 (1.2)
Conjunctivitis	4 (1.2)
Pain	4 (1.2)
Arthralgia	3 (0.9)
Tremor	3 (0.9)
Diarrhoea	3 (0.9)
Pharynx Disorder	3 (0.9)
Palpitation	3 (0.9)

Source: Applicant's table 5.2.3.2, clinical summary of safety

Table 26. Trial 0668: Subjects reporting adverse events in clinical at $\geq 1\%$ incidence

Preferred Term (AstraZeneca definition)	M3 360 µg bid n= 943
Respiratory Infection	177 (18.8)
Bronchitis	72 (7.6)
Pharyngitis	69 (7.3)
Rhinitis	56 (5.9)
Sinusitis	49 (5.2)
Headache	47 (5.0)
Asthma Aggravated	43 (4.6)
Infection Viral	36 (3.8)
Accident And/Or Injury	34 (3.6)
Back Pain	26 (2.8)
Coughing	20 (2.1)
Dysphonia	17 (1.8)
Gastroenteritis	17 (1.8)
Pain	17 (1.8)
Fracture	15 (1.6)
Abdominal Pain	15 (1.6)
Cystitis	13 (1.4)
Moniliasis	13 (1.4)
Rhinopharyngitis	12 (1.3)
Conjunctivitis	11 (1.2)

Preferred Term (AstraZeneca definition)	M3 360 µg bid n= 943
Diarrhoea	11 (1.2)
Hypertension	11 (1.2)
Pneumonia	11 (1.2)
Arthralgia	10 (1.1)
Myalgia	10 (1.1)
Dyspepsia	10 (1.1)
Tooth Disorder	10 (1.1)
Pharynx Disorder	10 (1.1)
Fever	10 (1.1)
Depression	9 (1.0)
Tracheitis	9 (1.0)
Allergic Reaction	9 (1.0)

Source: Applicant's table 5.2.3.3, clinical summary of safety

Table 27. Trial 0673: Subjects reporting adverse events at ≥1% incidence

Preferred Term (A)	M3 360 µg bid n= 925
Respiratory Infection	182 (19.7)
Pharyngitis	86 (9.3)
Rhinitis	76 (8.2)
Bronchitis	76 (8.2)
Headache	42 (4.5)
Asthma Aggravated	35 (3.8)
Sinusitis	33 (3.6)
Infection Viral	28 (3.0)
Accident And/Or Injury	22 (2.4)
Coughing	21 (2.3)
Fever	20 (2.2)
Tremor	19 (2.1)
Conjunctivitis	18 (1.9)
Back Pain	17 (1.8)
Hypertension	16 (1.7)
Chest Pain	15 (1.6)
Fracture	12 (1.3)
Dysphonia	12 (1.3)
Myalgia	11 (1.2)
Abdominal Pain	11 (1.2)
Gastroenteritis	11 (1.2)
Arthralgia	10 (1.1)
Mouth Dry	10 (1.1)
Moniliasis	10 (1.1)
Dyspepsia	9 (1.0)
Dyspnea	9 (1.0)
Pneumonia	9 (1.0)

Preferred Term (A)	M3 360 µg bid n= 925
Urinary Tract Infection	9 (1.0)
Otitis Media	9 (1.0)

Source: Applicant's table 5.2.3.4, clinical summary of safety

7.1.5.4 Common adverse event tables

Table 28, prepared by FDA, shows the incidences of common adverse events (denoted by preferred term) occurring during treatment, if they occurred in ≥1% of subjects in either M3 treatment arm and at an incidence greater than placebo, using pooled data. There were no notable differences between the two devices.

Table 28. Incidence of events (n and % per treatment arm) from pooled M0-ESP/M3 trials occurring at ≥1% incidence in either M3 arm and at a greater incidence than placebo

Preferred term	M0-ESP 200 µg QD (n=218)	M0-ESP 400 µg BID (n=232)	M3 180 µg QD (n=231)	M3 360 µg BID (n=226)	Placebo (n=230)
Cough	4 (1.8)	9 (3.9)	10 (4.3)	7 (3.1)	8 (3.5)
Diarrhoea	3 (1.4)	3 (1.3)	5 (2.2)	3 (1.3)	3 (1.3)
Dyspepsia	2 (0.9)	1 (0.4)	3 (1.3)	1 (0.4)	1 (0.4)
Gastroenteritis viral	3 (1.4)	4 (1.7)	2 (0.9)	4 (1.8)	1 (0.4)
Influenza	3 (1.4)	2 (0.9)	8 (3.5)	1 (0.4)	2 (0.9)
Joint sprain	0 (0)	2 (0.9)	2 (0.9)	3 (1.3)	2 (0.9)
Myalgia	2 (0.9)	6 (2.6)	3 (1.3)	1 (0.4)	1 (0.4)
Nasal congestion	4 (1.8)	5 (2.2)	4 (1.7)	6 (2.7)	1 (0.4)
Nasopharyngitis	18 (8.3)	21 (9.1)	13 (5.6)	21 (9.3)	20 (8.7)
Nausea	1 (0.5)	0 (0)	0 (0)	4 (1.8)	2 (0.9)
Oral candidiasis	1 (0.5)	1 (0.4)	0 (0)	3 (1.3)	1 (0.4)
Otitis media	1 (0.5)	1 (0.4)	2 (0.9)	3 (1.3)	2 (0.9)
Pharyngitis	2 (0.9)	6 (2.6)	1 (0.4)	6 (2.7)	4 (1.7)
Rhinitis allergic	2 (0.9)	2 (0.9)	2 (0.9)	5 (2.2)	3 (1.3)
Skin laceration	3 (1.4)	0 (0)	1 (0.4)	3 (1.3)	3 (1.3)
Sunburn	0 (0)	0 (0)	3 (1.3)	0 (0)	1 (0.4)
Upper respiratory tract infection	15 (6.9)	14 (6)	15 (6.5)	11 (4.9)	12 (5.2)
Viral upper respiratory tract infection	0 (0)	2 (0.9)	2 (0.9)	5 (2.2)	3 (1.3)
Vomiting	4 (1.8)	1 (0.4)	3 (1.3)	2 (0.9)	2 (0.9)

7.1.5.5 Identifying common and drug-related adverse events

Adverse events common to subjects with asthma occurred commonly during the clinical trials. However, any increases in adverse events associated with treatment were small. No new significant toxicities were commonly seen with use of the M3 device as compared to the approved product.

7.1.5.6 Additional analyses and explorations

As no new significant toxicities were seen with the M3 product, I did not perform additional explorations of the safety data to discern possible susceptibilities among different patient populations or other factors to explain the toxicities.

7.1.6 Less Common Adverse Events

The most severe and serious events did not fall into a concerning pattern. I did not perform a review of occasional, nonsevere events.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory testing is discussed with the design of the various trials included in the safety analysis above. Considering the pre-existing data concerning effects of inhaled corticosteroids that can be detected by means of blood and urine testing, the frequency of testing in trials 0620 and 0726 (see detailed reviews in the appendix) was adequate.

Generally, routine laboratory testing has revealed no significant toxicity of Pulmicort. AstraZeneca tested cortisol levels for the detection of suppression of the hypothalamic-pituitary-adrenal axis. These results are summarized in section 7.1.7.5.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The important trials for analysis of the short-term incidence of potential laboratory abnormalities associated with use of the M3 device were the newly submitted trials 0620 and 0726. No other controlled new data were submitted. Neither of these trials showed a concerning laboratory abnormality.

7.1.7.3 Standard analyses and explorations of laboratory data

Laboratory data from the original marketing application were not reviewed again for the current document. Data reviewed from the newly submitted trials included means and shifts from normal.

7.1.7.3.1 Analyses focused on measures of central tendency

Treatment with Pulmicort in the M3 placebo-controlled trials has produced no notable changes compared to control.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Treatment with Pulmicort in the M3 placebo-controlled trials has produced no notable changes compared to control.

7.1.7.3.3 *Marked outliers and dropouts for laboratory abnormalities*

Treatment with Pulmicort in the M3 placebo-controlled trials has produced no notable changes compared to control.

7.1.7.4 Additional analyses and explorations

AstraZeneca tested cortisol levels for the detection of suppression of the hypothalamic-pituitary-adrenal axis in the context of ongoing clinical trials. This testing is summarized below.

7.1.7.5 Special assessments

Suppression of the hypothalamic-pituitary-adrenal (HPA) axis, a potential concern with the administration of corticosteroids, may be detected by means of measuring serum or urinary cortisol. Although nonstimulated cortisol is a potential screening method, the most sensitive means of detecting suppression is by means of the ACTH stimulation test.

The submission contains a summary of cortisol results from the 1-year extension study (for the M0 device). These results were reviewed with the original marketing submission. Cortisol was not measured in the subsequent 5-year extension.

The results of nonstimulated cortisol testing in pediatric trial 0726 are discussed with the review of that trial. Results were inconclusive.

Further information related to the effects of the M3 device on cortisol was provided in the following noncontrolled studies:

- 0210: Morning plasma cortisol was tested in 87% of M3-treated subjects at the randomization visit and at 12 weeks. Table 29 shows that there was a slight drop in the geometric mean plasma cortisol at the higher dose. Although there was no nontreated control, the dose relation provides support for the effect of the product in producing these results.

Table 29. Trial 0210: Morning plasma cortisol (nmol/l) in M3-treated subjects

M3 treatment	Randomization visit			Week 12		
	n	Geometric mean	Range	N	Geometric mean	Range
90 µg bid	128	299	10-1130	128	303	10-814
540 µg bid	126	306	70-718	126	275	10-1030

AstraZeneca did not assess changes in individual subjects.

- 0667: Morning plasma cortisol was tested in approximately 30% of M3-treated subjects (Table 30). Interpretation of the results is problematic because of decreasing sample sizes and the noncontrolled nature of the trial.

Table 30. Trial 0667 (M3/360 µg QD): Morning plasma cortisol (nmol/l)

Randomization visit N=102		Week 12 N=95	
Geo. mean	Range	Geo. mean	Range
413	10-1340	397	10-110

Shifts between low and normal values occurred in similar numbers in both directions (Table 31). However, 2 of the 6 subjects who shifted from normal to low values had values below 51 nmol/L at end-of-treatment.

Table 31. Trial 0667: Morning plasma cortisol, shifts to last value (% of total n (95))

	Low	Normal	High
Low at baseline	4 (4%)	4 (4%)	0
Normal at baseline	6 (6%)	81 (85%)	0
High at baseline	0	0	0

- 0668: Morning plasma cortisol results are shown in Table 32. The interpretation of this table, which show an apparent decline at 6 months followed by stabilization, is problematic because of decreasing sample sizes and the noncontrolled nature of the trial.

Table 32. Trial 0668 (M3/360 µg BID): Morning plasma cortisol (nmol/l)

	n	Mean (nmol/L)	Range (nmol/L)
Randomization	206	278	10-990
6 months	173	242	10-1080
12 months	188	254	10-1250

Table 33 shows that slightly more subjects shifted from normal to low than from low to normal plasma cortisol, based on a lower threshold of 150 nmol/l.

Table 33. Trial 0668: Plasma cortisol, shifts to last value (% of total n (194))

Pretreatment condition	Last value	
	Low	Normal
Low	7 (4%)	17 (9%)
Normal	26 (13%)	144 (74%)

Table 34 shows the results of ACTH testing. There was no change in the geometric mean value after 12 months in the subset of subjects tested in the trial.

Table 34. Trial 0668: ACTH test results (nmol/l)

Randomization visit N=55		Month 12 N=46	
Geo. mean	Range	Geo. mean	Range
621	197-1340	635	67-1320

Table 35 shows that subjects shifted from low to normal and from normal to low (based on a lower threshold of 400 nmol/l) in equal numbers.

Table 35. Trial 0668: ACTH test shift results at end of treatment (% of total n (45))

Pretreatment condition	End of treatment	
	Low	Normal
Low	1 (2%)	3 (7%)
Normal	3 (7%)	38 (84%)

- 0673: Morning plasma cortisol results are summarized in Table 36. Decreasing sample sizes makes interpretation of the results problematic.

Table 36. Morning plasma cortisol (nmol/l) in trial 0673 (M3/360 µg BID)

Age group (yrs)	Time point	n	Mean (nmol/L)	Range (nmol/L)
12-80	Randomization	193	304	61-1090
	6 months	169	270	26-924
	12 months	168	255	10-785
4-11	Randomization	99	219	44-808
	12 months	77	222	10-744

In an analysis of shift status to last value on treatment (Table 37) more subjects 12-80 years old shifted from normal to abnormal than from abnormal to normal, but the numbers of subjects shifting between the two categories was equal in the age group 4-11 years. This is suggestive of a dose effect detectable in this trial at 360 µg BID.

Table 37. Trial 0673 (M3/360 µg BID): Morning plasma cortisol shifts from baseline to last value (% of total n per age group)

Age group (yrs)	Baseline	Last value	
		Abnormal	Normal
12-80 (n=179) 360 µg BID	Abnormal	6 (3%)	4 (2%)
	Normal	23 (13%)	146 (82%)
4-11 (n=76) 360 µg QD	Abnormal	4 (5%)	10 (13%)
	Normal	10 (13%)	52 (68%)

ACTH stimulation testing results in trial 0673 are summarized in Table 38. Decreasing subject numbers makes interpretation of these results problematic.

Table 38. Trial 0673: ACTH testing in a subset of subjects 4-11 years old

	n	Mean (nmol/L)	Range (nmol/L)
Randomization	55	627	298-1010
12 months	43	571	320-1240

Shift results show approximately equal numbers of subjects shifting from normal to abnormal or from abnormal to normal (Table 39).

Table 39. Trial 0673: ACTH test shift results at end of treatment (% of total n (41))

Pretreatment condition	End of treatment	
	Low	Normal
Low	0	2 (5%)
Normal	3 (7%)	36 (88%)

- 0600: A single set of inhalations (720 µg total) suppressed plasma cortisol 28% (95% CI 21.4-34.8%).

In summary, interpretation of the mean data, which show apparent small decreases in cortisol responses, is complicated by diminishing sample sizes with time. The data summary is insufficient to quantify the level of potential suppression. Upon request, AstraZeneca provided additional information, which will be reviewed in an addendum.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Changes in heart rate, blood pressure, and weight have not been identified as a concern with previous versions of Pulmicort. In the newly submitted trials comparing the M3, the currently available M0-ESP, and placebo, data were supplied on vital signs at baseline and at 12 or the end of treatment. None of the active treatment arms showed a notable effect.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Examination of vital sign data has been performed primarily through comparisons in the placebo-controlled trials in the original marketing application and those submitted here. These latter trials are summarized elsewhere in this review.

7.1.8.3 Standard analyses and explorations of vital signs data

Vital sign data from the original marketing application were not reviewed again for the current review. Data reviewed from the newly submitted trials included means and shifts from normal.

7.1.8.3.1 *Analyses focused on measures of central tendencies*

Treatment with Pulmicort has produced no notable changes compared to control.

7.1.8.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

Treatment with Pulmicort has produced no notable changes compared to control.

7.1.8.3.3 *Marked outliers and dropouts for vital sign abnormalities*

Treatment with Pulmicort has produced no notable changes compared to control.

7.1.8.4 Additional analyses and explorations

I have conducted no additional analyses or explorations.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

No additional preclinical data were included in the submission. Pulmicort has not been associated with abnormalities of the ECG, nor with a significantly increased risk of cardiac adverse events. The newly submitted trials did not conduct ECG testing.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Examination of ECG data was performed through comparisons in the placebo-controlled trials in the original marketing application. The newly submitted trials did not conduct ECG testing.

7.1.9.3 Standard analyses and explorations of ECG data

ECG data from the original marketing application was not reviewed again for the current review.

7.1.9.3.1 *Analyses focused on measures of central tendency*

ECG data from the original marketing application was not reviewed again for the current review.

7.1.9.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

ECG data from the original marketing application were not reviewed again for the current review.

7.1.9.3.3 *Marked outliers and dropouts for ECG abnormalities*

ECG data from the original marketing application was not reviewed again for the current review.

7.1.9.4 Additional analyses and explorations

I have conducted no additional analyses or explorations.

7.1.10 Immunogenicity

Immunogenicity has not been tested in the clinical program. Although immunological reactions to glucocorticoids have been reported, the overall immunogenicity of glucocorticoids, as small molecules, is expected to be small.

7.1.11 Human Carcinogenicity

Data with regards to the potential for carcinogenicity is in the label for Pulmicort. No new information has been submitted.

7.1.12 Special Safety Studies

AstraZeneca has conducted no trials targeted to address particular safety issues. AstraZeneca has studied the effect of Pulmicort on the hypothalamic-pituitary-adrenal axis in substudies within other trials (see reviews of these results elsewhere in this document).

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The potential for adverse consequences of the abrupt withdrawal of systemically administered (oral) glucocorticoids is addressed in labeling for Pulmicort.

7.1.14 Human Reproduction and Pregnancy Data

Labeling states, "Despite the animal findings, it would appear that the possibility of fetal harm is remote if the drug is used during pregnancy."

The information provided in the current submission, including the 4-month safety update report (budesonide formulations other than the M3, which is not marketed) and information from the newly submitted clinical trials, does not suggest that the section of labeling should be revised. No new animal data have been submitted.

7.1.15 Assessment of Effect on Growth

AstraZeneca has not conducted a program to assess the effect of Pulmicort Turbuhaler on growth. No new information is submitted on growth in the current submission.

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It is appropriate to include precautionary language on growth, based on recommendations of the combined Pulmonary-Allergy Drugs Advisory Committee and Endocrinologic and Metabolic Drugs Advisory Committee of July 30-31, 1998, which discussed the effect of orally inhaled and intranasal corticosteroids on growth in children.

7.1.16 Overdose Experience

The submission does not contain information on overdose from the time of approval, but the 4-month safety update (see section 7.2.9, medication errors), mentions this issue. No notable safety concern is generated from this information.

7.1.17 Postmarketing Experience

The proposed M3 device has not been marketed anywhere. Postmarketing data only derive from experience with other budesonide products. FDA agreed that AstraZeneca could submit an update of postmarketing safety from the point of data lock in the original NDA and the 4-month time point. Please see section 7.2.9 of this review (Additional Submissions, Including Safety Update).

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Please see section 7.1 for a summary of the data base used for the safety evaluation. In the M3 controlled-trial data base 457 subjects were exposed to Pulmicort Turbuhaler M3:

- 88 individuals 6 to <12 years old
- 116 individuals 12 to ≤17 years old
- 246 individuals 18 to ≤65 years old
- 7 individuals >65 years old

Because the M3 does not produce higher systemic levels of budesonide (see section 5.1) there is no expectation that systemic toxicities would be greater with its use. The controlled clinical trials did not show an increased incidence of local or systemic adverse events associated with use of the M3. These clinical trials were conducted in an adequate sample of patients.

In the noncontrolled M3 data base there were 2563 subjects. Three of these noncontrolled trials (see above, trials 0667, 0668, and 0673) tested 2210 subjects for durations of approximately 6 months to a year.

The current safety data base is adequate, and is consistent with ICH guidelines.

7.2.1.1 Study type and design/patient enumeration

Please see section 7.1.

7.2.1.2 Demographics

Please see section 7.1.

7.2.1.3 Extent of exposure (dose/duration)

Please see section 7.1.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Please see section 7.1.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Based on the safety record and the numbers of subjects treated with Pulmicort, the other safety experience with budesonide and lactose, and the demonstration that systemic levels of budesonide generated with use of the M3 device are no higher than those with the currently marketed product, the current safety data base is adequate.

7.2.8 Assessment of Quality and Completeness of Data

AstraZeneca submitted adequate information regarding the prior clinical experience with Pulmicort M3 and M0. Upon request, AstraZeneca provided additional information regarding cortisol levels in M3-treated subjects. This information will be reviewed in an addendum.

7.2.9 Additional Submissions, Including Safety Update

The 4-month safety update provides safety information from the data lock point for the NDA of 30 April 2005 up to October 31, 2005. AstraZeneca reports that there are no ongoing trials with the M3 and that it is not marketed anywhere. The safety update thus refers only to other formulations of inhaled budesonide.

Table 40 is a summary of estimated exposure during the reporting period, by budesonide product and dose.

Table 40. Estimated number of patient treatment days with Pulmicort (none on M3) from 01 May 2005 to 31 October 2005

Formulation	Strength (µg/dose)	Daily dose	Patient treatment days (million)
pMDI	50	400	5
	100	400	4
	200	600	66
Total	Recommended daily dose 200-1600 µg		75
Turbuhaler	100	400	23
	200	600	152
	400	800	91
Total	Recommended daily dose 200-1600 µg		266
Respules	125 µg/mL 2 mL	500	13
	250 µg/mL 2 mL	1000	28
	500 µg/mL 2 mL	2000	11
Total	Recommended daily dose 500-2000 µg		52

Source: Applicant table 1, safety update report

Three hundred fourteen case reports received, of which 86 were serious or unlisted (in parentheses):

- Turbuhaler (other than M3) - 184 (43)
- Respules - 87 (14)
- pMDI CFC - 3 (1)

- Unknown formulation of Pulmicort - 40 (28)

Deaths

There were 4 deaths reported, 2 of whom were in elderly patients with complicating medical conditions and 1 of whom was in an elderly patient but with insufficient information provided. In 1 case a stillbirth occurred at 33 weeks of gestation in which a twisted umbilical cord was suspected to be the proximate cause of death.

Serious or unlisted case reports

Serious or unlisted case reports did not follow a concerning pattern. In the following list, each term occurred once, except where noted: rhinitis, infectious croup, lymphoma, aplastic anemia, anaphylaxis, Cushing's syndrome, paresthesia, labile blood pressure, asthma (3 cases), wheezing (1 case), hematemesis, tongue edema, hepatic failure, acute hepatitis, renal failure, spontaneous abortion, stillbirth, ineffective drug, ankle fracture, drug exposure during pregnancy.

Pregnancy outcomes

There were 12 case reports in the reporting period. In 7 cases, the outcome was not reported, in 3 there was a healthy baby. There was one spontaneous abortion and there was one fatality (see *deaths* above).

Medication errors

There were two cases of overdose, one with a nonserious case of dizziness and the other with nonserious rash and bruising that disappeared with a decrease in dose (which had been up to 2400 µg per day). There were 6 cases of medication errors (2 incorrect route, 3 of drug administration error, and 1 of inappropriate schedule). None of the events resulted in a serious adverse event.

Newly analyzed studies

AstraZeneca completed SD-004-0764, which was a trial of 760 subjects 12 years old or older with moderate to severe asthma who after a run-in period were treated with Pulmicort Respules at 0.5, 1.0 QD, 1.0 BID, 2.0 BID, or Turbuhaler 400 BID for 12 weeks with a 2-week safety follow-up period. There were no deaths and no subject on the Turbuhaler discontinued due to an adverse event. The trial report is not included in the NDA submission.

The 4-month safety update report contains no information that would change the overall judgment of the safety of budesonide. It contains no information on the M3.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The data have brought to light no new toxicities due to Pulmicort or to the active moiety, budesonide. The important considerations of toxicity are noted in labeling.

The safety data base is adequate, based on the toxicities noted in the numbers of subjects treated in controlled and noncontrolled experiences, and on the lack of additional safety concern from pharmacokinetic analyses of the M3 and previous versions of the product.

Submitted information is not detailed enough to determine the risk of suppression of the hypothalamic-pituitary-adrenal axis in some noncontrolled trials using the M3 (see section 7.1.7.5). I will provide a review of additional information, submitted upon request, in an addendum.

7.4 General Methodology

Please see section 7.2.1 for a description of the data base. For evaluation of adverse events, controlled trials of similar design were able to be pooled; otherwise, individual trials were examined.

7.5 Pooling Data Across Studies to Estimate and Compare Incidence

The combined table of adverse events (Table 28) reflects the pooling of adverse events from the adolescent/adult trials and the pediatric trial. Although the technique increases the ability to detect differences between treatments due to larger sample sizes, the combined data set did not reveal significant safety concerns for the M3 product.

7.5.1.1 Pooled data vs. individual study data

It is appropriate to use the pooled data to detect differences in the incidences of more rarely occurring events, since the designs of the trials were very similar. The chief differences between the trials are outlined in section 10.1.22.

7.5.1.2 Combining data

AstraZeneca provided a single dataset of adverse events for the adult/adolescent trial 0620 and the pediatric trial 0726 together. This was used to create the combined table of adverse events (Table 28).

7.5.2 Explorations for Predictive Factors

During trial 0620, AstraZeneca increased the dose content of the Pulmicort Turbuhaler by approximately 5%. AstraZeneca submitted adverse event data compiled with respect to whether subjects had received a device manufactured before or after the change. There was no difference between the two subject groups in terms of safety.

7.5.2.1 Explorations for dose dependency for adverse findings

The clinical trials included two dose levels, tested for the M3 and the M0-ESP. safety was acceptable for either dose level.

7.5.2.2 Explorations for time dependency for adverse findings

Neither AstraZeneca nor I performed examinations of the timing of the occurrence of adverse events.

7.5.2.3 Explorations for drug-demographic interactions

The clinical trials did not reveal any concerning pattern of toxicity with regards to subgroups of age, sex, or race (or region, that is, U.S. or Asia).

7.5.2.4 Explorations for drug-disease interactions

The submission contains no studies of the effect of diseases (such as renal or hepatic disease) on the activity of Pulmicort. Because the new proposed device contains budesonide and lactose only, for which there is prior experience, new studies would not be required.

7.5.2.5 Explorations for drug-drug interactions

AstraZeneca did not perform additional studies of the interactions of budesonide, the active component in Pulmicort Turbuhaler, with other drugs that could have an impact on drug levels. Because the new proposed device contains budesonide and lactose only, for which there is prior experience, new studies would not be required.

7.5.3 Causality Determination

The submitted clinical data do not alter the current understanding of the toxicities associated with the administration of budesonide by inhalation as expressed in the label for Pulmicort.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

As described in section 1.1, insufficient information has been submitted to support a

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8.2 Drug-Drug Interactions

Labeling describes interactions with ketoconazole and cimetidine. The new clinical trials did not generate new data on drug-drug interactions. This is not required, given that the new product contains only lactose as an additional agent.

8.3 Special Populations

The submission contains pharmacokinetic substudies to the pediatric and adolescent/adult clinical trials and a population pharmacokinetic analysis. These are insufficient to generate new conclusions regarding the use of Pulmicort in any subgroup of age, sex, race, organ impairment, pregnancy, or lactation. However, definitive new information is not required.

8.4 Pediatrics

AstraZeneca markets an inhalational form of budesonide for children with asthma aged 12 months to 8 years of age as Pulmicort Respules. AstraZeneca has requested a partial pediatric waiver for the conduct of clinical trials for children under the age of 6 years of age under CFR 314.55 (c)(3)(i). This section of regulations allows a partial waiver if the drug does not represent a meaningful therapeutic benefit over existing treatments and is not likely to be used in a substantial number of patients in that age group. AstraZeneca's request is reasonable.

8.5 Advisory Committee Meeting

This application does not require an Advisory Committee meeting.

8.6 Literature Review

I did not perform a comprehensive literature review.

8.7 Postmarketing Risk Management Plan

AstraZeneca does not propose a special risk management plan. Based on the lack of identification of any new safety concerns with the new proposed device, one is not needed.

8.8 Other Relevant Materials

I reviewed no additional materials.

9 OVERALL ASSESSMENT

9.1 Conclusions

AstraZeneca proposes that efficacy was shown in both new clinical trials and that sufficient information has been submitted to allow a complete transfer of dosing recommendations to the new version of the product. However, clinical trial results were equivocal with regards to the comparability of the M3 to the M0-ESP. In the adult trial the M3 device produced less effect on treatment period mean FEV₁ than the M0-ESP device at 360 µg twice daily; in the pediatric trial, the M3 device produced more effect on FEV₁ % predicted.

The submission supports approval of the M3 at a twice-daily dose of 360 µg or 720 µg (equivalent to the currently labeled upper limit of recommended dosing). I base this primarily on the showing of a statistically significant difference from placebo of approximately 10% of baseline FEV₁ in the adult trial and on the finding of slightly better effect on FEV₁ compared to the M0-ESP version in a pediatric trial.

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9.2 Recommendation on Regulatory Action

I recommend that the application be approved, but substantially limited in scope to a dosing recommendation for 360 and 720 µg twice daily only.

9.3 Recommendation on Postmarketing Actions

✓
✓

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9.3.1 Risk Management Activity

Because of the safety record with the Pulmicort and the lack of information pointing to a concern over increased systemic levels, AstraZeneca does not have to perform special risk management activities.

9.3.2 Required Phase 4 Commitments

~~_____~~
See section 1.2.2.

b(5)

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

Labeling will be addressed after this review is made final.

9.5 Comments to Applicant

Subsequent to our review of NDA 21-949, the Pulmicort Turbuhaler version M3 is approved with labeling as revised. Dosing must be twice-daily at doses of 360 µg twice-daily up to 720 µg twice-daily.

✓
✓

b(5)

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 A Placebo-Controlled Comparison of the Efficacy and Safety of the Current US Version of Pulmicort (Budesonide) Turbuhaler® and the New Version of Pulmicort Turbuhaler® in Asthmatic Adults Currently Treated with Inhaled Steroids / SD-004-0620

10.1.2 Design/synopsis

The protocol was designed to randomize approximately 525 subjects to treatment with the M3 device, the M0-ESP device, or a matching placebo device (for each device) for 12 weeks. Subjects had to have mild asthma that was symptomatic after a run-in period on a placebo inhaler. The primary endpoint was the difference in FEV₁ between baseline and the average of post-baseline visit values.

10.1.3 Objectives

The trial was designed to assess efficacy in terms of FEV₁, safety, and pharmacokinetics.

10.1.4 Treatment regimens

Active treatment and placebo devices were manufactured by AstraZeneca.

Subjects were all placed on a placebo device (like an M0-ESP device) during run-in. Treatment was 1 puff twice a day. Subsequently, if eligible, subjects were to be randomized equally to one of the following for 12 weeks:

- M3 device: 180 mcg metered dose device
 - 2 puffs twice a day using a device that delivers 120 doses (360 µg BID)
 - 1 puff every morning using a device that delivers 60 doses (180 µg QD)
- M0-ESP: 200 mcg metered dose device
 - 2 puffs twice a day (400 µg BID)
 - 1 puff every morning (200 µg QD)
- A matching placebo was used for each active arm equally (M0-ESP and each M3) so that when pooled the size of the placebo arms would be equal to each active group.

Because the appearance of the M3 and the M0-ESP was not blinded, subjects could know which device they were given. In addition, the placebos for both devices contained lactose.