

Because of this, subjects could know whether they received an M0-ESP active device or its placebo. There was no assessment of the ability of the subjects to know the type of device to which they were assigned.

Subjects were to be instructed to rinse their mouths after each dose.

10.1.5 Placebo/study drug

Pulmicort Turbuhaler M0-ESP contains only budesonide. Pulmicort Turbuhaler M3 contains budesonide and lactose. Placebo for both devices contained lactose, as in trial 0620.

10.1.6 Treatment assignment/blinding

Subjects were assigned randomization numbers from portions of a randomization code that corresponded to whether or not they agreed to participate in the pharmacokinetic analysis. Cartons of medication were to be labeled with the study, subject, and visit numbers, and were blinded to treatment assignment but not dose level during the treatment period. While cartons contained instructions to take the placebo run-in medication identically (i.e., one inhalation twice a day) cartons of medication for the treatment period contained instructions to take the required number of inhalations according to dose level. Investigators could determine the treatment assignment if necessary by tearing off a label (US) or reference to a separate form (Asia). The sites dispensed either 1 or 2 devices and a spare device according to a prespecified plan. Personnel who administered medication were not supposed to direct the performance of spirometry (which included FEV₁, the primary endpoint).

10.1.7 Concomitant medications

Subjects were instructed to take inhaled albuterol (US) or salbutamol (Asia) for symptomatic relief.

Astemizole, hydroxyzine, nonprescription asthma medications, β -blockers, inhaled anticholinergics, and the use of systemic corticosteroids were prohibited; also prohibited were nasal corticosteroids or antidepressants if started less than 4 weeks prior to screening or if there was a change in the dosing regimen. Subjects on the PK subprotocol were further restricted from taking "Prescription, over-the-counter, or herbal medications that inhibit the CYP3A4 enzyme and are known to affect the activity of the enzyme, such as certain macrolide antibiotics, antifungals, and H₂ antagonists..." and any glucocorticoids containing budesonide.

The protocol specified that if a subject were to require systemic corticosteroids, he or she would be withdrawn from trial treatment. The protocol did not state a requirement for the withdrawal of a subject for the use of other prohibited medications.

10.1.8 Notable subject eligibility criteria

Subjects had to meet criteria to be placed in a placebo run-in period. They had between 5-40 days to meet further criteria to be eligible for randomization to treatment. AstraZeneca intended to enroll a population of subjects whose asthma was manageable on moderate, but not intensive pharmacotherapy and who became mildly symptomatic when removed from treatment.

Inclusion criteria

- ≥18 yrs old; either sex
- asthma for ≥6 months
- FEV₁ 60-90% predicted normal (Crapo 1981, American Review of Respiratory Disease)
- FEV₁ reversibility of ≥12% and ≥0.20 L from prebronchodilator FEV₁, at visit 1 or 2
- Treatment with inhaled corticosteroids for ≥3 months immediately preceding visit 1
- Dosage of specified inhaled corticosteroids for at least a month within minima and maxima
- If receiving allergen injections, dose stable for at least 3 months with expectation of remaining on them for duration of trial

Randomization criteria after placebo run-in (Visit 2)

- FEV₁ ≥55% and ≥85% of predicted normal (Crapo) at Visit 2
- Pre-bronchodilator FEV₁ at Visit 2 at least 5 percentage units lower than prebronchodilator FEV₁ at Visit 1 (both expressed as predicted normal value)
- ≥12 inhalations of albuterol or salbutamol during 5 consecutive days within 7 days of randomization
- Combined daytime and nighttime asthma symptom scores (see immediately below) of at least 10 points (total) during 5 consecutive days within 7 days of randomization

Exclusion criteria

- Life-threatening asthma including any prior intubation, respiratory arrest or seizures as a result of an exacerbation of asthma
- Severe asthma as judged by the investigator
- Meeting any of the following criteria:
 - Decrease in FEV₁ (L) ≥25 % from Visit 1 or to below 40% of predicted
 - Use of ≥12 actuations of albuterol or salbutamol MDI per day for 2 days within a 3-day period
 - A decrease in morning peak expiratory flow (PEF) > 25% from baseline (baseline defined as the mean of the last 7 days prior to randomization) on 3 days within a 5-day period. [*This criterion could only be applied after visit 2*]
 - Four nighttime awakenings requiring treatment with short-acting inhaled β₂-agonist within a 6-day period
- ≥2 inpatient hospitalizations for asthma within 1 year of Visit 1 or any emergency room visit for asthma within 6 months of Visit 1
- Use of oral, rectal, or parenteral steroids during the month (28 days) prior to Visit 1
- Use of leukotriene modifiers, inhaled long-acting β₂-agonists, oral β₂-agonists, theophyllines, anticholinergics, cromones, or ketotifen (oral), within 2 weeks prior to Visit 1
- Previous smokers with a history of > 10 pack years
- Smoking within 6 months of Visit 1
- “Clinically relevant” disease “such as” COPD, emphysema, cystic fibrosis, and others, with the exception of treated and stable TB
- “Clinically significant” medical condition
- Convulsive disorder

Any clinically significant deviation from normal in either the general physical examination or laboratory parameters, as evaluated by the investigator
An acute exacerbation of asthma or a respiratory tract infection within 30 days prior to Visit 1 that may affect the results of the study, as judged by the Investigator
History of malignancy (excluding basal cell carcinoma) in the past 5 years

*The asthma symptom score is:

Daytime score

0 = None No symptoms of asthma.
1 = Mild Asthma symptoms noticeable but were not bad enough to cause trouble with daily routine and activities. Did not require use of albuterol.
2 = Moderate Asthma symptoms noticed often which caused some interference with daily routines and activities. Required use of albuterol.
3 = Severe Asthma symptoms continuously or present most of the day which severely restricted daily routine and activities.

Nighttime score

0 = None No symptoms of asthma.
1 = Mild Awoke once because of asthma and/or cough but did not use albuterol.
2 = Moderate Awoke at least once because of asthma and/or cough and took albuterol.
3 = Severe Awake most of the night because of asthma and/or cough.

The protocol also excluded potential subjects with a planned in-patient surgery, pregnant or lactating women or those planning to become pregnant, potential subjects with hypersensitivity to the rescue agent, budesonide or lactose or history of substance abuse, previously randomized, those who had used an experimental drugs or devices within 30 days of visit 1, household members of subjects in the trial, those likely to begin β -blocker treatment.

These eligibility criteria were reasonably designed to enroll a population with symptomatic asthma without confounding conditions.

10.1.9 Plan of procedures and evaluations

Run-in period (Visit 1)

Eligible subjects were to enter a run-in period that lasted from 5-40 days during which time their inhaled corticosteroids were to be discontinued and they were to be placed on single-blind placebo inhaler with discontinuation of inhaled corticosteroids. Routine laboratory evaluations were to be obtained, spirometry performed, and training in the use of the electronic diary was to be conducted. Albuterol or salbutamol MDIs were to be dispensed.

Randomization (Visit 2, week 0)

If eligible, subjects were to be randomized to treatment.

Treatment period

Visits 2-5, weeks 0, 2 4, and 8

At these visits, spirometry was to be performed, subjects were to be queried about serious adverse events and concomitant medications they had taken, and the diaries were to be checked for peak flow data, asthma symptom scores, and rescue medication use.

Visit 5.1 (for PK subjects) and 6 (week 12)

Visit 5.1 was to occur in the week prior to week 12, only for subjects receiving a PK evaluation. At this visit, routine labs, blood for budesonide levels, and urinalysis were to be performed. Visit 6 was the final visit for all subjects. At this visit, all evaluations performed during the preceding treatment visits were to be performed; in addition, a physical examination with examination of the mouth and throat was to be performed.

Follow-up visit

Subjects were to return 2 weeks after the end of the treatment period to determine the presence of any adverse events that occurred since the end of the trial.

Determination of FEV₁ (primary endpoint data)

Spirometry was to be conducted at standardized times. At visit 1, it was to be conducted between 6 and 9:30 a.m. (± 30 minutes), after that, the time of day that a subject began spirometry maneuvers was to be consistent with the start time established at Visit 1 (± 60 minutes). Subjects were not to have taken bronchodilators. At least 3 technically satisfactory FVC maneuvers out of a possible 8 attempts were to be performed. The largest values were selected by machine; the difference between the largest and smallest of these was not to differ by more than 0.2 liters. The largest FEV₁ (and FVC and FEF₂₅₋₇₅) were chosen for analysis.

Functionality testing of devices

In the US only, devices were to be collected at visit 5 and 6 for functionality testing.

10.1.10 Discontinuation of subjects from trial (discharge criteria)

Subjects were to be removed from the trial for any of the following:

Run-in period

Decrease in FEV₁ ≥ 25 % from Visit 1 or to below 40% of predicted

Use of ≤ 12 actuations of albuterol or salbutamol MDI per day for 2 days within a 3-day period

Four nighttime awakenings requiring treatment with short-acting inhaled β_2 -agonist within a 6-day period

Treatment period

All of the above with the addition of

A decrease in morning peak expiratory flow (PEF) $> 25\%$ from baseline (baseline defined as the mean of the last 7 days prior to randomization) on 3 days within a 5-day period

Subjects removed from the trial were expected to return for evaluations as described for visit 6.

10.1.11 Analysis

10.1.11.1 General considerations

The statistical analytical plan was made final on 14 January 2005, the day after “clean file” was declared.

All statistical tests were to be carried out using 2-tailed tests, and the p-value was to be rounded to 3 significant digits.

The primary endpoint data were pulmonary function data. These data were excluded from the analysis in certain cases: "In cases where subjects took leukotriene modifiers within 1 day of pulmonary function testing, relevant test values from that measurement were excluded. In cases where subjects took leukotriene modifiers or theophylline for 3 or more consecutive days, any pulmonary function test value recorded within 1 week after the last dose (of leukotriene modifier or theophylline) was excluded."

The protocol did not contain a plan for an interim analysis.

10.1.11.2 Sample size determination

The size of the trial population was intended to provide 90% power to detect a difference of 0.23 liters, with a standard deviation of 0.5 liter) between active and placebo treatment arms, given a two-sided test using a 5% level of significance. The original protocol's unevaluable rate estimation was decreased in protocol amendment 9, resulting in a projected total enrollment of 525 subjects.

10.1.11.3 Analytical populations

Efficacy

The primary population for analysis was to be randomized subjects who received at least one dose of study medication after the baseline period and who had at least one observation taken while receiving study drug. This was not a true intent-to-treat population, but the numbers of subjects actually excluded was not excessive (see efficacy results).

Safety

The safety population included anyone who had received at least 1 dose of study drug.

10.1.11.4 Adjustments for missing data and calculation of treatment period mean

The primary analysis was to substitute the last value observed at an assigned clinic visit for post-baseline values in the case of early withdrawal of the subject. Values obtained at visits between assigned visits were not to be carried forward. Baseline data were not to be carried forward. Unassigned visit values were included in the treatment period mean.

10.1.11.5 Primary endpoint and its analysis

The primary endpoint was the difference between active treatment and placebo in the difference between the baseline (visit 2) FEV₁ and the mean of the treatment period FEV₁ measurements. The analysis was to be done using an analysis of covariance (ANCOVA) with the change from baseline as the dependent variable, treatment and country as the study factors, and the baseline value (Visit 2) for FEV₁ as a covariate. A "step-down" procedure was to be followed to control for multiplicity, comparing the high-dose (360 µg BID) arm to placebo first. If this were different at p=0.05, the low-dose group would be compared.

Note that the primary endpoint's statistical comparison was against placebo. Comparability was to be assessed between the M3 and M0-ESP groups (low- and high-dose separately) using 95% confidence intervals on the differences between treatment arms, calculated using the ANCOVA.

10.1.11.6 2° endpoints (bulleted) and their analyses

Secondary endpoints were not clearly placed in hierarchical order in the protocol. This review will discuss them in the order they appear in the text of the protocol.

- Morning PEF, Nighttime and Daytime Asthma Symptom Scores, β 2-Agonist Use (Number of Puffs Per Day, Number of Days Use), Evening PEF
For these variables, the change from baseline to treatment was to be analyzed, where baseline was defined as the mean value for the 7 days immediately prior to randomization and the treatment period values defined as the mean value over the 12 weeks of treatment. Statistical methods were to be identical to those used for the primary endpoint.
- FVC and FEF_{25-75%}
The analysis was the same as that for the secondary endpoints above, except that baseline was to be defined as the value recorded just prior to randomization.
- Percentage of Discontinuations and Time to Discontinuation
Differences between treatment arms were to be compared using Fisher's exact test. The time to discontinuation from the study was to be illustrated using Kaplan-Meier estimates of the survival functions and log-rank scores reported in comparisons of the M3 dose groups to placebo.

10.1.12 Changes to the protocol

The original protocol was dated 26 November 2001. Nine numbered amendments and three "administrative" changes were implemented. The first 3 amendments occurred before the first subject was enrolled (which was 16 July 2002). The following lists the notable features of changes that were implemented after amendment 3.

- (non-numbered "administrative change") 29 July 2002: changed the numbers of devices to be dispensed at certain visits; added that an assessment of causality would be made for adverse events as well as serious adverse events.
- Amendment 4. 29 August 2002: recommended treatment discontinuation to occur after 4 nighttime awakenings, not 3, to occur over a 6-day period, not 5-day period.
- Amendment 5. 3 October 2002: increase in placebo run-in period maximal duration from 28 days to 40 days.
- (non-numbered "administrative change") 2 December 2002: Specification of subject numbers assigned to PK analysis after a trial drug re-supply.
- (non-numbered "administrative change") 28 January 2003: qualified FEV₁ reversibility as up to 2.5, not 2.5 mg of nebulized albuterol
- Amendment 6. 25 February 2003: added 540-minute and 720-minute time point to PK analysis; disallowed use of astemizole and hydroxyzine; disallowed budesonide use in PK subjects

- Amendment 7. 6 June 2003: specified that sites only in the U.S. participate in device functionality testing and PK analyses; set date limits for reassignment of visit dates in the event of a missed visit; reassigned subject numbers for subjects who were to have pharmacokinetic analysis performed; added a 2nd resupply of products to the US sites; decreased the number of batches of inhalers and the number of inhalers/batch that were to be tested; decreased the number of inhalers for which certain assessments related to product quality were to be performed.
- Amendment 8. 20 October 2003; included salbutamol as an agent for the test of FEV₁ reversibility, qualifying for randomization, or qualifying for discontinuation; specified that salbutamol was to be used in Asia, and albuterol in the US; made minor changes to the doses of beclamethasone that were inclusionary; excluded subjects for use of oral β -agonists or oral ketotifen; allowed PFTs to be done on a different day from Visit 1; disallowed medications that affect the CYP3A4 enzyme for subjects who were to undergo PK analysis; added country as a factor in the ANCOVA; added requirement to store the drug between 15-30° C.
- Amendment 9. 27 May 2004: Lowered the number of subjects enrolled prior to concluding the trial from 650 to 525 and lowered the numbers per treatment arm proportionately.

The changes to the protocol do not cause concern over the conduct of the trial.

10.1.13 Results

10.1.13.1 Conduct of the trial

No events were reported that would have unblinded treatment arm assignments. The major issue in the analysis of this trial is that during the trial a change was made to the dose content of devices that were used in the United States, but not in Asia.

During the clinical trial AstraZeneca implemented an increase in the dose content of the M3 devices. Subjects in the US were initially randomized to treatment with devices containing _____ mg per gram (mg/g) reservoir contents (or matching placebo) _____ batches with a dose content of _____ mg/g of reservoir contents were used. Subsequently, the dose content was raised to _____ μ g/g and further subjects were randomized in the US (Table 41); all subjects in Asia were treated with the higher dose-content devices. Altogether _____ batches of devices with increased content were used. AstraZeneca compensated for the increase in dose content by providing matching placebo devices.

Table 41. Trial 0620: Numbers of subjects (US) assigned to different dose-content devices*

Treatment arm	Dose content	n
M3 180 QD	_____ mg/g	54
M3 180 QD	_____ μ g/g	35
M3 360 QD	_____ mg/g	55
M3 360 QD	_____ mg/g	40
Placebo	Matched to _____ mg/g	48
Placebo	Matched to _____ mg/g	42

*All Asian subjects received the higher dose content devices

b(4)

b(4)

The numbers of subjects in the primary analytical population assigned to the lower- and higher-dose content devices is shown in Table 53, which accompanies the discussion of the primary endpoint results.

10.1.13.2 Screening and enrollment

Screening of 2027 persons occurred at 127 sites (110 US, 17 Asian); 1406 were not randomized at visit 2. Thirty sites did not enroll subjects. Over half the subjects enrolled were not randomized due to not meeting eligibility criteria (Table 42).

Table 42. Trial 0620: Reasons for failing to be randomized at Visit 2

Reason	N (%)
Adverse event	48 (3.4%)
Developed discharge criteria	3 (0.2%)
Eligibility criterion	876 (62.3%)
Lost to Follow-up	37 (2.6%)
Not willing	132 (9.4%)
Other	310 (22.0%)
Total	1406

Overenrollment resulted in 621 adult asthmatic subjects randomized at Visit 2 to double-blind treatment. Most of the 90 sites had very few subjects; 2 sites in the Philippines shared the highest enrollment at 39 subjects (Table 43).

The first subject was enrolled 16 July 2002; the last subject completed 28 October 2004.

Table 43. Trial 0620: Enrollment by site and country (n=621 overall)

Country	Subjects/site	Number of sites
US	1-5	42
	6-10	16
	11-14	12
	16-22	4
	Total n=450	
Indonesia	1-3	3
	10-13	3
	Total n= 41	
Philippines	1-5	4
	6-10	3
	13	1
	39	2
	Total n= 130	

10.1.13.3 Baseline characteristics of the subjects

Treatment arms were balanced for sex proportions, race proportions, age, duration of asthma, and FEV₁ (Table 44). The majority of subjects were Caucasian and there were more female than male subjects. The latter is consistent with the overall preponderance of asthma in females in the adult population. (reference 2).

Table 44. Trial 0620: Baseline characteristics (safety population*)

		M3 360 µg bid (n=130)	M0-ESP 400 µg bid (n=130)	M3 180 µg qd (n=123)	M0-ESP 200 µg qd (n=114)	Combined Placebo (n=124)
Sex, n (% of subjects)	Male	53 (40.8)	45 (34.6)	37 (30.1)	40 (35.1)	42 (33.9)
	Female	77 (59.2)	85 (65.4)	86 (69.9)	74 (64.9)	82 (66.1)
Race, n (% of subjects)	Caucasian	85 (65.4)	81 (62.3)	80 (65.0)	71 (62.3)	83 (66.9)
	Black	8 (6.2)	11 (8.5)	5 (4.1)	7 (6.1)	7 (5.6)
	Oriental	37 (28.5)	38 (29.2)	36 (29.3)	35 (30.7)	34 (27.4)
	Other	0	0	2 (1.6)	1 (0.9)	0
Age (y)	Mean	41.1	39.1	39.1	39.1	40.0
	SD	11.7	12.0	11.4	10.8	14.1
	Range	18 to 80	18 to 69	18 to 70	19 to 66	19 to 78
Age group, n (% of subjects)	18 to 65 y	125 (96.2)	128 (98.5)	121 (98.4)	112 (98.2)	115 (92.7)
	65+ y	5 (3.8)	2 (1.5)	2 (1.6)	2 (1.8)	9 (7.3)
Asthma history (y)	Mean	20.8	19.9	21.9	18.2	19.9
	SD	16.0	14.6	14.6	13.7	14.0
	Range	0.5 to 61.7	0.4 to 64.4	0.8 to 65.0	0.2 to 53.6	0.2 to 62.4
FEV ₁ at visit 2*	n	130	129	121	113	119
	Mean ±SD	2.13 ± 0.56	2.16 ± 0.58	2.10 ± 0.51	2.19 ± 0.66	2.12 ± 0.58
	range	0.73-3.48	1.16-4.25	0.77-3.53	1.15-4.30	0.63-3.69

Source: Applicant's table 12, clinical trial report. Racial terms as used by applicant.
* FEV₁ data are from efficacy analysis data set, applicant table 13

Treatment arms were balanced for diary-recorded symptoms and rescue medication use. Nighttime symptoms were recorded as "mild" by the trial population; day symptoms were recorded as between mild and moderate. The trial population was enrolled with a percent predicted FEV₁ of approximately 64.

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Table 45. Trial 0620: Baseline disease characteristics (efficacy analysis population)

		M3 360 µg bid (n=123)¹	M0-ESP 400 µg bid (n=121)¹	M3 180 µg qd (n=113)¹	M0-ESP 200 µg qd (n=105)¹	Combined Placebo (n=110)¹
Night asthma symptom score	Mean	0.96	0.90	0.93	0.98	1.00
	SD	0.55	0.57	0.51	0.54	0.57
	Range	0 to 2.25	0 to 2.14	0 to 2.00	0 to 2.00	0 to 3.00
Day asthma symptom score	Mean	1.74	1.73	1.71	1.73	1.75
	SD	0.38	0.39	0.36	0.34	0.36
	Range	0.57 to 2.50	0.33 to 2.50	0.57 to 2.43	0.57 to 2.67	1.00 to 2.67
% of days rescue medication was used *	Mean	87.99	89.45	88.25	84.94	87.15
	SD	19.13	15.28	15.49	18.19	17.98
	Range	0 to 100.00	33.33 to 100.00	25.00 to 100.00	0 to 100.00	0 to 100.00
% of nights subject was awakened due to asthma symptoms**	Mean	25.69	26.44	24.68	27.56	25.66
	SD	30.55	28.95	27.38	28.67	27.35
	Range	0 to 100.00	0 to 100.00	0 to 100.00	0 to 100.00	0 to 100.00

¹ Numbers of subjects with observations may not equal the numbers of subjects in the efficacy analysis treatment arm

*Number of days of albuterol use divided by the number of days with non-missing albuterol data.

**Number of days of nighttime awakening divided by the number of days with non-missing nighttime awakening data.

Source: Applicant's table 13, clinical trial report

Review of the listings of concomitant medication use before treatment, based on the safety population, showed the following:

- 1 subject (M0-ESP 400] was taking oral corticosteroid (methylprednisolone)
- only 1 subject (M3 180) was not on a “selective” β agonist
- <10% of any treatment arm were on leukotriene receptor antagonists
- 10 subjects in the M0/200 arm were on allergen injections, vs. 2, 4, 5, 4, in the M0/400, M3/180, M3/360, and placebo arms, respectively.

There were no notable imbalances in the treatment arms with regards to important therapies for asthma.

10.1.13.4 Protocol violations

Protocol violations are shown in Table 46. The numbers of subjects with various violations was reasonably balanced across treatment groups, making it unlikely that they would have a notable impact on the results of the trial.

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Table 46. Trial 0620: Protocol violations [n, % of dosing arm]

	M3 360 µg bid (n=130)	M0-ESP 400 µg bid (n=130)	M3 180 µg qd (n=123)	M0-ESP 200 µg qd (n=114)	Combined Placebo (n=124)
Subjects with at least 1 protocol deviation	65 (50.0)	63 (48.5)	78 (63.4)	58 (50.9)	69 (55.6)
% predicted FEV ₁ at Visit 1 was not 60% to 90%	3 (2.3)	0	1 (0.8)	2 (1.8)	2 (1.6)
% predicted FEV ₁ at Visit 2 was not <5% lower than at Visit 1	8 (6.2)	8 (6.2)	11 (8.9)	5 (4.4)	9 (7.3)
% predicted FEV ₁ at Visit 2 was not 55% to 85%	8 (6.2)	5 (3.8)	6 (4.9)	4 (3.5)	7 (5.6)
Reversibility was not ≥12% at Visit 1	12 (9.2)	3 (2.3)	8 (6.5)	7 (6.1)	3 (2.4)
Met pre-randomization discontinuation criteria for FEV ₁ but was randomized	10 (7.7)	7 (5.4)	4 (3.3)	7 (6.1)	9 (7.3)
Did not have at least 12 puffs of albuterol for 5 days within 7 days of randomization	17 (13.1)	16 (12.3)	16 (13.0)	16 (14.0)	19 (15.3)
Did not have day and night asthma score at least 10 points for 5 days within 7 days of randomization	12 (9.2)	13 (10.0)	10 (8.1)	14 (12.3)	13 (10.5)
Met pre-randomization discontinuation criteria for diary, but was randomized	4 (3.1)	3 (2.3)	3 (2.4)	4 (3.5)	6 (4.8)
Met pre-randomization discontinuation criteria for diary, but was randomized	4 (3.1)	3 (2.3)	3 (2.4)	4 (3.5)	6 (4.8)
Did not meet ICS inclusion criteria					
Not constant dose	2 (1.5)	1 (0.8)	1 (0.8)	0	0
Out of dose range	0	3 (2.3)	0	1 (0.9)	0
Therapy switch	0	1 (0.8)	1 (0.8)	0	1
Unknown start date	0	0	0	0	1 (0.8)
<90 days	20 (15.4)	27 (20.8)	29 (23.6)	21 (18.4)	20 (16.1)
Took disallowed medication	15 (11.5)	20 (15.4)	20 (16.3)	16 (14.0)	25 (20.2)
<80% compliant with single-blind placebo during the run-in period	4 (3.1)	1 (0.8)	4 (3.3)	4 (3.5)	5 (4.0)
Did not record diary scores for 5 consecutive days before Visit 2	9 (6.9)	4 (3.1)	5 (4.1)	12 (10.5)	6 (4.8)
Diagnosis of asthma was made <6 months before study entry	0	1 (0.8)	0	1 (0.9)	1 (0.8)

Sponsor's table 11 from trial report.

10.1.13.5 Discontinuations

The discontinuation rate in the trial was high (Table 47), the main reason being worsened asthma symptoms or signs as measured by the development of discharge criteria. The overall discontinuation rate was roughly inversely proportional to the dose intensity, being similar in both high- or low-dose active groups. Discontinuations due to adverse events are discussed in section 10.1.16.2. They were primarily related to asthma.

Electronic diary data on albuterol use, night awakenings, and rescue medication use was not usable for the 41 subjects in Indonesia. As a result, these subjects were discontinued from the trial (39 of these subjects were in the ITT population). Nearly equal numbers of these

subjects had been assigned to each treatment arm, so it is unlikely that their discontinuation had a biasing effect on the results of the trial.

Table 47. Trial 0620: Discontinuations among randomized subjects [n, % of dosing arm]

	M3 360 µg BID (n=130)	M0-ESP 400 µg BID (n=130)	M3 180 µg QD (n=123)	M0-ESP 200 µg QD (n=114)	Combined Placebo (n=124)
Total discontinued	29 (22.3)	25 (19.2)	39 (31.7)	32 (28.1)	60 (48.4)
Eligibility criteria not fulfilled	4 (3.1)	2 (1.5)	2 (1.6)	1 (0.9)	3 (2.4)
Adverse event	2 (1.5)	1 (0.8)	8 (6.5)	5 (4.4)	10 (8.1)
Developed study-specific discontinuation criteria	10 (7.7)	12 (9.2)	15 (12.2)	13 (11.4)	36 (29.0)
Subject not willing to continue the study	1 (0.8)	2 (1.5)	6 (4.9)	2 (1.8)	5 (4.0)
Subject lost to follow-up	2 (1.5)	1 (0.8)	0	0	0
Other	10 (7.7)	7 (5.4)	8 (6.5)	11 (9.6)	6 (4.8)

10.1.13.6 Performance of devices

Eleven devices were returned, and none of the complaints about them were confirmed. The batch average-delivered dose for the clinical returns compared to the release ranged from 92% to 103% for the returned inhalers. The corresponding range at release was 98% to 104%. These results suggest that the devices generally functioned adequately.

10.1.14 Efficacy results

10.1.14.1 Primary endpoint

Twenty-two subjects were excluded from the primary efficacy analysis population because no efficacy data were available after baseline (Table 48). Almost all of these subjects were from US sites. The subjects came from a variety of sites in the trial. Although there was a preponderance of subjects excluded from the placebo arm, the numbers of excluded subjects is small. Further, review of demographic data for these excluded subjects does not indicate that these subjects come from a particular group or consequently that a bias would be introduced into the analysis by the lack of data from these subjects.

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Table 48. Trial 0620: Modified intent-to-treat (mITT) population

Treatment	All randomized	Excluded	Modified ITT population
M3 360 µg bid	130	2	128
M0-ESP 400 µg bid	130	2 (1 Asia)	128
M3 180 µg qd	123	4	119
M0-ESP 200 µg qd	114	4 (1 Asia)	110
Placebo (pooled)	124	10 (1 Asia)	114

Differences from baseline to treatment period mean for FEV₁ in the placebo groups were small and showed no particular pattern, so the results were pooled for the primary endpoint analysis. The values were:

- M3/360 µg BID placebo: 0.18 liters/min
- M0-ESP/400 µg BID placebo: 0.11 liters/min
- M3/180 µg QD placebo: -0.02 liters/min
- M0-ESP 200 µg QD placebo: 0.19 liters/min

Table 49 shows differences from baseline to the mean of the treatment period in each treatment arm. The smallest mean change in an active treatment group was seen in the low-dose group using the M3 device (the difference from baseline is similar to that seen in two of the placebo subgroups). There is a clear trend for less improvement in FEV₁ with use of the M3 device for both the low- or high-dose treatment arms.

Table 49. Trial 0620: FEV₁ means, ITT population, LOCF imputation

Treatment	n	FEV ₁ mean (SE)			ANCOVA		
		Baseline	Treatment period	Change	LS mean Change	SE	95% CI
M3 360 µg bid	128	2.14 (0.05)	2.44 (0.06)	0.30 (0.02)	0.28	0.029	0.22 to 0.34
M0-ESP 400 µg bid	128	2.15 (0.05)	2.52 (0.06)	0.36 (0.03)	0.34	0.029	0.29 to 0.40
M3 180 µg qd	119	2.09 (0.05)	2.29 (0.06)	0.19 (0.02)	0.18	0.030	0.12 to 0.24
M0-ESP 200 µg qd	110	2.19 (0.06)	2.46 (0.07)	0.27 (0.03)	0.25	0.031	0.19 to 0.31
Placebo (pooled)	114	2.14 (0.05)	2.26 (0.06)	0.12 (0.03)	0.10	0.031	0.04 to 0.16

Applicant table 16, final report.

Table 50 shows the treatment effect on FEV₁ and the primary statistical analysis. The low-dose M3 device group did not reach the nominal criterion for statistic significance (p=0.05); the other treatment arms bettered this mark.

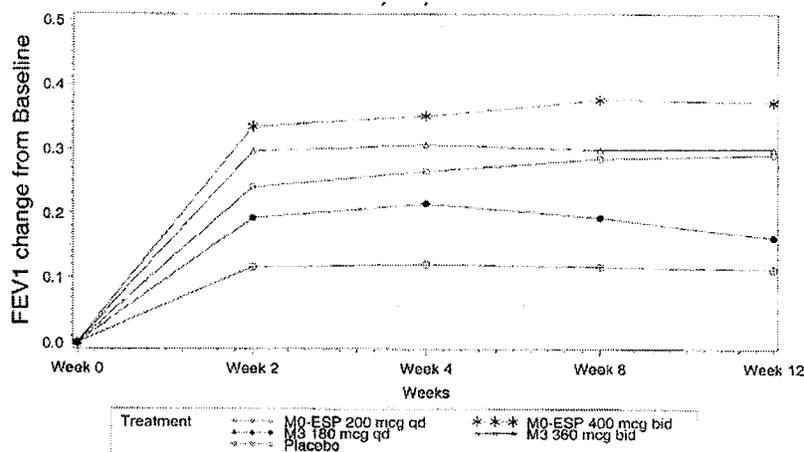
Table 50. Trial 0620: Primary endpoint: FEV₁ change from baseline to treatment period mean*

Comparison	LS mean difference (liters)	SE	95% CI	p-value
M3 360 µg bid – placebo	0.18	0.041	0.10 to 0.26	<0.001
M0-ESP 400 µg bid – placebo	0.24	0.041	0.16 to 0.32	<0.001
M3 180 µg qd – placebo	0.07	0.042	-0.01 to 0.16	0.078
M0-ESP 200 µg qd – placebo	0.15	0.043	0.06 to 0.23	<0.001
M3 360 µg bid –M0-ESP 400 µg bid	-0.06	0.04	-0.14 to 0.02	0.117
M3 180 µg qd –M0-ESP 200 µg qd	-0.07	0.042	-0.16 to 0.01	0.089

* ANCOVA, mITT population, LOCF
 Source: Applicant's table 17, clinical trial report

Figure 2 shows mean FEV₁ for each treatment arm by visit. End of treatment period values for FEV₁ paralleled the mean treatment period differences from baseline. The maximal or near-maximal treatment effect occurred at about 2 weeks for each group, and remained fairly constant to the end of the treatment period. There is a suggestion of a tapering of effect in the low-dose M3 treatment arm.

Figure 2. Trial 0620: Mean FEV₁ change from baseline by treatment visit (mITT data, last observation carried forward)



Source: Applicant's Figure 11.2.1.3.1, clinical trial report

As a comparison to trial 0726 (reviewed subsequently), the differences from baseline in terms of percent predicted are shown Table 51. In the high-dose groups, the differences from placebo in change from baseline were approximately 5-7 points of percent predicted values, slightly more than in trial 0726. This is probably due to the relatively more severely affected population in trial 0620.

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Table 51. Trial 0620: Changes from baseline in % predicted FEV₁

Treatment	n	Baseline FEV ₁ % predicted (SE)	Mean treatment period FEV ₁ % predicted (SE)	Change in FEV ₁ % predicted	Difference from placebo*
M3 360 mcg bid	128	63.7 (0.8)	72.5 (1.0)	8.8	5.3
M0 400 mcg bid	128	64.7 (0.8)	75.3 (0.9)	10.6	7.1
M3 180 mcg qd	119	64.1 (0.8)	69.9 (0.9)	5.8	2.3
M0 200 mcg qd	110	64.5 (0.8)	72.7 (1.1)	8.1	4.6
Placebo	114	65.0 (0.8)	68.5 (1.2)	3.5	-

Source: Applicant's table 11.2.1.2.1, clinical trial report

*Calculated from changes shown

10.1.14.1.1 Sensitivity analyses

FDA conducted the following sensitivity analyses and compared them to AstraZeneca's analysis of observed data only (Table 52). Using the mITT data set, missing data were substituted for any visit, whether or not it was followed by a visit value, with either the worst value obtained in any subject at that particular time point, or the median value of the entire population with values at that time point. Values between visits (unassigned values) were omitted.

In almost all the analyses, each active treatment was different from placebo at a p-value less than 0.05. The exception was comparison of the low-dose M3 treatment to placebo using the imputation to the observed data set with median values.

Table 52. Trial 0620: Sensitivity analysis of primary endpoint: Applicant's and worst case, and median imputation using observed values data set (see text)

Treatment	N	FEV ₁					
		AstraZeneca		Worst		Median	
		LS Mean Change ¹	P-value vs. Placebo	LS Mean Change ¹	P-value vs. Placebo	LS Mean Change ¹	P-value Vs Placebo
M3 360 mcg BID	128	0.28	<0.0001	0.08	<0.0001	0.29	0.0022
M0-ESP 400 mcg BID	128	0.35	<0.0001	0.17	<0.0001	0.35	<0.0001
M3 180 mcg QD	119	0.18	0.0663	-0.02	0.0005	0.21	0.2937
M0-ESP 200 mcg QD	110	0.25	0.0007	0.03	<0.0001	0.28	0.0074
Placebo	114	0.10	-	-0.25	-	0.17	-

¹ Compared to baseline

The same pattern of effects was seen, showing that the efficacy findings were not critically dependent on the exact method used in their calculation.

The applicant's per-protocol analysis was not reviewed, as it excluded 174 subjects, nearly one third of the trial population.

10.1.14.1.2 Subgroup analyses of the primary endpoint

10.1.14.1.2.1 Effect of change in dose content

The numbers of subjects exposed to lower- and higher-dose content devices is shown in Table 53 (no subject received both). A little less than half of the subjects received a device whose dose content was less than that of the proposed product. Twenty sites that used M3 devices used devices with both dose contents, and 64 used only the low- or high-dose content device (6 sites did not randomize a subject to an M3 device).

Table 53. Trial 0620. Randomized subjects exposed to higher and lower dose content devices

Treatment arm	Dose content	n
M3 180 QD (US)		54
M3 180 QD (US)		35
M3 180 QD (Asia)		34
M3 360 QD (US)		55
M3 360 QD (US)		40
M3 360 QD (Asia)		35
Placebo	Matched to	42
Placebo	Matched to	76

*Source: Applicant's Pulm_02 data file

b(4)

Table 54 shows AstraZeneca's analysis of change in FEV₁ (ANCOVA with baseline value as the covariate) by dose-content for the US alone with respect to the dose content change. There was a similar increase in the FEV₁ in each treatment arm, including the placebo arm. This may have been because of a time effect in the trial. There was no notable effect of the change in dose content on the difference from placebo.

Table 54. Trial 0621: Primary endpoint (FEV₁ change from baseline) before and after increase in dose content of M3 device (US sites only)—modified ITT population

Treatment	N*	FEV ₁ , mean (SE)		
		Baseline	Treatment period	Change
M3 360 mg bid	54	2.26(0.07)	2.56 (0.09)	0.30 (0.03)
M3 360 mg bid	39	2.25 (0.09)	2.63 (0.11)	0.38 (0.05)
M3 180 mg bid	51	2.18 (0.07)	2.32 (0.09)	0.14 (0.04)
M3 180 mg bid	34	2.26 (0.08)	2.54 (0.09)	0.28 (0.04)
Placebo	42	2.30 (0.08)	2.40 (0.10)	0.10 (0.05)
Placebo	39	2.12 (0.07)	2.31 (0.10)	0.19 (0.07)

*These numbers may be smaller than the number exposed (Table 53) due to exclusions of some subjects due to lack of efficacy data.

Source: Applicant's table 47, clinical trial report

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Pharmacokinetic substudy of dose content change

AstraZeneca analyzed pharmacokinetics of budesonide in a small subset of subjects in each of the treatment arms (7-13 subjects who took either the low-dose-content or high-dose-content device). In the 180 µg QD treatment arm, the area under the curve of exposure was higher in the high-dose-content group than in the low-dose-content group; however, the opposite finding (i.e., lower exposure in the high-dose content group) was seen in the 360 µg BID treatment arm. Because these results are based on small numbers of subjects, they cannot be interpreted with confidence.

10.1.14.1.2.2 Treatment effect by region (Asia or U.S.)

Active treatment was associated with a greater change than placebo in FEV₁ in both the U.S. and Asia, but there was no notable dose relation of the treatment effect in Asia (Table 55).

Table 55. Trial 0620: Regional difference in FEV₁ (US compared to Asia). mITT population, unadjusted means

Region	Region	<i>n</i> in active group (s)	Treatment group difference	Region	<i>n</i> in active group (s)	Treatment group difference
M3 360 µg bid – placebo*	US	93	0.20	Asia	35	0.14
M0-ESP 400 µg bid – placebo*	US	94	0.27	Asia	34	0.16
M3 180 µg qd – placebo*	US	85	0.06	Asia	34	0.12
M0-ESP 200 µg qd – placebo*	US	78	0.16	Asia	32	0.12
M3 360 µg bid – M0-ESP 400 µg bid	US	93, 94	-0.07	Asia	35, 34	-0.02
M3 180 µg qd – M0-ESP 200 µg qd	US	85, 81	-0.1	Asia	34, 32	0

*pooled placebo: U.S. *n*=81, Asia *n*=33

Sources of data: Applicant's table 18 and 11.2.1.1.3

10.1.14.1.2.3 Treatment effect by other subject groups

The overall pattern of effect by dose and by device type was not clearly seen in either the male or female groups considered separately (Table 56); however, in both groups both of the higher dose groups showed a separation from placebo. Not surprisingly, the subgroups of Caucasian and "Oriental" paralleled the regional (U.S. and Asian) analysis shown above. Although there appeared to be no treatment effect for either treatment in the subgroup of "Blacks," conclusions about a lack of effect are problematic due to the small sample size.

Table 56. Trial 0620: FEV₁ change from baseline (liters) by subgroups, LOCF, mean ± sd

Subgroup	M3 360 µg bid (n=128)	M0-ESP 400 µg bid (n=128)	M3 180 µg qd (n=119)	M0-ESP 200 µg qd (n=110)	Combined Placebo (n=114)
Sex					
Female	0.27 ±0.24	0.27 ±0.23	0.17 ±0.22	0.27 ±0.28	0.12 ±0.34
<i>n</i>	75	84	83	71	75
Male	0.34 ±0.30	0.54 ±0.49	0.25 ±0.35	0.28 ±0.46	0.13 ±0.38
<i>n</i>	53	44	36	39	39
Race					
Caucasian	0.37 ±0.29	0.42 ±0.41	0.22 ±0.29	0.28 ±0.37	0.12 ±0.37
<i>n</i>	83	80	76	69	76
Oriental	0.20 ±0.17	0.23 ±0.21	0.18 ±0.23	0.20 ±0.20	0.07 ±0.27
<i>n</i>	37	37	36	34	33
Black	0.05 ±0.14	0.44 ±0.28	0.11 ±0.10	0.27 ±0.25	0.43 ±0.53
<i>n</i>	8	11	5	6	5
Other	-	-	-0.20 ±0.08	1.90	-
<i>n</i>	-	-	2	1	-

Data based on applicant analyses as presented in Applicant's tables 11.2.1.1.4-5, clinical trial report. Racial terms as used by applicant.

10.1.14.1.2.4 Treatment effect by baseline FEV₁

FDA analyzed the primary endpoint with respect to baseline FEV₁ (Table 57). In general, there was a trend toward more effect with increasing FEV₁ at baseline, but there was an increase compared to placebo for all quartiles for all treatments.

Table 57. Trial 0620: FDA analysis of primary endpoint (FEV₁ difference from baseline)

	Q1	n	Q2	n	Q3	n	Q4	n
M3 360 mcg QD	0.22	30	0.27	31	0.3	37	0.35	30
M0-ESP 400 mcg BID	0.24	32	0.33	32	0.33	31	0.49	33
M3 180 mcg QD	0.16	27	0.16	36	0.17	27	0.21	29
M0-ESP 200 mcg QD	0.26	31	0.27	23	0.15	25	0.32	31
Placebo	0.09	27	0.05	30	0.12	28	0.14	29

* cutoff at 1.71, 2.04, 2.47, and uppermost was 4.3

10.1.14.1.2.5 Effect of the number of actuations per device

Randomization to M3-device dose level also randomized to devices with smaller and larger numbers of actuations per device, that is, subjects randomized to 360 µg BID received devices with 120 actuations, those randomized to 180 µg QD received devices with 60 actuations. Because of this, a difference in efficacy with respect to the number of actuations in the device is confounded by dose level and would be uninformative.

10.1.14.1.2.6 Summary of subgroup analyses

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 in "Blacks" and the trials enrolled very few subjects over the age of 65.

10.1.14.2 Secondary endpoints

10.1.14.2.1 Treatment-period FVC

FVC measured during the treatment period trended in the same way as the FEV₁ data, with subjects on the M0-ESP device showing more improvement compared to placebo than those on the M3 device. The low-dose devices were not different from placebo.

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Table 58. Trial 0620: Secondary endpoint: FVC

Comparison	LS mean difference	SE	95% CI	p-value
M3 360 µg bid – placebo	0.11	0.056	0.00 to 0.22	0.051
M0-ESP 400 µg bid – placebo	0.15	0.056	0.04 to 0.26	0.007
M3 180 µg qd– placebo	-0.04	0.057	-0.15 to 0.07	0.519
M0-ESP 200 µg qd – placebo	0.07	0.058	-0.05 to 0.18	0.245
M3 360 µg bid –M0-ESP 400 µg bid	-0.04	0.054	-0.15 to 0.06	0.436
M3 180 µg qd –M0-ESP 200 µg qd	-0.10	0.057	-0.22 to 0.01	0.070

10.1.14.2.2 *Treatment-period FEF₂₅₋₇₅*

Results for this measure trended in the same direction as the primary endpoint.

Table 59. Trial 0620: Secondary endpoint: FEF₂₅₋₇₅

Comparison	LS mean difference	SE	95% CI	p-value
M3 360 mcg bid - Placebo	0.24	0.07	0.1 to 0.38	<0.001
M0-ESP 400 mcg bid - Placebo	0.35	0.07	0.21 to 0.48	<0.001
M3 180 mcg qd - Placebo	0.12	0.071	-0.02 to 0.26	0.088
M0-ESP 200 mcg qd - Placebo	0.24	0.072	0.1 to 0.39	<0.001
M3 360 mcg bid - M0-ESP 400 mcg bid	-0.11	0.068	-0.24 to 0.03	0.113
M3 180 mcg qd - M0-ESP 200 mcg qd	-0.12	0.072	-0.26 to 0.02	0.086

10.1.14.2.3 *Diary-derived morning peak expiratory flow*

The treatment effect was dose-dependent, with statistically significant differences from placebo for every active treatment arm. Baseline values were 335-352 l/min at baseline and the placebo group worsened slightly during the treatment period (drop in PEF of 9.24 l/min). The low-dose groups showed a very slight improvement compared to placebo; the high-dose groups showed a bigger improvement that was bigger in the M0-ESP device group.

Table 60. Trial 0620: Secondary endpoint: Morning PEF treatment group comparisons

Comparison	LS mean difference	SE	95% CI	p-value
M3 360 µg bid – placebo	27.37	4.589	18.35 to 36.38	<0.001
M0-ESP 400 µg bid – placebo	34.41	4.609	25.36 to 43.46	<0.001
M3 180 µg qd– placebo	17.23	4.698	8.00 to 26.46	<0.001
M0-ESP 200 µg qd – placebo	15.53	4.789	6.12 to 24.93	0.001
M3 360 µg bid –M0-ESP 400 µg bid	-7.04	4.513	-15.91 to 1.82	0.119
M3 180 µg qd –M0-ESP 200 µg qd	1.7	4.806	-7.74 to 11.14	0.724

10.1.14.2.4 *Diary-derived evening peak expiratory flow*

These results were very similar to those for the morning PEF (Table 61).

Table 61. Trial 0620: Secondary endpoint: Evening PEF treatment group comparisons

Comparison	LS mean difference	SE	95% CI	p-value
M3 360 µg bid – placebo	19.18	4.545	10.25 to 28.10	<0.001
M0-ESP 400 µg bid – placebo	27.71	4.574	18.73 to 36.70	<0.001
M3 180 µg qd – placebo	12.47	4.650	3.34 to 21.61	0.008
M0-ESP 200 µg qd – placebo	11.54	4.750	2.21 to 20.87	0.015
M3 360 µg bid –M0-ESP 400 µg bid	-8.54	4.448	-17.27 to 0.20	0.055
M3 180 µg qd –M0-ESP 200 µg qd	0.94	4.732	-8.36 to 10.23	0.843

10.1.14.2.5 *Diary derived asthma symptom score*

- Morning (night symptoms): Differences from placebo in the difference in treatment period from baseline ranged from -0.23 to -0.44. Although all active treatment groups differed from placebo at p=0.004 or less, the clinical meaning of these differences is not clear. The trends were consistent with the FEV₁ results in that the high-dose M0-ESP group was better than the high-dose M3 group, low-dose M0-ESP was better than the low-dose M3.
- Evening (daytime symptoms): Differences from placebo in the difference in treatment period from baseline ranged from -0.15 to -0.33. Although all active treatment groups differed from placebo at p=0.032 or less, the clinical meaning of these differences is not clear. The high-dose M0-ESP group did better than the high-dose M3 group, but the differences were reversed in the low-dose groups, M3 doing better than the M0-ESP group.

10.1.14.2.6 *Change in albuterol use*

Table 62 shows summary statistics on daily use of albuterol (puffs). Trends in the data parallel those for the primary endpoint. Effects were driven by daytime use, where baseline use across treatment arms was about 3 puffs; baseline night use was about 0.6 puffs.

Table 62. Trial 0620: Secondary endpoint: Daily albuterol use (puffs)

Comparison	LS mean difference	SE	95% CI	p-value
M3 360 µg bid – placebo	-1.35	0.244	-1.83 to -0.87	<0.001
M0-ESP 400 µg bid – placebo	-1.74	0.245	-2.22 to -1.25	<0.001
M3 180 µg qd – placebo	-0.85	0.249	-1.34 to -0.36	<0.001
M0-ESP 200 µg qd – placebo	-0.96	0.255	-1.46 to -0.46	<0.001
M3 360 µg bid –M0-ESP 400 µg bid	0.38	0.240	-0.09 to 0.86	0.109
M3 180 µg qd –M0-ESP 200 µg qd	0.11	0.255	-0.39 to 0.61	0.674

AstraZeneca also summarized the difference in the treatment period compared to baseline in the number of days that rescue medication was used. These data trended in the same direction as the number of puffs.

10.1.14.2.7 *Meeting discontinuation criteria*

Table 63 shows summaries of discontinuation criteria met during the treatment period. For this analysis subjects are counted more than once when more than one criterion was met at the first time a discontinuation criterion was met. These criteria are clustered into related

categories: nighttime awakenings (the criterion for 3 nighttime awakenings was not protocol-defined), expiratory physiology (FEV₁ and peak expiratory flow), and medication use.

Active treatment was associated with lower percentages of almost all discontinuation criteria. Discontinuations occurred in inverse proportion to dose, and there was little difference between the rates for subjects treated with different devices at each dose level.

Table 63. Trial 0620: Discontinuation criteria met (ITT population) after randomization*

Criterion	M3 360 µg bid (n=130)	M0-ESP 400 µg bid (n=129)	M3 180 µg qd (n=121)	M0-ESP 200 µg qd (n=113)	Placebo (n=119)
Subjects with at least 1 study-specific predefined asthma-related discontinuation criterion	19 (14.6)	20 (15.5)	30 (24.8)	33 (29.2)	57 (47.9)
3 nighttime awakenings requiring β ₂ -agonist within 5 days**	10 (7.7)	12 (9.3)	15 (12.4)	18 (15.9)	36 (30.3)
4 nighttime awakenings requiring β ₂ -agonist within 6 days***	7 (5.4)	3 (2.3)	9 (7.4)	10 (8.8)	19 (16.0)
Decrease in morning PEF >25% from baseline on 3 days within 5 days	2 (1.5)	4 (3.1)	2 (1.7)	5 (4.4)	9 (7.6)
Decrease in FEV ₁ ≥25% from Visit 1	5 (3.8)	2 (1.6)	11 (9.1)	7 (6.2)	21 (17.6)
Decrease in FEV ₁ from V1 >40% of predicted	1 (0.8)	0	2 (1.7)	0	3 (2.5)
≥12 actuations of albuterol per 2 days within 3 days	1 (0.8)	1 (0.8)	0	2 (1.8)	7 (5.9)
Used disallowed concomitant medication	4 (3.1)	4 (3.1)	8 (6.6)	5 (4.4)	8 (6.7)

Source: Applicant table 43 from clinical trial report.

*For this table, a subject may be counted more than once, if more than one criterion was met at the first time a subject qualified for discontinuation.

** In original protocol.

*** In protocol as amended (protocol amendment 4)

In a survival analysis of time to first event, AstraZeneca found that each active treatment arm separated from placebo with a p-value ≤0.003 (based on the log-rank test, Wilcoxon test, or the Fisher exact test). Twice-daily dosing with either device was superior to once-daily dosing with either device.

10.1.14.2.8 Summary of effect of dose content change on secondary endpoints

Table 64, constructed by FDA from data provided by the applicant, shows that changes in the secondary endpoints were to be small with the increase in dose content.

Table 64. Trial 0620: Secondary endpoints* (changes from baseline) as a function of dose content

M3 Treatment arm	Secondary endpoint	168 mg/g - placebo	178 mg/g - placebo
180 mcg daily	FEV ₁	0.04	0.09
	FVC	-0.02	-0.09
	Night symptoms	-0.23	-0.19
	Day symptoms	-0.22	-0.18
	Morning PEF	12.17	24.59
	Evening PEF	2.82	22.14
	Albuterol use	-0.83	-0.69
360 mcg BID	FEV ₁	0.2	0.19
	FVC	0.1	0.13
	Night symptoms	-0.18	-0.25
	Day symptoms	-0.19	-0.42
	Morning PEF	17.37	42.69
	Evening PEF	9.02	31.94
	Albuterol use	-1.48	-1.04

Source of data: Applicant's table 11.2.1.1.7 and 11.2.2.1.7

*Discontinuations: For the M3 180 µg QD treatment arm, 14/53 (26.4%) of subjects in the group met the asthma-related discontinuation criteria compared with 4/34 (11.8%) of subjects in the group. For the M3 360 µg BID treatment arm, 7/55 (12.7%) of the subjects in the group met the asthma-related discontinuation criteria compared with 6/40 (15.0 %) of subjects in the group.

b(4)

10.1.15 Pharmacokinetics

The pharmacokinetic substudy was to enroll 24 subjects in each treatment arm; however, 77 subjects were studied (AstraZeneca states that recruiting was more difficult due to the demands of the 12-hour assessment). The sex, and age distribution of this subpopulation was not notably different from that of the overall population; there were minor differences from the overall population in the racial balance (Caucasians 59/77 (77%); "Blacks" 10/77 (13%); "Oriental" 8/77 (10%); for comparison see Table 44).

Figure 3 shows the mean curve of systemic concentration as a function of time, and Figure 4 shows individual plasma concentration curves. These results are inconclusive, due to the presence of outlying data and small numbers of subjects. However, they do not point to an increase in systemic exposure with the M3, which might in turn point to a safety concern.

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Figure 3. Trial 0620 pharmacokinetic substudy mean plasma concentration with time

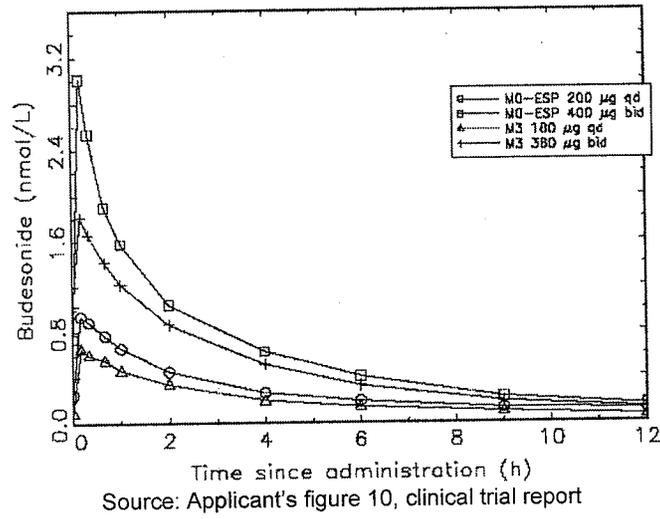


Figure 4. Trial 0620 individual plasma concentration curves (linear scale)

b(4)

10.1.16 Safety

10.1.16.1 Exposure

Duration of exposure to trial drug was dose-related (Table 65).

Table 65. Trial 0620: Exposure in safety population

		M3 360 µg bid (n=130)	M0-ESP 400 µg bid (n=130)	M3 180 µg qd (n=123)	M0-ESP 200 µg qd (n=114)	Placebo (n=124)
Duration of exposure to study treatment	≤2 weeks	5 (3.8)	2 (1.5)	7 (5.7)	10 (8.8)	9 (7.3)
	>2 weeks to ≤4 weeks	7 (5.4)	5 (3.8)	13 (10.6)	9 (7.9)	27 (21.8)
	>4 weeks to ≤8 weeks	7 (5.4)	8 (6.2)	13 (10.6)	7 (6.1)	11 (8.9)
	>8 weeks to <12 weeks	24 (18.5)	21 (16.2)	19 (15.4)	21 (18.4)	19 (15.3)
	≥12 weeks	87 (66.9)	94 (72.3)	71 (57.7)	67 (58.8)	58 (46.8)
Days of days treated	Mean (SD)	76.02 (22.96)	78.89 (19.80)	68.94 (27.77)	69.82 (27.88)	60.03 (32.55)
	Range (min to max)	8 to 104	6 to 123	1 to 98	2 to 93	1 to 101

*Source: Applicant table 61, clinical trial report

10.1.16.2 Deaths, serious adverse events, and discontinuations due to adverse events

No deaths occurred. Two subjects, both treated with the M0-ESP device, experienced serious adverse events during treatment:

- M0-ESP 400 µg BID: 41 year-old man with myocardial infarction at day 1; anal fistula and perirectal abscess at day 25. Both resolved.
- Mo-ESP 200 µg BID: 21 year-old woman with acute bronchitis and asthma exacerbation at day 12, resolved. Subject discontinued participation in trial.

An additional subject, a 42 year-old woman randomized to M3 180 µg QD, experienced an incarcerated ventral hernia a day after discontinuing treatment due to worsened asthma on day 79 of treatment.

Ten subjects experienced serious adverse events prior to randomization: 1) cholelithiasis in a 44 year-old woman; 2) acute bronchitis and asthma in a 21 year-old woman; 3) ventricular ectopy and asthma exacerbation in a 40 year-old man; 4) uterine fibroid in a 46 year-old woman; 5) choledocholithiasis with obstruction in a 54 year-old woman; 6) acute cholecystitis in a 44 year-old woman; 7) acute exacerbation of asthma in a 72 year-old woman; 8) exacerbation of asthma in a 23 year-old woman; 9) worsening asthma and a cough in a 41 year-old man; 10) acute exacerbation of bronchial asthma in a 40 year-old woman.

Most of the discontinuations due to adverse events were due to asthma, and occurred in inverse relation to dose (placebo and low- or high-dose groups).

Table 66. Trial 0620: Subjects with at least 1 adverse event leading to discontinuation

	M3 360 µg bid (n=130)	M0-ESP 400 µg bid (n=130)	M3 180 µg qd (n=123)	M0-ESP 200 µg qd (n=114)	Placebo (n=124)
Total	2 (1.5)	1 (0.8)	8 (6.5)	5 (4.4)	10 (8.1)
Respiratory, thoracic, and mediastinal disorders	2 (1.5)	1 (0.8)	8 (6.5)	5 (4.4)	10 (8.1)
Asthma	1 (0.8)	1 (0.8)	8 (6.5)	5 (4.4)	10 (8.1)
Nasal congestion	1 (0.8)	0	0	0	0
Infections and infestations	0	1 (0.8)	1 (0.8)	1 (0.9)	0
Upper respiratory tract infection	0	1 (0.8)	1 (0.8)	0	0
Bronchitis acute	0	0	0	1 (0.9)	0

Source: Applicant's table 66 from clinical trial report

Six subjects (4 subjects in the M3 180 µg qd group and 2 subjects in the placebo group) discontinued due to the adverse event asthma that was considered by the investigator to be causally related to study drug.

10.1.16.3 Adverse events

Table 67 shows a summary of the numbers and percents of subjects with adverse events that occurred in at least 3% of any treatment arm. "Asthma" as an adverse event occurred in inverse proportion to dose level, regardless of device type.

Table 67. Subjects with adverse events occurring at ≥3% in any treatment arm

	M3 360 µg bid (n=130)	M0-ESP 400 µg bid (n=130)	M3 180 µg qd (n=123)	M0-ESP 200 µg qd (n=114)	Placebo (n=124)
Total	55 (42.3)	71 (54.6)	58 (47.2)	60 (52.6)	63 (50.8)
Headache	11 (8.5)	18 (13.8)	9 (7.3)	7 (6.1)	11 (8.9)
Nasopharyngitis	11 (8.5)	13 (10.0)	7 (5.7)	13 (11.4)	8 (6.5)
Asthma	3 (2.3)	1 (0.8)	12 (9.8)	9 (7.9)	17 (13.7)
Upper respiratory tract infection	9 (6.9)	6 (4.6)	10 (8.1)	8 (7.0)	7 (5.6)
Pharyngolaryngeal pain	4 (3.1)	5 (3.8)	4 (3.3)	5 (4.4)	4 (3.2)
Sinusitis	3 (2.3)	3 (2.3)	1 (0.8)	5 (4.4)	2 (1.6)
Cough	1 (0.8)	1 (0.8)	3 (2.4)	3 (2.6)	4 (3.2)
Back pain	2 (1.5)	2 (1.5)	0	2 (1.8)	4 (3.2)
Rhinitis	0	3 (2.3)	1 (0.8)	5 (4.4)	1 (0.8)
Gastroenteritis viral	1 (0.8)	4 (3.1)	1 (0.8)	1 (0.9)	1 (0.8)
Influenza	0	1 (0.8)	5 (4.1)	1 (0.9)	1 (0.8)
Myalgia	1 (0.8)	4 (3.1)	2 (1.6)	0	0

Oral candidiasis occurred in one subject each in the M0-ESP 200 µg QD and placebo groups and two subjects in the M3 360 µg BID group. Hoarseness occurred in two subjects in the M3 360 µg BID group.

Review of listings showed that the incidence of adverse events was not changed by the increase in dose content during the trial.

Listings of adverse events grouped by site (US and Asia), sex, and race did not reveal any differences in the incidences of adverse events that were notable. Very few subjects were older than 65 years of age. The numbers of individual events and the sizes of the subgroups made these comparisons inconclusive; however, no safety concern emerged.

Drug-related adverse events

Although drug-relatedness is sometimes difficult to assess with certainty, it is useful to examine events that the investigator thought were due to treatment (number of subjects in parentheses):

- Placebo: asthma (3), pharyngolaryngeal pain (2), and glossitis
- M3 180 µg QD: acute sinusitis (1), asthma (5), lichen planus (1 subject), seasonal rhinitis (1), and anemia (1)
- M0-ESP 200 µg QD: asthma (1) and candidiasis (1)
- M3 360 µg BID: upper respiratory tract infection (1 subject), oral candidiasis (2), pharyngolaryngeal pain (1), insomnia and nervousness (1)
- M0-ESP 400 µg BID: bronchitis and myalgia (1), pharyngolaryngeal pain (2)

Severe adverse events

There were very few severe events during treatment. The events that occurred do not show a pattern of toxicity:

- Placebo: asthma, headache, ligament sprain, sinusitis
- M3 180 µg QD: asthma, acute sinusitis, drug interaction, joint sprain, major depression, seasonal rhinitis
- M0-ESP 200 µg QD: asthma, skin laceration, viral infection
- M3 360 µg BID: nasal congestion, sciatica
- M0-ESP 400 µg BID: Acute myocardial infarction, anal fistula, perirectal abscess

The events do not show a pattern of toxicity.

10.1.16.4 Vital signs

No notable changes occurred in heart rate, blood pressure, or weight during the clinical trial.

10.1.16.5 Laboratory abnormalities

There was no trend in laboratory abnormalities reported as adverse events, which occurred infrequently. ECGs were not assessed.

AstraZeneca expressed laboratory data in terms of shifts into and out of the central laboratory reference range. Review of these data showed that shifts to low hematocrit at week 12 or the end of treatment occurred more frequently in three of the four treatment groups as compared to placebo (shifts from baseline normal to low at the end of treatment occurred in 8, 1, 4, and 6 subjects in the M3/360 BID, M0-ESP/400 BID, M3/180 QD, and M0-ESP 200 QD groups as compared to 1 in the placebo group). In addition, subjects in the treated groups had more shifts from “negative” to “≥1+” on the occult blood urine test (results for the groups previously mentioned: 6, 7, 4, and 4 as compared to 0 in the placebo group).

The clinical significance of these findings, which occurred in small numbers of subjects, is unclear. Other laboratory tests did not show notable trends. Anemia was reported as an adverse event in only one subject, in the M3/180 µg QD treatment arm.

10.1.16.6 Concomitant medications

There was no concerning pattern of increased use of particular concomitant medications among the active treatment groups.

10.1.17 Summary of trial 0620

Trial SD-004-0620 was adequately conducted to address the question of the effect of two dosing regimens using the 180 mcg/dose M3 device. 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. The chief findings of the trial were:

- The M0-ESP device produced a greater treatment effect than the M3 device at each of two dose levels on the primary endpoint
- ~~_____~~
- 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 in "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 high-dose 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.
- Pharmacokinetic results were inconclusive but did not show a concern for the safety of the M3 based on systemic exposure.
- There was no new safety concern with the use of either the M0-ESP or the M3 device.

b(4)

In summary, the trial showed that effectiveness was less with the M3 device, ~~_____~~
~~_____~~ No new safety concerns emerged.

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10.1.18 A Placebo-Controlled Comparison of The Efficacy, Safety, And Pharmacokinetics Of The Current Us Version Of Pulmicort (Budesonide) Turbuhaler® And The New Version Of Pulmicort Turbuhaler® In Asthmatic Children And Adolescents / SD-004-0726

Note: This trial was very similar to trial SD-004-0620. The review of the design is intended mainly to point out the similarities to and differences from that trial.

AstraZeneca is proposing to market a device whose budesonide content per dose is greater by about 5% than the one tested in this clinical trial. No one in this clinical trial used a device with the to-be-marketed dose content. However, the results of trial 0620 indicate that any differences in results between the device tested and the to-be-marketed device would be negligible.

10.1.19 Design/synopsis/objectives

Like trial 0620, trial 0726 randomized subjects to treatment with the M3, M0-ESP, or matching placebo device in a double-blind manner for 12 weeks. The basic objectives were the same as in trial 0620.

10.1.20 Treatment regimens:

In this trial the M3 device tested metered 90 mcg, so more puffs were required for the same expected delivered dose. The M0-ESP device was the same as that tested in trial 0620. Subjects were randomized to 12 weeks of:

- M3 device: 90 mcg metered dose device
 - 4 puffs twice a day (360 µg BID) or
 - 2 puffs every morning (180 µg QD)
- M0-ESP: 200 mcg metered dose device
 - 2 puffs twice a day (400 µg BID) or
 - 1 puff every morning (200 µg QD)

A matching placebo was used for each active arm (M0-ESP and each M3). As in trial 0620, because the appearance of the M3 and the M0-ESP was not blinded, subjects could know which device they were given. As in trial 0620, the placebo for the M0-ESP device contained lactose.

10.1.21 Concomitant medications:

Permitted and prohibited concomitant medications were similar to those in trial 0620.

10.1.22 Subject eligibility criteria:

This trial was designed to enroll subjects with minimal asthma severity, whose asthma was controlled without the need for inhaled corticosteroids. The chief differences between the trial population for this trial and that of trial 0620 were:

- The population was pediatric: 6-17 years old

- The duration of asthma required for eligibility was shorter: ≥ 3 months
- Criteria for baseline FEV₁ (as % predicted) were established according to age, using criteria published by Polgar:
 - (6-11 yrs old): 75-90% predicted
 - (12-17 yrs old): 60-90% predicted
 - FEV₁ could be 90-95% predicted if FEV₁/FVC were $< 80\%$
- Subjects 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. As in 0620, limits for inhaled corticosteroid use were provided, which applied only to a current therapeutic regimen. These limits did not apply if the potential subject had been on inhaled corticosteroids in the past; such a therapeutic regimen could not abut the current one.
- Unlike trial 0620 minimal criteria for change in asthma did not have to be met after a placebo run-in period.
- Exclusion criteria did not include an exclusion for drops in peak expiratory flow.

10.1.23 Plan of procedures and evaluations:

The chief difference between this trial and trial 0620 was that during the run-in period subjects were not placed on placebo (subjects did not have to meet a minimal requirement for deterioration to be eligible for enrollment). Otherwise, the schedule of procedures was not notably different. Minor differences included the fact that in this trial peak inspiratory flow (PIF) measurements were performed and that urinary cortisol was measured.

10.1.24 Discontinuation of subjects from trial

As for trial 0620, subjects were to be removed from the trial for a worsening of asthma. A minor difference was that three nighttime awakenings would qualify a subject for removal from trial 0726 as compared to four from trial 0620.

10.1.25 Analysis

The primary endpoint of this trial differed from that of trial 0620 in that it was based on the percent predicted FEV₁, not the absolute FEV₁. FEV₁ was converted to a percent predicted value based on equations published by Polgar; the predicted normal value used at visit 1 was used even if a subject's numerical age changed during the trial.

The efficacy analysis was to be performed in a manner similar to that of trial 0620.

The sample size was established in amendment 1 but the power calculation was first stated in amendment 7. It established 460 subjects as the sample size based on a standard deviation in the FEV₁% predicted, 90% power, a two-sided statistical test at 5% level of significance, the detection of an 8% difference between the Pulmicort Turbuhaler and placebo treatment arms, and 5% unevaluable subject rate.

10.1.26 Changes to the protocol

The original protocol was dated 26 November 2001. Seven numbered amendments and one “administrative” change were implemented. The first 4 amendments, including the first amendment (which converted the trial to a placebo-controlled trial) occurred before the first subject was enrolled (which was 14 Nov 2002). The following lists the notable features of changes that were implemented after amendment 4.

- (non-numbered “administrative change”) 16 January 2003: changed the preparation of urine aliquots for measurement of urinary cortisol
- Amendment 5. 25 March 2003: qualified FEV₁ reversibility as up to 2.5, not 2.5 mg of nebulized albuterol; extended time points for collection of PK samples; added prohibited medications astemizole and hydroxyzine.
- Amendment 6. 6 June 2003: Relaxed eligibility by including subjects with FEV₁ between 90-95% predicted if they also had a ratio of FEV₁/FVC <80%; eliminated functionality testing of the M3 device and PK analysis in non-US sites (this reduced the projected number of inhalers to be tested from approximately 900 to approximately 400); added time windows for evaluations; clarified that unblinding information would be on the carton in the US or on a separate card in Asia. Note that while routine functionality testing of MDIs was to be done for US sites only, malfunctioning MDIs were to be returned for testing regardless of where they had been used (specified in protocol amendment 7)
- Amendment 7. 20 October 2003: allowed salbutamol (to be used in Asia) to be used for FEV₁ reversibility testing and rescue; added exclusion of potential subjects for use of ketofen or β -agonists used in fixed medication combinations or as oral preparations; added exclusion for active or untreated TB; added exclusion for hypersensitivity to rescue medication; added use of salbutamol, ≥ 12 actuations by MDI, as a reason for treatment discontinuation, added herbal medications including ephedrine-like compounds to the prohibited medications; increased enrollment period from 12 to 18 months; allowed pulmonary function testing for visit 1 to be done on a day different from other procedures; specified that randomization would be with respect to codes that were from different portions of the randomization codes depending upon whether subjects were or were not in the PK analysis; added country as a “study factor” in the ANCOVA analysis of the primary endpoint.

These protocol amendments would not be expected to affect the interpretability of the trial results.

10.1.27 Results

10.1.27.1 Conduct of the trial

The trial was conducted without major issues that would complicate its analysis.

10.1.27.2 Screening and enrollment

Attempted enrollment occurred at 84 sites (69 US, 15 Asian). Sixteen sites did not enroll subjects. 1656 subjects were screened; 1140 potential subjects were not randomized.

Table 68 shows summary statistics on the numbers of potential subjects who were enrolled but failed to be randomized. Over half the subjects screened could not participate due to not meeting eligibility criteria. This was by a large margin the largest group of subjects who failed to be randomized.

Table 68. Trial 0726: Reasons for failing to be randomized

Reason	N (%)
Adverse event	10 (1%)
Developed discharge criteria	3 (0.3%)
Eligibility criterion	1049 (92%)
Lost to Follow-up	23 (2%)
Not willing	46 (4%)
Other	9 (1%)
Total	1140

Overenrollment resulted in 516 subjects randomized to double-blind treatment at 54 sites in the U.S. and 14 sites in Asian. Most sites had 10 or fewer subjects (Table 69).

The first subject was enrolled on 14 November 2002 and the last subject completed the study on 21 September 2004.

Table 69. Trial 0726: Enrollment by site and country (n=516 overall)

Country	Subjects/site	Number of sites
US	1-5	28
	6-10	16
	11-15	6
	16-22	4
n=347		
Indonesia	2	1
	14-18	2
	22-30	2
n= 86		
Philippines	4	1
	10-16	3
n=41		
Singapore	2-3	2
n= 5		
Thailand	9	1
	13-15	2
n= 37		
Total n= 516		

10.1.27.3 Baseline characteristics of the subjects

Subjects in this trial had mild asthma. Treatment arms were balanced for sex proportions, race, age, duration of asthma, and FEV₁ (Table 70). There were more males than females (consistent with the overall preponderance of boys than girls with asthma, see reference 2), and while the majority of subjects were Caucasian, a greater proportion of subjects in this trial were

“Oriental.” A very small number of subjects used an inhaled corticosteroid during the placebo run-in, and lung function expressed as FEV₁ percent predicted was quite good, and notable better than that for the subjects in trial 0620.

Table 70. Trial 0726: Baseline subject characteristics (safety population)

		M3 360 µg BID (n=96)	M0-ESP 400 µg BID (n=102)	M3 180 µg QD (n=108)	M0-ESP 200 µg QD (n=104)	Combined Placebo (n=106)
Sex, n (% of subjects)	Male	67 (69.8)	64(62.7)	76 (70.4)	59 (56.7)	71 (67)
	Female	29 (30.2)	38 (37.3)	32 (29.6)	45 (43.3)	35 (33)
Race, n (% of subjects)	Caucasian	50 (52.1)	52 (51)	54 (50)	53 (51)	60 (56.6)
	Black	12 (12.5)	12 (11.8)	13 (12)	17 (16.3)	10 (9.4)
	Oriental	34 (35.4)	35 (34.3)	35 (32.4)	34 (32.7)	34 (32.1)
	Other	0	3 (2.9)	6 (5.6)	0	2 (1.9)
Age (y)	Mean	11.5	11.5	11.7	11.7	11.8
	SD	2.9	2.9	2.9	2.8	2.9
	Range	6 to 17	6 to 17	6 to 17	6 to 17	6 to 17
Age group, n (% of subjects)	6 to 11 y	45 (46.9)	51 (50)	43 (39.8)	47 (45.2)	46 (43.4)
	12 to 17 y	51 (53.1)	51 (50)	65 (60.2)	57 (54.8)	60 (56.6)
ICS run-in, n (% of subjects)	Yes	4 (4.2)	3 (2.9)	5 (4.6)	1 (1)	5 (4.7)
	No	92 (95.8)	99 (97.1)	103 (95.4)	103 (99)	101 (95.3)
Asthma history (y)	Mean	7.2	6.8	7.1	6.7	7.1
	SD	4.1	3.9	4.2	3.7	4.5
	Range	0.3 to 21.1	0.1 to 16.6	0.3 to 16.1	0.3 to 17.1	0.2 to 16.3
FEV ₁ % predicted at visit 1	n	91	96	101	99	101
	Mean ±SD	82.4±8	83.1±8	81±10	81.3±8	80.6±8
	Range	63.8 to 106.0	65.1 to 101.0	49.6 to 117.2	62.7 to 100.0	44.6 to 94.4

Source: Applicant's tables 12 and 13, clinical trial report. Racial terms as used by applicant.

Treatment arms were balanced for diary-recorded symptoms and rescue medication use (Table 71).

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Table 71. Trial 0726: Baseline disease characteristics-mITT analysis population

		TBH M3 360 µg bid	TBH M0- ESP 400 µg bid	TBH M3 180 µg qd	TBH M0- ESP 200 µg qd	Combined Placebo
Night asthma symptom score	<i>n</i>	91	97	103	100	101
	Mean	0.27	0.23	0.19	0.28	0.27
	SD	0.40	0.36	0.33	0.38	0.44
	Range	0 to 1.40	0 to 1.29	0 to 1.57	0 to 1.43	0 to 2.00
Day asthma symptom score	<i>n</i>	90	97	103	98	100
	Mean	0.39	0.39	0.37	0.46	0.36
	SD	0.50	0.51	0.50	0.54	0.50
	Range	0 to 2.00	0 to 1.75	0 to 2.00	0 to 2.00	0 to 2.00
% of days rescue medication was used *	<i>n</i>	91	97	104	100	101
	Mean	18.47	13.51	17.17	21.75	12.59
	SD	29.61	20.92	26.23	27.89	22.85
	Range	0 to 100.00	0 to 100.00	0 to 100.00	0 to 100.00	0 to 100.00
% of nights subject was awakened due to asthma symptoms**	<i>n</i>	91	97	103	100	101
	Mean	9.16	6.57	5.87	11.41	7.57
	SD	19.73	15.38	13.66	21.42	16.21
	Range	0 to 100.00	0 to 71.43	0 to 75.00	0 to 100.00	0 to 85.71

*Number of days of albuterol use divided by the number of days with non-missing albuterol data.

**Number of days of nighttime awakening divided by the number of days with non-missing nighttime awakening data.
 Derived from applicant's table 14 from clinical trial report.

Use of common asthma controller medications (safety analysis population) was consistent with fairly well-controlled asthma:

- No subjects were taking an oral corticosteroid or a “selective” β agonist
- Between 5-9% of subjects were on an inhaled corticosteroid
- <14% of any treatment arm were on leukotriene receptor antagonists
- 3 subjects in the M0-ESP/400 treatment arm were on allergen injections; all other groups had 2 subjects except the M3/180 treatment arm (none)

10.1.27.4 Protocol violations

Protocol violations included categories of eligibility, the receipt of disallowed medications, and failure to follow protocol. The numbers of subjects with various violations was reasonably balanced and reasonably small across treatment groups, making it unlikely that the protocol violations would have a notable impact on the results of the trial.

Table 72. Trial 0726: Protocol violations [n, % of dosing arm]

	M3 360 µg bid n=96	M0-ESP 400 µg bid n=102	M3 180 µg qd n=108	M0-ESP 200 µg qd n=104	Combined Placebo N=106
Subjects with at least 1 protocol deviation	38 (39.6)	42 (41.2)	50 (46.3)	42 (40.4)	56 (52.8)
% predicted FEV1 at Visit 1 was not					
• 60-90% (ages 12 to 17)	5 (5.2)	5 (4.9)	5 (4.6)	0	5 (4.7)
• 75-90% (ages 6 to 11)	4 (4.2)	5 (4.9)	1 (0.9)	4 (3.8)	2 (1.9)
Reversibility was not ≥12% at Visit 1	3 (3.1)	5 (4.9)	5 (4.6)	3 (2.9)	6 (5.7)
Met prerandomization discontinuation criteria, but was randomized	3 (3.1)	0	2 (1.9)	6 (5.8)	3 (2.8)
Did not meet ICS inclusion criteria					
• Days	0	0	2 (1.9)	0	0
• Dose	2 (2.1)	0	1 (0.9)	0	1 (0.9)
<80% compliant with single-blind placebo during the run-in period	8 (8.3)	5 (4.9)	8 (7.4)	10 (9.6)	10 (9.4)
<80% compliant with study treatment during the treatment period	4 (4.2)	2 (2.0)	9 (8.3)	6 (5.8)	8 (7.5)
Did not record diary scores for 5 consecutive days before Visit 2	12 (12.5)	15 (14.7)	18 (16.7)	24 (23.1)	20 (18.9)
Diagnosis of asthma was made <3 months before study entry	0	2 (2.0)	0	0	1 (0.9)
Took:					
• ADD medication not constant Visit 1-Visit 6	0	2 (2.0)	0	0	0
• Anticholinergic medication 2 weeks before Visit 1-Visit 6	0	0	0	0	1 (0.9)
• Combination β-agonist and ICS 2 weeks before Visit 1-Visit 6	0	0	1 (0.9)	0	0
• Cromone 2 weeks before Visit 1-Visit 6	0	1 (1.0)	0	0	0
• Disallowed antihistamine Visit 1-Visit 6	0	0	0	1 (1.0)	1 (0.9)
• ICS Visit 1-Visit 6	0	0	1 (0.9)	0	2 (1.9)
• Leukotriene modifier 2 weeks before Visit 1-Visit 6	0	1 (1.0)	1 (0.9)	1 (1.0)	3 (2.8)
• Medium or high potency topical steroid Visit 1-Visit 6	0	0	3 (2.9)	2 (1.9)	2 (1.9)
• Nasal steroid not constant Visit 1-Visit 6	4 (4.2)	2 (2.0)	5 (4.6)	2 (1.9)	1 (0.9)
• Oral β-agonist 2 weeks before Visit 1-Visit 6	3 (3.1)	2 (2.0)	3 (2.8)	1 (1.0)	4 (3.8)
• Systemic corticosteroid 28 days before Visit 1-Visit 6	1 (1.0)	2 (2.0)	1 (0.9)	1 (1.0)	3 (2.8)

Source: Applicant's table 11 from clinical trial report

10.1.27.5 Discontinuations

The discontinuation rate in the trial was high (Table 73). Consistent with the low degree of severity of asthma at baseline, the discontinuation rates were lower than in trial 0626, and there was a much lower percent of discontinuations from the placebo arm. This resulted in a more balanced proportion of discontinuations among the treatment arms. Expressed as percents of each treatment arm, the reasons were reasonably similar among all the treatment groups. Most subjects discontinued due to worsening asthma.

Table 73. Trial 0726: Discontinuations of randomized subjects (n, % of dosing arm)

	M3 360 µg bid (n=96)	M0-ESP 400 µg bid (n=102)	M3 180 µg qd (n=108)	M0-ESP 200 µg qd (n=104)	Combined Placebo (n=106)
Total discontinued	20 (20.8)	17 (16.7)	23 (21.3)	21 (20.2)	25 (23.6)
Eligibility criteria not fulfilled	3 (3.1)	3 (2.9)	5 (4.6)	7 (6.7)	4 (3.8)
Adverse event	2 (2.1)	2 (2.0)	1 (0.9)	0	5 (4.7)
Developed study-specific discontinuation criteria	7 (7.3)	6 (5.9)	8 (7.4)	10 (9.6)	6 (5.7)
Subject not willing to continue the study	3 (3.1)	1 (1.0)	1 (0.9)	1 (1.0)	4 (3.8)
Subject lost to follow-up	1 (1.0)	1 (1.0)	4 (3.7)	1 (1.0)	1 (0.9)
Other	4 (4.2)	4 (3.9)	4 (3.7)	2 (1.9)	5 (4.7)

Source: Applicant's table 10 from clinical trial report

10.1.27.6 Performance of the devices

Three devices were returned (all with active product), and none of the complaints about them were confirmed. The batch average-delivered dose for the clinical returns compared to the release ranged from 88% to 93% for the returned inhalers. The corresponding range at release was 93% to 96%. These results suggest that the devices generally functioned adequately.

10.1.28 Efficacy results

10.1.28.1 Primary endpoint

Twenty-three subjects were excluded from the primary efficacy analysis population because no efficacy data were available after baseline (Table 74). These subjects were distributed fairly evenly among the treatment arms. Nine of these subjects came from one site in Indonesia, but were distributed among a variety of treatment arms. The majority (17/23) were male. Despite these minor imbalances, the numbers of subjects with no data would not be expected to have had a major impact on the conclusions of the trial.

Table 74. Trial 0726: Modified intent-to-treat population

Treatment	All randomized	Excluded	Modified ITT population
M3 360 µg bid	96	6 (3 US, 3 Asia)	90
M0-ESP 400 µg bid	102	4 (2 US, 2 Asia)	98
M3 180 µg qd	108	5 (4 US, 1 Asia)	103
M0-ESP 200 µg qd	104	3 (3 Asia)	101
Placebo (pooled)	106	5 (3 US, 2 Asia)	101

Differences from baseline to treatment period mean in the placebo groups were similar, and the results were pooled. The values were, in percents predicted:

- M3/360 µg BID placebo: 0.24
- M0-ESP/400 µg BID placebo: -0.54
- M3/180 µg QD placebo: 1.81
- M0-ESP 200 µg QD placebo: 0.11

Table 75 shows differences from baseline to the mean of the treatment period in each treatment arm.

There was a dose-dependent increase from baseline, with the placebo group experiencing no notable change from baseline. The two low-dose treatment arms exhibited similar effects, with a slightly bigger increase in the M3 group for the higher dose regimen.

Table 75. Trial 0726: FEV₁ % predicted means, ITT population, LOCF imputation

Treatment	n	FEV ₁ % predicted mean (SE)			ANCOVA		
		Baseline	Treatment period	Change	LS mean change	SE	95% CI
M3 360 µg bid	90	84.2 (1.0)	90.0 (1.1)	5.8 (1.0)	5.6	0.8	3.9 to 7.2
M0-ESP 400 µg bid	98	86.6 (0.7)	90.7 (0.8)	4.1 (0.7)	4.4	0.8	2.9 to 6.0
M3 180 µg qd	103	84.7(1.0)	87.3 (1.2)	2.7 (0.8)	2.6	0.8	1.0 to 4.1
M0-ESP 200 µg qd	101	84.4 (0.9)	87.3 (1.0)	2.9 (0.8)	2.7	0.8	1.2 to 4.2
Placebo (pooled)	101	84.5 (0.9)	84.8 (1.0)	0.4 (0.8)	0.2	0.8	-1.4 to 1.7

Source: Applicant's table 16, clinical trial report

Table 76 shows the treatment effect on FEV₁ % predicted and the primary statistical analysis. All intertreatment group differences exceeded the threshold p-value of 0.05. The differences from placebo were slightly lower than those in trial 0620 (Table 51).

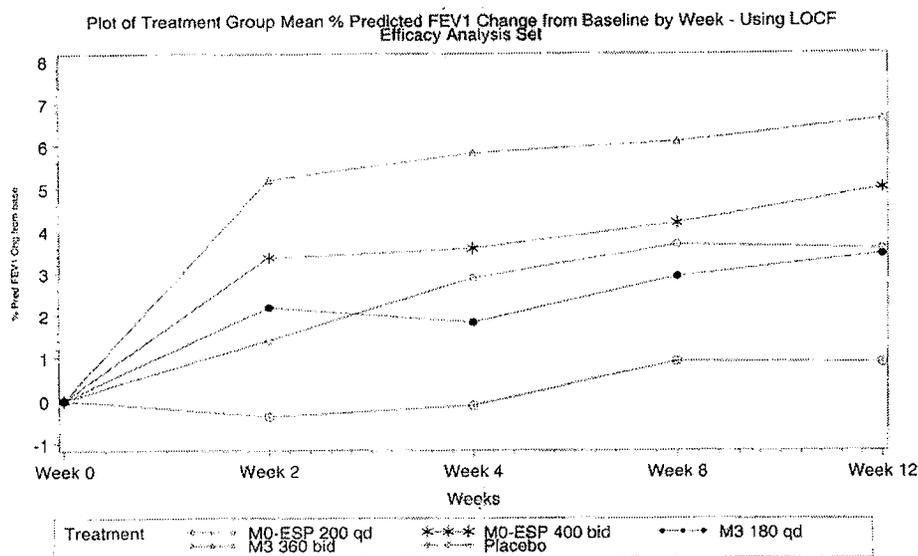
Table 76. Trial 0726: Primary endpoint: FEV₁ % predicted change from baseline to treatment period mean, treatment arm differences*

Comparison	LS mean difference	SE	95% CI	p-value
M3 360 µg bid – placebo	5.4	1.1	3.2 to 7.6	<0.001
M0-ESP 400 µg bid – placebo	4.3	1.1	2.1 to 6.4	<0.001
M3 180 µg qd – placebo	2.4	1.1	0.2 to 4.5	0.03
M0-ESP 200 µg qd – placebo	2.5	1.1	0.4 to 4.7	0.022
M3 360 µg bid –M0-ESP 400 µg bid	1.1	1.1	-1.1 to 3.4	0.323
M3 180 µg qd –M0-ESP 200 µg qd	-0.1	1.1	-2.3 to 2.0	0.897

* ANCOVA, ITT population, LOCF

Figure 5 shows mean FEV₁ % predicted for each treatment arm by visit. End of treatment period values for FEV₁ % predicted paralleled the mean treatment period differences from baseline. For all active groups except the low-dose M0-ESP treatment arm, near-maximal effect was seen at the week 2 visit. End of treatment effect was similar in both low-dose treatment arms. End-of-treatment FEV₁ % predicted difference from placebo (by ANCOVA) reached a nominal level of statistical significance (p<0.05) for each treatment except in the M3 low-dose arm (p-value was 0.06).

Figure 5. Trial 0726: Mean FEV₁ % predicted by treatment visit (LOCF)



10.1.28.1.1 Sensitivity analyses

FDA conducted analyses of FEV₁ % predicted similar to those described for trial 0620. Using a “worst case” imputation, differences from baseline in all treatment groups were lowered, with both low-dose treatment groups showing a deterioration from baseline, but not as much as placebo (Table 77). The p-values are shown not to suggest statistical significance but to help in the understanding of the consistency of any effects seen. The results do not invalidate the primary analysis, but show the weakness in the daily dosing regimen.

Table 77. Trial 0726: Sensitivity analysis of primary endpoint: Applicant, worst case, and median imputation using observed values data set (see text)

Treatment	N	Percent Predicted FEV ₁					
		AstraZeneca		Worst		Median	
		LS Mean Change ¹	P-value vs. Placebo	LS Mean Change ¹	P-value vs. Placebo	LS Mean Change ¹	P-value vs. Placebo
M3 360 mcg BID	90	5.54	<0.0001	1.42	0.0041	5.65	<0.0001
M0-ESP 400 mcg BID	98	4.48	0.0001	1.64	0.0022	4.62	0.0001
M3 180 mcg QD	103	2.66	0.0277	-2.58	0.5679	2.88	0.0348
M0-ESP 200 mcg QD	101	2.86	0.0176	-2.06	0.3777	3.08	0.0211
Placebo	101	0.31	-	-3.53	-	0.90	-

¹ Compared to baseline

AstraZeneca's per-protocol data set excluded 79 subjects overall (about 14% of the trial population, Table 78).

Table 78. Trial 0726: Numbers of subjects excluded from mITT population to get per-protocol population

Treatment arm	Modified ITT	Excluded	Per-protocol
M0-ESP 200 mcg qd	104	12	92
M0-ESP 400 mcg bid	102	14	88
M3 180 mcg Qd	108	15	93
M3 360 mcg Qd	96	18	78
Placebo	106	20	86
Totals	516	79	437

In the per-protocol analysis (Table 79 and Table 80) the differences from placebo for both low-dose treatment arms did not reach the nominal p-value of 0.05, but the results were numerically similar to the primary analysis.

Table 79. Trial 0726: FEV₁ % predicted means (LOCF), per-protocol population

Treatment	n	FEV ₁ % predicted mean (SE)			ANCOVA		
		Baseline	Treatment period	Change	LS mean change	SE	95% CI
M3 360 µg bid	78	83.5 (1.0)	89.4 (1.1)	6.0 (1.1)	5.5	0.9	3.8 to 7.2
M0-ESP 400 µg bid	88	86.0 (0.8)	89.7 (0.8)	3.6 (0.8)	4.0	0.8	2.4 to 5.6
M3 180 µg qd	93	84.8 (0.9)	87.8 (1.2)	3.0 (0.8)	3.0	0.8	1.4 to 4.6
M0-ESP 200 µg qd	92	84.2 (0.9)	87.4 (1.1)	3.2 (0.8)	3.0	0.8	1.4 to 4.6
Placebo (pooled)	86	84.7 (0.9)	85.6 (0.9)	0.9 (0.8)	0.8	0.8	-0.8 to 2.5

Source: Applicant's table 22, clinical trial report

Table 80. Trial 0726: Primary endpoint: FEV₁ % predicted change from baseline to treatment period mean, treatment arm differences, per-protocol population

Comparison	LS mean difference	SE	95% CI	p-value
M3 360 µg bid – placebo	4.7	1.2	2.3 to 7.0	<0.001
M0-ESP 400 µg bid – placebo	3.2	1.2	0.9 to 5.4	0.006
M3 180 µg qd – placebo	2.1	1.1	-0.1 to 4.4	0.060
M0-ESP 200 µg qd – placebo	2.1	1.1	-0.12 to 4.4	0.063
M3 360 µg bid – M0-ESP 400 µg bid	1.5	1.2	-0.8 to 3.9	0.202
M3 180 µg qd – M0-ESP 200 µg qd	0.0	1.1	-2.2 to 2.2	0.989

Source: Applicant's table 23, clinical trial report

10.1.28.1.2 Subgroup analyses of the primary endpoint

10.1.28.1.2.1 Treatment effect by baseline peak inspiratory flow rate

Delivery of particles from the device changes with inspiratory flow rates below 60 l/min. (see the product review and the summary of the issue in section 3.1). Table 81 shows that there was no notable trend toward a drop in efficacy in subjects with PIF below 60 l/min at baseline for either device. However, conclusions from this analysis are problematic due to the small sample sizes and the lack of randomization in the subset.

Table 81. Trial 0726: Mean change from baseline with respect to baseline PIF*

	<40 l/min*		<60 l/min*		All subjects	
	n (% of treatment arm)	Change from baseline	n	Change from baseline	n	LS Change from baseline
M3 360 µg bid	6 (6.8%)	3.903	22	4.1	90	5.6
M0-ESP 400 µg bid	6 (6.4%)	9.338	16	8.9	98	4.4
M3 180 µg qd	5 (4.9%)	-3.842	32	3.4	103	2.6
M0-ESP 200 µg qd	3 (3.1%)	5.319	23	1.3	101	2.7
Placebo (pooled)	4 (4.0%)	-1.935	20	0.7	101	0.2

*FDA analyses. One subjects is not included (M3/100 µg QD) due to no data past baseline.

AstraZeneca explored the potential effect of low PIF on efficacy by adding a term for baseline PIF in the primary analytical model. According to the statistical reviewer, in this analysis a linear relation of PIF on mean % predicted FEV₁ only explains 6% of the variation in mean % predicted FEV₁. However, considering the numbers of subjects with PIF below the 60 l/min cutoff, clear conclusions cannot be made using this analysis.

The numbers of subjects with peak inspiratory flow rates below 60 l/min is too small for any conclusion to be made with respect to trends related to peak inspiratory flow.

10.1.28.1.2.2 Treatment effect by region

Table 82 shows FEV₁ % predicted data by region. All active treatment groups produced more effect than placebo. In contrast to trial 0620, larger treatment effects (as compared to placebo) for either device occurred in Asia.

In the U.S. the high-dose M0-ESP device produced the same effect as the low-dose device, but the high-dose M3 device was more effective than its low-dose counterpart.

The size of the US treatment groups was from just over twice to just under three times the size of the Asian populations, making the estimate of treatment effect in the U.S. more reliable.

Table 82. Trial 0726: Regional difference in FEV₁ % predicted compared to placebo; unadjusted values

Comparison	Region	
	US	Asia
M3 360 µg bid – placebo	4.6	7.3
M0-ESP 400 µg bid – placebo	2.4	6.6
M3 180 µg qd – placebo	2.2	2.7
M0-ESP 200 µg qd – placebo	2.2	3.2
M3 360 µg bid – M0-ESP 400 µg bid	2.2	0.7
M3 180 µg qd – M0-ESP 200 µg qd	0	-0.5

n in active groups: US:60-70, Asia 30-32

n in pooled placebo: U.S.*n*=69, Asia *n*=32

Sources: Applicant's table 18 and 11.2.1.1.3

10.1.28.1.2.3 Treatment effect by age group

Table 83 shows that for minimal differences were seen at the lower doses for each device. Slightly larger treatment effects were seen in the higher age group for both devices in the lower dose groups and for the M3 high-dose group. However, this trend did not occur for the M0-ESP high-dose group. Overall, these effects do not show a consistent effect of age on efficacy.

Table 83. Trial 0726: Differences in FEV₁% predicted by age group

Comparison	Age group (years)	
	6-11	12-17
M3 360 µg bid – placebo	4.1	6.6
M0-ESP 400 µg bid – placebo	4.1	3.5
M3 180 µg qd – placebo	1.9	2.5
M0-ESP 200 µg qd – placebo	1.4	3.5
M3 360 µg bid – M0-ESP 400 µg bid	0.1	3.1
M3 180 µg qd – M0-ESP 200 µg qd	0.6	-1.0

n in active treatment arms: 6-11: 39-50; 12-17:48-64. *n* in placebo: 6-11:43; 12-17: 58

Sources: Applicant's table 19 and 11.2.1.1.1

10.1.28.1.2.4 Treatment effect by sex

Table 84 shows mean changes in FEV₁ % by sex. All treatment arms showed some increase compared to placebo. Females in the M3 360 µg BID group did not show the increase in effect with the higher dose, but the numbers of females makes this observation tentative.

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Table 84. Trial 0726: FEV₁ % predicted change from baseline by sex (mean ±sd)

	Female		Male	
	Change	Diff. from placebo*	Change	Diff. from placebo*
M3 360 µg bid	2.27 ± 7.8 n=27	2.61	7.34 ± 9.5 n=63	6.61
M0-ESP 400 µg bid	4.82 ± 5.9 n=37	5.16	3.64 ± 8.1 n=61	2.91
M3 180 µg qd	3.75 ± 10.5 n=31	4.09	2.23 ± 7.1 n=72	1.5
M0-ESP 200 µg qd	2.37 ± 8.0 n=44	2.71	3.28 ± 7.9 n=57	2.55
Placebo (pooled)	-0.34 ± 6.4 n=34	-	0.73 ± 8.1 n=67	-

Source of data: Applicant's table 11.2.1.1.4

*Reviewer's calculation based on numbers in table

10.1.28.1.2.5 Treatment effect by race

Results in the various racial subgroups tended to show a greater effect in the M3/360 BID treatment arm. In the small subgroup of "Black" subjects low-dose treatment for either device resulted in less effect than placebo treatment, but the reliability of this result is compromised by the very small numbers of subjects in this particular subgroup.

Table 85. Trial 0726: FEV₁ % predicted change from baseline by race

	Caucasian		Oriental		Black	
	Change	Diff. from placebo*	Change	Diff. from placebo*	Change	Diff. from placebo*
M3 360 µg bid	6.03 ± 8.9 n=48	4.89	6.19 ± 11.2 n=31	7.36	3.87 ± 4.2 n=11	1.87
M0-ESP 400 µg bid	3.33 ± 7.1 n=51	2.19	5.64 ± 7.3 n=33	6.81	3.59 ± 9.0 n=12	1.59
M3 180 µg qd	3.98 ± 7.9 n=52	2.84	1.92 ± 9.1 n=33	3.09	-0.04 ± 8.1 n=12	-2.04
M0-ESP 200 µg qd	4.11 ± 8.5 n=53	2.97	1.99 ± 8.2 n=31	3.16	0.70 ± 4.8 n=17	-1.3
Placebo (pooled)	1.14 ± 6.5 n=57	-	-1.17 ± 9.1 n=32	-	2.00 ± 8.0 n=10	-

Source of data: Applicant's table 11.2.1.1.5. Racial terms as used by applicant.

*Reviewer's calculation based on numbers in table

10.1.28.1.2.6 Summary of subgroup analyses

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."

10.1.28.2 Secondary endpoints

10.1.28.2.1 FEV₁

Table 86 shows FEV₁ at baseline and mean during treatment; Table 87 shows the analysis of the intertreatment group differences. Not surprisingly, the trends in the numerical differences from placebo were similar to those for the primary endpoint.

Table 86. Trial 0726: FEV₁ means, ITT population, LOCF imputation

Treatment	n	FEV ₁ % predicted mean (SE)			ANCOVA		
		Baseline	Treatment period	Change	LS mean change	SE	95% CI
M3 360 µg bid	90	2.12 (0.07)	2.28 (0.08)	0.16 (0.03)	0.16	0.02	0.11 to 0.20
M0-ESP 400 µg bid	98	2.23 (0.07)	2.33 (0.08)	0.10 (0.02)	0.09	0.02	0.05 to 0.14
M3 180 µg qd	103	2.24 (0.07)	2.30 (0.07)	0.07 (0.02)	0.06	0.02	0.02 to 0.10
M0-ESP 200 µg qd	101	2.08 (0.06)	2.16 (0.07)	0.08 (0.02)	0.08	0.02	0.04 to 0.12
Placebo (pooled)	101	2.20 (0.07)	2.21 (0.07)	0.01 (0.02)	0.01	0.02	-0.04 to 0.

Table 87. Trial 0726: FEV₁ treatment group comparisons

Comparison	LS mean difference	SE	95% CI	p-value
M3 360 µg bid – placebo	0.15	0.03	0.09 to 0.21	<0.001
M0-ESP 400 µg bid – placebo	0.09	0.03	0.03 to 0.15	0.005
M3 180 µg qd – placebo	0.05	0.03	0.00 to 0.11	0.071
M0-ESP 200 µg qd – placebo	0.07	0.03	0.01 to 0.13	0.017
M3 360 µg bid – M0-ESP 400 µg bid	0.06	0.03	0.00 to 0.13	0.039
M3 180 µg qd – M0-ESP 200 µg qd	-0.02	0.03	-0.08 to 0.04	0.551

10.1.28.2.2 FVC

No treatment showed an effect on FVC compared to placebo (Table 88).

Table 88. Trial 0726: FVC treatment group comparisons

Comparison	Adjusted Mean	SE	95% CI	p-value
M3 360 mcg bid - Placebo	0.07	0.05	-0.03 to 0.16	0.157
M0-ESP 400 µg bid – placebo	0.05	0.05	-0.04 to 0.14	0.289
M3 180 mcg qd - Placebo	0.05	0.04	-0.04 to 0.14	0.238
M0-ESP 200 mcg qd - Placebo	0.03	0.04	-0.06 to 0.12	0.484
M3 360 mcg bid - M0-ESP 400	0.02	0.05	-0.07 to 0.11	0.707
M3 180 mcg qd - M0-ESP 200 mcg qd	0.02	0.04	-0.07 to 0.11	0.633

Source: Applicant table 11.2.1.2.1

10.1.28.2.3 FEF₂₅₋₇₅

Results are shown in Table 89. The increase in FEF₂₅₋₇₅ in the high-dose groups was numerically about three times that in the low-dose groups. The results trended in the same direction as the primary endpoint.

Table 89. Trial 0726: FEF₂₅₋₇₅ treatment group comparisons (ANCOVA, LOCF)

Comparison	Adjusted Mean	SE	95% CI	p-value
M3 360 mcg bid - Placebo	0.31	0.07	0.10 to 0.39	<0.001
M0-ESP 400 µg bid – placebo	0.24	0.07	0.12 to 0.47	<0.001
M3 180 mcg qd - Placebo	0.08	0.07	-0.06 to 0.22	0.265
M0-ESP 200 mcg qd - Placebo	0.08	0.07	-0.06 to 0.23	0.245
M3 360 mcg bid - M0-ESP 400	0.06	0.08	-0.08 to 0.21	0.401
M3 180 mcg qd - M0-ESP 200 mcg qd	0	0.07	-0.15 to 0.14	0.954

Source: Applicant table 11.2.1.2.1

10.1.28.2.4 *Diary-derived morning peak expiratory flow*

Baseline peak expiratory flow was approximately 300 l/min for all subjects. Differences from baseline to treatment mean were small. (Table 90).

Table 90. Trial 0726: Morning PEF treatment group comparisons

Comparison	LS mean difference	SE	95% CI	p-value
M3 360 µg bid – placebo	11.38	4.44	2.65 to 20.10	0.011
M0-ESP 400 µg bid – placebo	3.71	4.37	-4.87 to 12.30	0.396
M3 180 µg qd– placebo	2.00	4.30	-6.46 to 10.45	0.643
M0-ESP 200 µg qd – placebo	6.83	4.34	-1.69 to 15.35	0.116
M3 360 µg bid –M0-ESP 400 µg bid	7.67	4.48	-1.14 to 16.47	0.088
M3 180 µg qd –M0-ESP 200 µg qd	-4.84	4.32	-13.33 to 3.65	0.263

10.1.28.2.5 *Diary-derived evening peak expiratory flow*

The results in Table 91 parallel those for morning PEF.

Table 91. Trial 0620: Evening PEF treatment group comparisons

Comparison	LS mean difference	SE	95% CI	p-value
M3 360 µg bid – placebo	11.75	4.45	3.00 to 20.50	0.009
M3 180 µg qd– placebo	1.84	4.31	-6.62 to 10.30	0.669
M0-ESP 400 µg bid – placebo	0.34	4.37	-8.24 to 8.93	0.937
M0-ESP 200 µg qd – placebo	6.82	4.36	-1.75 to 15.38	0.118
M3 360 µg bid –M0-ESP 400 µg bid	11.40	4.49	2.59 to 20.22	0.011
M3 180 µg qd –M0-ESP 200 µg qd	-4.97	4.34	-13.49 to 3.55	0.252

10.1.28.2.6 *Diary derived asthma symptom score*

Baseline scores were low (no mean morning asthma score exceeded 0.28; no evening asthma score exceeded 0.46), and for neither morning nor evening scores were notable or statistically significant differences from placebo or baseline seen.

10.1.28.2.7 *Change in albuterol use*

Baseline use of albuterol was very low in all treatment arms (no mean morning albuterol use (in puffs) exceeded 0.18; no evening albuterol use (in puffs) exceeded 0.42), and for neither

morning nor evening use were notable or statistically significant differences from placebo or baseline seen.

10.1.28.2.8 Meeting discontinuation criteria

Table 92 summarizes numbers of subjects who met discontinuation criteria, similar to the summary in trial 0620. Consistent with the relatively well population, there was little difference between active groups and placebo. AstraZeneca’s statistical analysis of the numbers of subjects meeting any discontinuation criterion showed no statistical differences between any treatment arm and placebo. In addition, referring to these data, AstraZeneca states that there “no clinically relevant or statistically significant differences between any of the treatment groups as determined from the survival analysis.”

Table 92. Trial 0726: Subjects with discontinuation events (n, % of group)

Criterion	M3 360 µg bid (n=94)	M0-ESP 400 µg bid (n=99)	M3 180 µg qd (n=106)	M0-ESP 200 µg qd (n=101)	Placebo (n=104)
Subjects with at least 1 study-specific predefined asthma-related discontinuation criterion	13 (13.8)	11 (11.1)	12 (11.3)	12 (11.9)	18 (17.3)
3 nighttime awakenings requiring β2-agonist within 5 days	7 (7.4)	5 (5.1)	5 (4.7)	7 (6.9)	5 (4.8)
Decrease in morning PEF >25% from baseline on 3 days within 5 days	3 (3.2)	5 (5.1)	5 (4.7)	1 (1.0)	8 (7.7)
Decrease in FEV ₁ ≥25% from Visit 1-Visit 2	3 (3.2)	2 (2.0)	1 (0.9)	3 (3.0)	3 (2.9)
Used disallowed concomitant medication	1 (1.1)	1 (1.0)	2 (1.9)	1 (1.0)	3 (2.9)
% predicted FEV ₁ <40% of predicted	0	0	0	0	2 (1.9)
≥12 actuations of albuterol per 2 days within 3 days	1 (1.1)	0	0	0	1 (1.0)

Exploratory endpoint: peak inspiratory flow

Baseline peak inspiratory flow ranged from 70-76 l/min (sample sizes from 77-94 subjects). Based on observed data, the changes from baseline to treatment period mean varied from -0.14 l/min to 3.7 l/min (sample sizes from 84-99), with no relation to dose.

10.1.29 Pharmacokinetics

The pharmacokinetic substudy was to enroll about 15 subjects in each treatment arm; however, 32 subjects were studied (AstraZeneca states that recruiting was more difficult due to the demands of the 12-hour assessment). The sex and age distribution of this subpopulation was not notably different from that of the overall population; there were minor differences from the overall population in the percents of Caucasians and “Blacks” (Caucasians 9/32 (28%); “Blacks” 12/32 (38%); for comparison see Table 70).

The study was done using M3 devices with approximately 5% less dose content than the to-be-marketed devices.

The mean results (Figure 6) resemble those in trial 0620. However, individual variability was high (Figure 7) and the numbers of subjects small, so clear conclusions cannot be drawn from these analyses.

Figure 6. Trial 0726 pharmacokinetic substudy mean plasma concentration with time

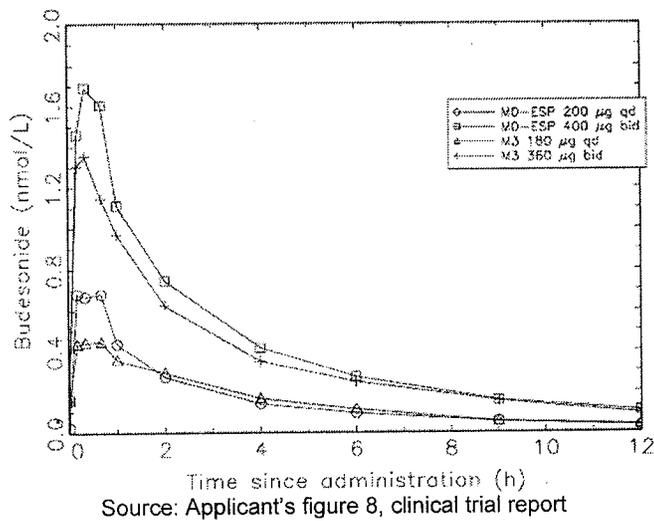


Figure 7. Trial 0726 Individual plasma concentration curves

b(4)

10.1.30 Safety

10.1.30.1 Exposure

Duration of exposure was similar across treatment arms, with the mean number of days slightly below the nominal 84 (12 weeks) (Table 93). This is consistent with the similar discontinuation rates.

Table 93. Trial 0726: Exposure in safety population

		M3 360 µg bid (n=96)	M0-ESP 400 µg bid (n=102)	M3 180 µg qd (n=108)	M0-ESP 200 µg qd (n=104)	Placebo (n=106)
Duration of exposure to study treatment	≤2 weeks	2 (2.1)	3 (2.9)	4 (3.7)	1 (1.0)	1 (0.9)
	>2 weeks to ≤4 weeks	6 (6.3)	4 (3.9)	5 (4.6)	9 (8.7)	7 (6.6)
	>4 weeks to ≤8 weeks	5 (5.2)	3 (2.9)	7 (6.5)	5 (4.8)	4 (3.8)
	>8 weeks to <12 weeks	18 (18.8)	17 (16.7)	17 (15.7)	18 (17.3)	21 (19.8)
	≥12 weeks	65 (67.7)	75 (73.5)	75 (69.4)	71 (68.3)	73 (68.9)
Days of days treated	Mean (SD)	76.34 (22.33)	78.32 (19.49)	77.3 (22.37)	76.46 (23.07)	77.75 (20.38)
	Range (min to max)	8 to 121	5 to 96	7 to 121	1 to 112	10 to 122

*Source: Applicant table 57, clinical trial report

10.1.30.2 Deaths, serious adverse events, and discontinuations due to adverse events

No deaths occurred. Three subjects experienced serious adverse events after randomization:

- Placebo: 10 year-old female with an asthma exacerbation on day 72. The treatment was discontinued, with the outcome reported as no longer present
- Placebo: 15 year-old male with food poisoning on day 13, with the outcome reported as no longer present.
- M0-ESP 400 µg BID: 12 year-old male with gastric pain on day 33. The product was temporarily discontinued; the outcome reported as no longer present.

Additional serious adverse events occurred in the trial prior to randomization: 1) post-auricular abscess in a 14 year-old male; 2) psychotic depression in a 15 year-old male; 3) fever with headache and viral infection in a 14 year-old male.

Discontinuations due to adverse events were due to respiratory events; these occurred slightly more frequently in the placebo group (Table 94).

Table 94. Trial 0726: Subjects who discontinued

Treatment	Sex/age/ race*	Adverse event according to investigator	Latency to onset (days)	Duration if resolved (days)	Intensity	Causality per investigator	Determination if serious
M3 360 µg bid	M/12/C	Asthma exacerbation	33	8	Moderate	Yes	No
M3 360 µg bid	M/14/C	Upper respiratory infection	29	6	Moderate	No	No
M0-ESP 400 µg bid	M/9/C	Asthma exacerbation	14	18	Moderate	No	No
M0-ESP 400 µg bid	F/6/O	Asthma exacerbation	17	6	Moderate	No	No
M3 180 µg qd	M/8/C	Asthma exacerbation	10	5	Moderate	Yes	No
Placebo	F/10/C	Asthma exacerbation	72	4	Severe	No	Yes
Placebo	M/14/C	Bronchitis	12	6	Moderate	No	No
Placebo	M/8/C	Asthma exacerbation	31	13	Moderate	No	No
Placebo	F/10/C	Acute asthma exacerbation	56	6	Severe	No	No
Placebo	F/12/C	Acute asthma exacerbation	17	5	Moderate	No	No

*Race: Caucasian; O=Oriental

Source: Applicant table 62, clinical trial report. Racial terms as used by applicant.

10.1.30.3 Adverse events

Table 95 shows that there was little difference among the treatment arms in the incidence of particular adverse events.

Table 95. Trial 0726: Summary of numbers of subjects with adverse events (safety population), among events that occurred with ≥3% incidence in any treatment arm

Preferred term	M3 360 µg bid (n=96)	M0-ESP 400 µg bid (n=102)	M3 180 µg qd (n=108)	M0-ESP 200 µg qd (n=104)	Placebo (n=106)
Total	44 (45.8)	49 (48.0)	57 (52.8)	53 (51.0)	58 (54.7)
Headache	5 (5.2)	6 (5.9)	9 (8.3)	13 (12.5)	7 (6.6)
Nasopharyngitis	10 (10.4)	8 (7.8)	6 (5.6)	5 (4.8)	11 (10.4)
Pharyngolaryngeal pain	6 (6.3)	5 (4.9)	7 (6.5)	4 (3.8)	10 (9.4)
Pyrexia	6 (6.3)	5 (4.9)	6 (5.6)	2 (1.9)	8 (7.5)
Upper respiratory tract infection	2 (2.1)	7 (6.9)	5 (4.6)	7 (6.7)	5 (4.7)
Cough	6 (6.3)	8 (7.8)	6 (5.6)	1 (1.0)	4 (3.8)
Asthma	2 (2.1)	3 (2.9)	3 (2.8)	2 (1.9)	6 (5.7)
Nasal congestion	4 (4.2)	5 (4.9)	3 (2.8)	2 (1.9)	0
Pharyngitis	4 (4.2)	4 (3.9)	1 (0.9)	1 (1.0)	2 (1.9)
Abdominal pain, upper	1 (1.0)	2 (2.0)	1 (0.9)	6 (5.8)	2 (1.9)
Sinusitis	1 (1.0)	2 (2.0)	4 (3.7)	1 (1.0)	4 (3.8)
Diarrhea	3 (3.1)	1 (1.0)	4 (3.7)	2 (1.9)	1 (0.9)
Allergic rhinitis	4 (4.2)	2 (2.0)	2 (1.9)	2 (1.9)	1 (0.9)
Epistaxis	2 (2.1)	1 (1.0)	1 (0.9)	1 (1.0)	5 (4.7)
Otitis media	3 (3.1)	1 (1.0)	2 (1.9)	0	1 (0.9)
Skin laceration	3 (3.1)	0	1 (0.9)	1 (1.0)	2 (1.9)
Gastroenteritis, viral	3 (3.1)	0	1 (0.9)	1 (1.0)	0
Neck pain	0	0	0	1 (1.0)	4 (3.8)

Source: Applicant table 60, clinical trial report

Oral candidiasis occurred in one subject each in the M0-ESP 400 µg BID and M3 360 µg BID groups. Hoarseness occurred in one subject in the placebo group.

Listings of adverse events grouped by site (US and Asia), sex, age (6-11 and 12-17), and race did not reveal any notable differences in the incidences of particular adverse events. The numbers of individual events and the sizes of the subgroups made these comparisons inconclusive; however, no safety concern emerged.

Drug-related adverse events

Although drug-relatedness is sometimes difficult to assess with certainty, it is useful to examine events that the investigator thought were due to treatment. The pattern of events (number of subjects in parentheses) does not show a pattern of toxicity:

- Placebo: pharyngolaryngeal pain and cough (1 subject)
- M3 180 µg QD: asthma (1)
- M0-ESP 200 µg QD: (none)
- M3 360 µg BID: candidiasis, asthma, dry throat (1 subject each)
- M0-ESP 400 µg BID: oral candidiasis (1)

Severe adverse events

There were very few severe events during treatment. The events that occurred do not show a pattern of toxicity:

- Placebo: asthma (two events), food poisoning
- M3 180 µg QD: headache
- M3 360 µg BID: muscle strain, skin laceration
- M0-ESP 400 µg BID: upper abdominal pain, cough

10.1.30.4 Vital signs

No notable changes occurred in heart rate, blood pressure, or weight during the clinical trial.

10.1.30.5 Laboratory abnormalities

Urinary cortisol

Of special concern with the administration of a corticosteroid is the potential for suppression of the hypothalamic-pituitary axis. The protocol called for determinations of serum cortisol in a 24-hour urine collected in a subset of randomized subjects in each treatment group. Table 96 shows urinary cortisol results. Baseline urinary cortisols varied widely. The unexpected increase in urinary cortisol in the low-dose M0-ESP group suggests a wide error of measurement (urinary volumes collected for this substudy varied from 150 ml to 2600 ml, suggesting the possibility that incomplete collections may have influenced the results). Although there may have been a decrease in urinary cortisol in the high-dose groups, these results are inadequate to show this clearly.

The results do not show a safety concern for the use of the M3 product.

Table 96. Trial 0726: Urinary cortisol (geometric means)

	M3 360 µg bid n=13	M0-ESP 400 µg bid n=13	M3 180 µg qd n=14	M0-ESP 200 µg qd n=12	Placebo n=17
Baseline	25.4 (n=10)	35.9 (n=10)	14.1 (n=7)	25.9 (n=11)	29.8 (n=15)
End of treatment	18.8 (n=10)	20.7 (n=10)	20.9 (n=7)	36.9 (n=11)	32.6 (n=15)

Source: Applicant table 11.3.7.2.1.3

There was one laboratory abnormality listed as an adverse event during treatment: “bacteria urine” in a 9 year-old male subject in the M3/180 mcg arm.

AstraZeneca reports that a statistically significant increase was noted (ANCOVA on the mean change from baseline to the end of treatment) in white cell count in the M3/360 BID treatment arm. Based on subsets of the patient population (numbers of subjects between 66 and 77 subjects), baseline white counts were approximately equal across treatment groups (approximately $6.5 \times 10^9/l$). The difference between placebo and the M3/360 BID, M0-ESP/400 BID, M3/180 QD, and the M0-ESP 200 QD was approximately $0.6 \times 10^9/liter$, $0.16 \times 10^9/l$, $0.05 \times 10^9/l$, and $-0.01 \times 10^9/l$. While there appears to be a slight dose relation of these results, the significance of these results is unclear. They are based on a subset of the randomized subjects, and the numbers of subjects who shifted from normal to high ($13 \times 10^9/liter$) white counts did not show a trend.

Review of shift data for other hematologic and chemistry parameters did not show a trend to suggest a toxicity of Pulmicort or of a difference between the M0-ESP and the M3.

EKGs were not assessed.

10.1.30.6 Concomitant medications

There was no concerning pattern of increased use of particular concomitant medications among the active treatment groups.

10.1.31 Summary of trial 0726

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. 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 trial population. The principal findings of the trial were:

- All treatment arms separated from placebo statistically on the primary endpoint, FEV₁ % predicted. In the twice-daily treatment comparison, the M3 device arm showed a larger treatment effect.
- 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 these 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.
- Peak expiratory flow rates measured at home were higher in the high-dose M3 treatment arm than in the other treatment arms. The importance of this is lessened by the fact that PEF is a home-measured outcome, and is less reliable than spirometrically-measured outcomes (FVC, FEF₂₅₋₇₅, FEV₁).
- Pharmacokinetic analysis showed a similar pattern to that in the adult/adolescent trial, but were based on small numbers of subjects, and firm conclusions cannot be drawn from it. This 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.

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This trial did not test the M3 device containing the to-be-marketed dose content. However, the results of trial 0620 indicate that any differences between the device tested and the to-be-marketed device would be negligible.

In summary, the trial showed a slightly greater effect of the M3 device on the primary endpoint. Overall, the relatively weak support from the secondary endpoints was probably due to the relatively well population of subjects with asthma who were tested. Where differences occurred, the M3 high-dose arm produced slightly better results than the M0-ESP high-dose treatment arm.

No new safety concerns emerged in trial 0726.

10.1.32 Review of Pertinent Results from Previously Submitted Trials

The designs of clinical trials 04-CR-3020A (GHBA-165) and 04-CR-3023A (GHBA-168) are summarized in Table 3. Subjects for these trials were predominantly taking inhaled corticosteroids, in which respect they resembled those in clinical trial 0620 and would be expected to be more severely affected than those in trial 0726.

Table 97, as represented in the original IND review, summarizes the FEV₁ component of the primary endpoint results for trial GHBA-165.

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Table 97. 04-CR-3020A (M0 device) primary endpoint results (FEV₁) as shown in original NDA review

TABLE 2.3.2A. FEV₁: Mean baseline, change from baseline in liters and as percentages.

	Placebo		PULMICORT, mcg BID							
			100		200		400		800	
n	82		91		92		97		97	
Baseline	2.08		2.054		2.056		2.056		1.97	
Weeks 2	-0.09	-4.1%	0.12	5.8%	0.26	12.8%	0.18	8.7%	0.22	11.4%
Weeks 4	-0.18	-8.6%	0.15	7.3%	0.23	11.1%	0.20	9.9%	0.27	13.9%
Weeks 8	-0.21	-9.9%	0.15	7.5%	0.27	13.1%	0.26	12.4%	0.29	14.7%
Weeks 12	-0.21	-10%	0.15	7.3%	0.24	11.5%	0.24	11.8%	0.29	14.6%
Weeks 0-12	-0.17	-8.0%	0.14	6.9%	0.25	12.1%	0.22	10.7%	0.27	13.7%
P value vs placebo wks 0-12			<.001		<.001		<.001		<.001	

In contrast to the results of trial SD-004-0626, FEV₁ in placebo subjects deteriorated during the clinical trial. The 100 µg BID dosing arm showed an approximate 0.3 liter difference from placebo, which was less than all the other doses tested, but statistically different from placebo.

Peak expiratory flow results showed a similar pattern of effect and all dose comparisons to placebo were different from placebo with p-values < 0.001.

Table 98, as represented in the original IND review, summarizes the FEV₁ % predicted component of the primary endpoint results for trial GHBA-168.

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Table 98. 04-CR-3023A (M0 device) primary endpoint results (FEV₁) as shown in original NDA review

TABLE 5.3.2A. FEV₁ (percent predicted): Baseline and mean change from baseline.

	Placebo	100 mcg BID	200 mcg BID	400 mcg BID
n	97	99	99	99
Baseline	73.8	75.68	74.55	74.75
Change at...				
Week 2	-4.02	3.02	7.22	6.99
Week 4	-5.62	2.15	6.89	7.56
Week 8	-4.59	3.79	8.98	7.62
Week 12	-4.48	3.56	7.74	7.04
Weeks 0-12 average	-4.64	3.13	7.71	7.30
P values vs placebo weeks 0-12		<0.001	<0.001	<0.001

In contrast to the results of trial SD-004-0720, FEV₁ % predicted in placebo subjects deteriorated during the clinical trial. The 100 µg BID dosing arm showed an approximate 7.6-point difference from placebo, which was less than either other doses tested, but statistically significant from placebo.

Peak expiratory flow results showed a dose-related pattern of effect; all doses were different from placebo with p-values < 0.001.

10.2 Line-by-Line Labeling Review

This section of the review will be addressed after this review is made final.

10.3 REFERENCES

1. Saag KG, Furst DE, Drazen JM. Major side effects of inhaled corticosteroids. UpToDate version 14.1, August 22, 2005.
2. Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention. NIH Publication 02-3659, updated 2004.

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James Kaiser
5/17/2006 04:32:39 PM
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1. Regulatory Background

AstraZeneca (AZ) submitted this NDA for the Pulmicort Turbuhaler (budesonide inhalation powder) on September 12, 2005. Although the Pulmicort Turbuhaler has been marketed since 1997, the information contained in the current submission is intended to represent a significant change in the delivery of budesonide (see “Changes to the product” below) and so merits an independent NDA.

The original NDA application contained information on 100 mcg, 200 mcg, 400, and 800 mcg devices. The 100 mcg device exhibited unacceptable dose content uniformity; AZ decided only to market the 200 mcg device. In response to a postmarketing commitment, AZ developed and obtained approval in 2000 to market a modified device called the “M0-ESP,” which is the currently marketed product. The product proposed in the current application is termed “M3.” AZ intends to discontinue marketing the M0-ESP if the M3 is approved.

This is a 505(b)(1) application.

The M3 inhaler is not approved or marketed in any country.

2. Changes To The Product

Important changes to the product include:

- The currently approved device meters 200 mcg per puff; AZ proposes to market a 180 mcg metered dose and a 90 mcg metered dose device.
- The formulation now includes lactose
- The process by which the product is prepared (“spheronisation”) has been modified
- The device includes a new dose indicator and a new cleaning feature

3. Summary Of The Contents Of The Submission

The application is submitted electronically, and includes information in Common Technical Document Modules 1, 2, 3, and 5.

1. Clinical data

The principal trials submitted are 12-week, randomized double-blind, placebo-controlled trials:

New trials

- SD-004-0620 randomized adults with asthma. It studied metered doses of 180 mcg QD and 360 mcg BID using the M3 device that meters 180 mcg, and 200 mcg QD and 400 mcg BID using the currently approved device.
- SD-004-0726 randomized a pediatric population with asthma. It studied the same doses, but studied the M3 device that meters 90 mcg.

Data from the trials are submitted.

Previously submitted trials

AZ resubmitted clinical trial reports intended to support the lowest proposed dose (see summary of labeling changes). These trials were submitted with the original NDA and study the M0 device:

- 04-3020A (called GHBA 165 in the original NDA review) was performed in adults on inhaled corticosteroids, with or without oral corticosteroid, studying 100, 200, 400, and 800 mcg BID.
- 04-3023a (called GHBA 168 in the original NDA review) was performed in subjects 6-18 years old previously treated with inhaled corticosteroid, studying 100, 200, and 400 mcg BID.

Data from the trials are submitted.

AZ has also submitted summary safety information regarding subjects who have received the M3 device in seven other clinical trials. Summaries of clinical safety and efficacy are submitted.

Device and chemistry information are submitted. The discussion of the adequacy of these data is left to the respective review divisions.

Required elements of an NDA submission

The required elements of an NDA submission are present.

4. Proposed Labeling

The applicant proposes numerous changes in the currently approved package insert. The most noteworthy changes to the labeling include 1) the elimination of reference to a 200 mcg dose strength and replacement with reference to a 180 mcg and 90 mcg dosage strength with proportionate changes to recommended dosages, and 2) proposal for a

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5. Clinical information in newly submitted trials

This section of the review presents notable efficacy information in the newly submitted trials, as submitted. It does not contain a critical review of the data. The information is presented here solely to provide background to a discussion of review issues.

1. Adult trial SD-004-0620. After a run-in period 621 asthmatic adults were randomized at 90 centers in the US and Asia to M3, M0-ESP, or placebo inhalers for 12 weeks of treatment. The primary endpoint was the difference between baseline FEV₁ and the treatment period mean. Subjects were to have been treated with inhaled corticosteroids for at least 3 months. Table 2 shows the treatment arms:

Table 2: Adult trial SD-004-0620 treatment arms

Device	Dose & frequency	# puffs/dose
M3	360 BID	2
M0-ESP	400 BID	2
M3	180 Q am	1
M0-ESP	200 Q am	1
Placebo	Q am/ BID (2 arms)	1 or 2

The trial tested the 180 mcg M3 device against the approved device.

Table 3 shows efficacy results as presented by the applicant:

Table 3: Adult trial SD-004-0620 differences from pooled placebo (FEV₁)

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

Based on my preliminary review, there do not appear to be any major safety issues. There were no deaths in the trial. Two subjects had serious adverse events, both on the approved device.

One conduct issue is noted: The applicant increased the budesonide content of the device after the trial had started. This will be a review issue.

2. Pediatric trial SD-004-0726. After a run-in period 516 asthmatic subjects 6-17 years old were randomized at 84 centers in the US and Asia to M3, M0-ESP, or placebo inhalers for 12 weeks of treatment. The primary endpoint was the difference in between baseline percent predicted FEV₁ and the treatment period mean. The great majority of subjects were not treated with inhaled corticosteroids prior to enrollment. Table 4 shows the treatment arms:

Table 4: Pediatric trial SD-004-0726 treatment arms

Device	Dose & frequency	# puffs/dose
M3	360 BID	4
M0-ESP	400 BID	2
M3	180 Q am	2
M0-ESP	200 Q am	1
Placebo	QD/ BID (4 arms)	To match

The trial tested the 90 mcg M3 device against the approved device.

Table 5 shows efficacy results as presented by the applicant:

Table 5: Pediatric trial SD-004-0726 differences from pooled placebo (FEV₁ % predicted)

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

Based on my preliminary review, there do not appear to be any major safety issues. There were no deaths in the trial. One subject on the approved device experienced a serious adverse event of gastric pain; two subjects on a placebo device experienced serious adverse events.

The applicant increased the budesonide content of the device after the last resupply of products for the clinical trial. This will be a review issue.

6. Filing Decision

The application contains all the requisite components and may be filed.

Review issues identified to this point are:

- AZ increased the product content of the device it studied in the newly submitted adult trial, and intends to market the increased-dose device. The marketing application will be reviewed to determine whether the data are adequate to support approval of the device to be marketed.
- Both the newly submitted adult and pediatric trials showed the least efficacy with the lowest dose administered by means of the M3 device. In the adult trial, the difference between this lowest treatment arm and placebo did not meet the nominal standard of statistical significance. ~~_____~~
- AZ is proposing consideration of the use of 90 mcg and 720 mcg twice daily, treatment regimens that were not studied in the newly submitted trials. The marketing application will be reviewed to determine if the data are adequate to support this dosing.

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7. Comments to the Applicant

The following comment will be sent to the applicant.

1. Please describe the basis for the selection of case report forms submitted in the application.

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

/s/

James Kaiser
11/2/2005 12:28:45 PM
MEDICAL OFFICER

Peter Starke
11/2/2005 12:55:13 PM
MEDICAL OFFICER
I concur.

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