U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	sNDA021929
Supplement #:	s-013
Drug Name:	SYMBICORT AC pMDI 80/4.5
Indication(s):	Asthma
Applicant:	AstraZeneca Pharmaceuticals LP
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Keywords: crossover design, dose-response, combination drug

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1 EXECUTIVE SUMMARY

AstraZeneca Pharmaceuticals LP has submitted this supplemental new drug application (sNDA) 21929/S-013, for SYMBICORT® (budesonide/formoterol) inhalation aerosol to support the maintenance treatment of asthma in patients 6 years of age to < 12 years. The proposed dose is 80/4.5 μg, 2 actuations twice daily (bid). The developmental program included a budesonide dose selection study (Chase 1), a formoterol dose selection study (Chase 2), and a confirmatory efficacy study of the SYMBICORT combination product (Chase 3).

In Chase 1 study, budesonide 160 μg bid (80 μg x 2 inhalations bid) was superior to placebo in improving pre-dose morning peak expiratory flow (PEF) and in-clinic morning pre-dose forced expiratory volume in one second (FEV1) from baseline to treatment period average. The treatment effect of 13.6 L/min for PEF (p-value<0.0001) and 0.06 L for FEV1 (p-value=0.0047) were in favor of budesonide. Other efficacy variables such as lung function measures and asthma symptoms were numerically supportive. A large proportion of patients (approximately 30%) discontinued the study due to pre-defined asthma events, but additional sensitivity analyses supported the efficacy of budesonide as a single ingredient product to treat asthma patients.

In Chase 2 study, all 3 formoterol doses (2.25 μg, 4.5 μg, and 9.0 μg) given in combination with budesonide 160 μg provided statistically significant improvements in lung function compared with placebo plus budesonide 160 μg therapy. Results showed a dose response of formoterol for the primary endpoint of FEV1 averaged over 12 hours post-dose and supported formoterol doses of 4.5 μg and 9.0 μg in the combination product with the 9.0 μg dosage strength showing numerically similar results compared to the active control Foradil Aerolizer.

In Chase 3 study, treatment with SYMBICORT 80/4.5 μg led to a statistically significant increase in lung function measured by the primary endpoint of change from baseline to Week 12 in 1-hour post-dose FEV1. In patients receiving SYMBICORT 80/4.5 μg, 1-hour post-dose FEV1 improved by 0.28 L from baseline to Week 12, as compared with 0.17 L for those receiving budesonide (mean difference 0.12 L; 95% CI: 0.03, 0.20, p-value=0.006). Findings from various sensitivity analyses were consistent with the primary results. Therefore, this study confirmed the efficacy of SYMBICORT 80/4.5 μg and demonstrated the contribution of the formoterol component to the efficacy of the combination product. It should be noted that besides the primary endpoint, statistically significant comparisons (nominal p-value<0.05) were only observed for a few post-dose lung function tests, such as change from baseline to Week 12 for 1-hour post-dose forced mid-expiratory flow between 25% and 75% of forced vital capacity (FEF25_75), PEF, and 15-minute post-dose FEV1. There were no statistically significant differences between SYMBICORT 80/4.5 μg and budesonide for other efficacy outcomes, including change from baseline to Week 12 for 1-hour post-dose forced vital capacity (FVC) or any of the pre-dose lung function, health-related quality of life, or symptom-related variables, or for time to first asthma exacerbation or time to treatment discontinuation. It is recommended that results for quality of life or symptom-related parameters be included in the labeling since these are direct measures of how patients function and feel in daily life.

In summary, these studies provided adequate support for the effectiveness of SYMBICORT 80/4.5 μg, 2 inhalations bid, for the treatment of asthma in patients aged 6 to <12 years old.

2 INTRODUCTION

2.1 OVERVIEW

2.1.1 Drug Class and Indication

This resubmission to NDA 21929/S-013 is being provided for SYMBICORT pressurized metered-dose inhaler (pMDI) to support the maintenance treatment of asthma in patients 6 years of age to < 12 years. SYMBICORT pMDI, marketed in the United States (US) under the name SYMBICORT Inhalation Aerosol, is a fixed-combination product containing budesonide, an inhaled corticosteroid (ICS), and formoterol fumarate dehydrate (hereafter formoterol), a long-acting β2-agonist (LABA) with a rapid onset of action.

2.1.2 History of Drug Development

SYMBICORT pMDI was approved in July 2006 for the long-term maintenance treatment of asthma in patients 12 years of age and older (NDA 21-929). It was approved in February 2009 for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The approved dosage strengths for asthma in patients 12 years of age and older are SYMBICORT 80/4.5 μg (budesonide 90 μg + formoterol fumarate dihydrate 4.5 μg) or SYMBICORT 160/4.5 μg (budesonide 160 μg + formoterol fumarate dihydrate 4.5 μg) 2 inhalations daily (bid).

A supplemental New Drug Application (sNDA) was submitted to the FDA on 3 June 2008 in support of extending the indication for the long-term maintenance treatment of asthma in pediatric patients 6 to <12 years of age (NDA 21929/S-013). This sNDA consisted of seven completed studies: one Phase 1 pharmacokinetic study, five Phase 3 active-controlled efficacy and safety studies, and one Phase 3 device functionality study. Only one of the studies had a factorial design which evaluated the contribution of the individual components to the combination drug product. Although the primary endpoint pre-dose morning PEF for the budesonide component met statistical significance, the secondary endpoint pre-dose FEV1 did not. The FDA issued a complete response (CR) letter for this supplement on 3 April 2009, citing deficiencies and further stating that the Pediatric Research Equity Act (PREA) requirements regarding the development of prescription drugs for use in children had not been met. To support approval in patients 6 to <12 years of age, the FDA advised that the following should be provided:

a. Data to establish efficacy and safety of appropriate dose or doses of budesonide inhalation aerosol and dose of formoterol inhalation aerosol as single ingredient products for patients 6 to 11 years of age, and provide convincing evidence of the contribution of the selected dose or doses of the individual components to SYMBICORT Inhalation Aerosol.

b. A comparative assessment of various dosage strengths of SYMBICORT Inhalation Aerosol to justify approval of the various strengths

The applicant had several interactions with the FDA, including a Type C meeting 28 July 2009 that discussed the CR letter, an End-of-Phase 2 Type C meeting on 30 July 2013 which discussed the design and dose selection for the Phase 3 study, and two Type C meetings (23 December 2015 and 11 March 2016) via written responses. A formal Written Request for pediatric studies was issued by the FDA on 28 January 2011 (amended 5 May 2011, 6 April 2012, 9 March 2015, and 19 October 2015), which stated that the studies to be conducted should have the following objectives:

Study 1: To determine the appropriate dose(s) of budesonide HFA pMDI for pediatric patients 6 to <12 years of age to be carried into the combination product.

Study 2: To determine the appropriate dose(s) of formoterol HFA pMDI for pediatric patients 6 to <12 years of age to be carried into the combination product. The study will evaluate at least 3 doses of formoterol fumarate in an HFA pMDI formulation to find a dose that provides comparable bronchodilation with that of an approved formulation and dose of formoterol fumarate in this age group.

Study 3: To demonstrate the efficacy and safety of SYMBICORT HFA pMDI as a fixed dose combination containing budesonide and formoterol compared with the corresponding dose or doses of budesonide HFA pMDI monotherapy, each administered as 2 inhalations twice daily, in children aged 6 to <12 years not adequately controlled on low-dose ICS. The dose or doses of budesonide and formoterol to be used in Study 3 will be determined by the results of Studies 1 and 2.

Pertinent statistical parts of these meetings and correspondences are summarized herein:

- *Study 1:* A minimum of 133 patients per treatment group (2 or more groups) must be randomized and treated with at least one dose of study treatment.
- *Study 2:* An adequate number of patients must be randomized to obtain a minimum of 50 completed patients (patients who completed all treatment periods).
- *Study 3:*
  - The proposed trial design using budesonide as active comparator was acceptable and the doses of formoterol in the Phase 3 trial were 4.5 μg bid (2.25 μg × 2 inhalations bid) and 9 μg bid (4.5 μg × 2inhalations bid).
  - The study intended to randomize approximately equal numbers of children <9 years of age and children aged 9 years and over in the study.
  - The primary endpoint was 1-hour post-dose FEV1 and the primary analysis should be based on change from baseline to the end of treatment (Week 12). The average 1-hour post-dose FEV1 would be a secondary analysis.
  - The primary analysis should use all clinic FEV1 data from all patients, regardless of discontinuation of investigational product (IP).

- For all three studies, the primary analysis of efficacy should be based on an analysis set that include all randomized patients who took at least one dose of study medication.

Accordingly, the CHASE program of three studies (D589GC00001, referred to as Chase 1; D589GC00002, referred to as Chase 2; D589GC00003, referred to as Chase 3) was initiated and conducted under IND 63394 to meet the terms of the SYMBICORT pediatric Written Request, to address the deficiencies identified in the CR letter, and to fulfil PREA Post Marketing Requirements (PREA PMR #1749-2). With this resubmission, the applicant intends to seek approval for SYMBICORT 80/4.5 for the treatment of asthma in patients 6 years of age and older.

2.1.3 Current Submission

The purpose of this resubmission is to respond to the CR letter for NDA 21929/S- 013, to fulfil the requirements of PREA PMR #1749-2), and to request Pediatric Exclusivity for SYMBICORT. The current package contains two Phase 2 studies (Chase 1 and Chase 2) and one Phase 3 study (Chase 3) in support of SYMBICORT 80/4.5 μg for treatment of asthma in children 6 to <12 years of age. The Chase 1 and Chase 2 studies address CR letter deficiency point a) on appropriate dose for each monotherapy while the Chase 3 study addresses CR letter point b) of the data required to support approval in the pediatric population, ie, "comparative assessment of various dosage strengths of SYMBICORT Inhalation Aerosol to justify approval of the various strengths."

These three studies are the focus of this statistical review.

2.2 DATA SOURCES

The applicant submitted clinical study reports, protocols, statistical analysis plans, and all referenced literature to the Agency. The data and all documents for the electronic submission were archived under the network path location:

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3 STATISICAL EVALUATION

3.1 DATA AND ANALYSIS QUALITY

In general, the electronic data submitted by the applicant are of sufficient quality to allow a thorough review of the data. I am able to reproduce the analyses of the primary and key secondary efficacy endpoints for each clinical study submitted. My results are presented in this review and match those from the applicant unless otherwise noted.

3.2 EVALUATION OF EFFICACY

The chase program consists of two Phase 2 studies and one Phase 3 trial, which are reviewed in this document. Outline of the study designs is given in Table 1.

Study D589GC00001 (Chase 1): A Phase 2, double-blind, randomized, parallel-group, placebo-controlled, multicenter study, comparing budesonide pMDI 160 µg bid with placebo: a 6-week efficacy and safety study in children aged 6 to <12 years with Asthma

Study D589GC00002 (Chase 2): A Phase 2, randomized, blinded, 5-period cross-over, placebo and active-controlled, multicenter, dose-finding study of single doses of formoterol 2.25 µg, 4.5 µg, and 9 µg delivered via SYMBICORT pMDI and Foradil® Aerolizer® 12 µg evaluating the bronchodilating effects and safety in children, ages 6 to <12 years, with asthma who are receiving background treatment with budesonide pMDI 160 µg bid

Study D589GC00003 (Chase 3): A Phase 3, 12-week, double-blind, randomized, parallel-group, multicenter study investigating the efficacy and safety of SYMBICORT pMDI 80/2.25 µg, 2 actuations twice daily, and SYMBICORT pMDI 80/4.5 µg, 2 actuations twice daily, compared with budesonide pMDI 80 µg, 2 actuations twice daily, in children ages 6 to <12 Years with asthma

Table 1 Design of Chase Trials

Study	D589GC00001 CHASE 1	D589GC00002 CHASE 2	D589GC00003 CHASE 3
Trial Date	8/7/2011 to 4/5/2013	10/7/2010 to 1/3/2012	4/14/2014 to 4/14/2016
Centers	72	19	88
Number of Patients	304	54	279
Population	Age 6-11 years with asthma with PEF ≥50% predicted on daily ICS 375-1000 mcg/d	Age 6-11 years with asthma all receiving background budesonide 160 mcg BID	Age 6-11 years with asthma on med- to high-dose ICS or ICS/LABA, not controlled on low-dose ICS during run-in
Design	Randomized (1:1), double-blind, placebo-controlled, parallel-group 6 weeks	Single-dose, Randomized (1:1:1:1:1), blinded, 5-period crossover 4-8 weeks	Randomized (1:1:1), double-blind, active-controlled, parallel-group 12 weeks
Treatment	Bud 80, 2 bid (Bud 160) Placebo, 2 bid	Bud 160/FM 2.25 (SYM 80/2.25) Bud 160/FM 4.5 (SYM 80/4.5) Bud 160/FM 9.0 (SYM 80/9) Bud 160/Placebo (Bud 80, 2 bid) Bud 160/Foradil 12.0	SYM 80/2.25, 2 bid SYM 80/4.5, 2 bid Bud 80, 2 bid (Bud 160)
Primary Endpoint	morning PEF	Average 12-hour FEV_1	1-hour post-dose FEV_1

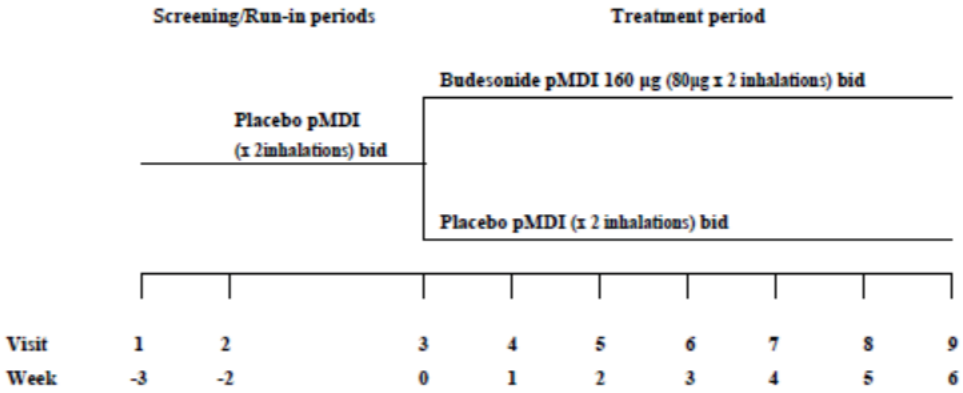
Source: Reviewer

3.2.1 Study D589GC00001 (Chase 1)

3.2.1.1 Study Design and Endpoints

Chase 1 was a 6-week, randomized, double-blind, parallel-group, placebo-controlled, multicenter, Phase 2 efficacy and safety study comparing inhaled budesonide 160 µg bid (as 80 µg pMDI x 2 actuations) with placebo in pediatric patients with asthma ages 6 to <12 years who demonstrate the need for inhaled glucocorticosteroid(s)(ICS) controller therapy. Following a run in or qualification period of 7 to 21 days, eligible patients were stratified by age group (<8 years and ≥8 years) and randomly assigned in a blinded fashion (1:1) to one of the two treatment groups: budesonide pMDI 160 µg bid (80 µg x 2 inhalations bid) or placebo pMDI (2 inhalations or actuations bid). Patients received study drug over the 6-week treatment period and had weekly study visits for lung function evaluations. A daily electronic diary (eDairy) was used by patients to record disease status and evaluated by investigators to determine if patients had experienced a "pre-defined asthma event" as specified in the protocol. Some of these events, such as a decrease in morning pre-dose FEV1 ≥20% since randomization or a clinical exacerbation requiring emergency treatment, would mandate subject withdrawal from the study. Other pre-defined asthma events, for example, nighttime awakenings due to asthma that required the use of reliever medication, would not require study termination if patients were otherwise clinically well and stable as determined by the investigator. The flow chart of Chase 1 study is depicted in Figure 1.

Figure 1 Chase 1 study design



Source: Chase 1 study report Figure 1.

The primary efficacy variable in this study was the change in pre-dose morning peak expiratory flow (PEF) from baseline (mean of last 7 days of run-in period) to the treatment period average (i.e. average of the available data in the treatment period). The PEF was collected in an electronic daily diary. The run-in period was defined as any day between the date of first dose of run-in placebo (visit 2) up until the date of first dose of randomized treatment (visit 3) including pre-dose measurements at visit 3 only. The treatment period was defined as any day between the date of first dose of randomized treatment (including post-dose measurements at visit 3 only) to the date of study completion/discontinuation inclusively.

The key secondary variable was the change from baseline to the treatment period average for in-clinic pre-dose forced expiratory volume in one second (FEV1). Other secondary efficacy measures included:

- change from baseline to the treatment period average and end of treatment for
  - in-clinical spirometry measures:
    - pre-dose FEV1
    - forced vital capacity (FVC)
    - forced mid-expiratory flow between 25% and 75% of the FVC (FEF25-75).
  - diary variables:
    - morning PEF(end of treatment average only),
    - evening PEF
    - morning and evening eFEV1
    - asthma symptom scores (daytime, nighttime and total daily)
    - percentage of nighttime awakenings (overall and with reliever medication use)
    - reliever medication use (daytime, nighttime and total inhalations/day).
- Time to withdrawal due to pre-defined asthma event
- Time to first pre-defined asthma event

3.2.1.2 Statistical Methodologies

The following analysis datasets were defined in the protocol:

- All randomized patients set: contained patients who were randomized and were used for summarizing the demographic and patient characteristics data.
- Efficacy analysis set (EAS): consisted of all patients who were randomized, took at least one dose of study medication, and contributed data for at least one efficacy endpoint. Patients were accounted for according to treatment as they were randomized, regardless of treatment actually received.
- Per-Protocol analysis set: included all patients in the full analysis set except those with major protocol deviations and/or systemic corticosteroid use, as described in the statistical analysis plan. Analyses on the Per-Protocol analysis set were to be performed only if 20% or more of the patients were excluded.
- Safety analysis set: included all randomized patients who took at least one dose of study medication and had data collected after randomization.

The primary variable was analyzed using an analysis of covariance (ANCOVA) model with terms for treatment, age group (<8 years and ≥8 years of age) and country with baseline morning PEF as a covariate. Treatment comparisons were made within the context of this model using appropriate contrasts. The key secondary variable pre-dose FEV1, along with FVC and FEF25-75 from spirometry, were analyzed using an ANCOVA model similar to the primary analysis. The model compared treatment groups, with a term for country, age group (<8 years and ≥8 years of age) and adjusting for the covariate of baseline value of the variable. For secondary diary variables, the same approach was utilized and the ANCOVA model included terms for treatment, country, age group (<8 years and ≥8 years of age) with adjustment for baseline value of the respective analysis variable. Time to the first pre-defined asthma event and time to

withdrawal due to a predefined asthma event were analyzed using a log-rank test. For patients completing the study without a pre-defined asthma event, this variable was censored at the day of study completion up to a maximum of the last randomized dose day. For patients who withdraw from the study for reasons other than a predefined asthma event, this variable was censored at the last day of treatment.

A step-down procedure was applied to the primary endpoint and key secondary endpoint to adjust for multiplicity. If the treatment difference for the primary variable, morning PEF, was statistically significant (p-value<0.05), then the key secondary variable, FEV1, would be tested at the 0.05 level of significance. For all other variables, nominal p-values were reported.

Two sensitivity analyses were conducted by the applicant on the primary efficacy endpoint and key secondary endpoint:

- End of treatment average: Analyses performed on change from baseline to end of treatment average defined as the mean of the last 7 available treatment days.
- Treatment Period Average using last observation carried forward (LOCF): LOCF carried forward the mean of a patient's last 3 observations (into all missing days post last observation up to and including day 42) for the patients who terminated the study prematurely. No baseline values were carried forward.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

The Chase 1 study randomized 304 patients; all received at least one dose of study drug (Table 2). Patients who discontinued treatment also withdrew from the study. A total of 91 patients (29.9%) did not complete the study, with more in the placebo group (39.5%) than the budesonide group (20.4%). The most common reason for withdrawal from the study was development of study-specific withdrawal criteria, accounting for 75 (24.7%) of the 91 withdrawal patients. The number of patients withdrawn due to development of study-specific withdrawal criteria was 50 (32.9%) in the placebo group and 25 (16.4%) in the budesonide group, respectively (see more discussion in Section 3.2.1.4). The efficacy analysis set included all 304 randomized patients.

Table 2 Patient disposition in the Chase 1 study

	Placebo	Bud 160 N (%)	Total N (%)
Randomized	152	152	304
Never dosed	0	0	0
Treated	152 (100%)	152 (100%)	304 (100%)
Completed treatment	92 (60.5%)	121 (79.6%)	213 (70.1%)
Discontinued treatment	60 (39.5%)	31 (20.4%)	91 (29.9%)
Completed study	92 (60.5%)	121 (79.6%)	213 (70.1%)
Discontinued study	60 (39.5%)	31 (20.4%)	91 (29.9%)
Discontinue due to pre-defined asthma event	50 (32.9%)	25 (16.4%)	75 (24.7%)
Discontinue due to other reason	10 (6.6%)	6 (4.0%)	16 (5.2%)
Analysis Datasets			
All Randomized Analysis Set	152	152	304
Efficacy Analysis Set	152	152	304
Safety Analysis Set	152	152	304
Per-Protocol Set	132	134	266

Source: Reviewer

In Chase 1 study, baseline demographic characteristics were similar between treatment groups (Table 3). Most patients randomized were White, male, and aged 8 years or older.

Table 3 Chase 1 Study demographics and baseline characteristics (All Randomized Analysis Set)

	Placebo (N=152)	**Bud 160 (N=152)**	**Total (N=304)**
Age (years)	n=152	n=152	n=304
Mean	9.0	9.0	9.0
SD	1.62	1.63	1.62
Median	9.0	9.0	9.0
Age group, n (%)			
<8 years	33 (21.7%)	33 (21.7%)	66 (21.7%)
≥8 years	119 (78.3%)	119 (78.3%)	238 (78.3%)
Gender, n (%)			
Male	94 (61.8%)	98 (64.5%)	192 (63.2%)
Female	58 (38.2%)	54 (35.5%)	112 (36.8%)
Race, n (%)			
White	138 (90.8%)	132 (86.8%)	270 (88.8%)
Black or African American	7 (4.6%)	13 (8.6%)	20 (6.6%)
Asian	0	1 (0.7%)	1 (0.3%)
Other	7 (4.6%)	6 (3.9%)	13 (4.3%)
Ethnicity, n (%)			
Hispanic or Latino	10 (6.6%)	11 (7.2%)	21 (6.9%)
Non-Hispanic or non-Latino	142 (93.4%)	141(92.8%)	283 (93.1%)
Region, n (%)			
US	54 (35.5)	56 (36.8)	110 (36.2)
Non-US	98 (64.5)	96 (63.2)	194 (63.8)
FEV1 (L) at randomization			
Mean	1.70	1.69	1.70
SD	0.416	0.388	0.401
Median	1.70	1.67	1.67

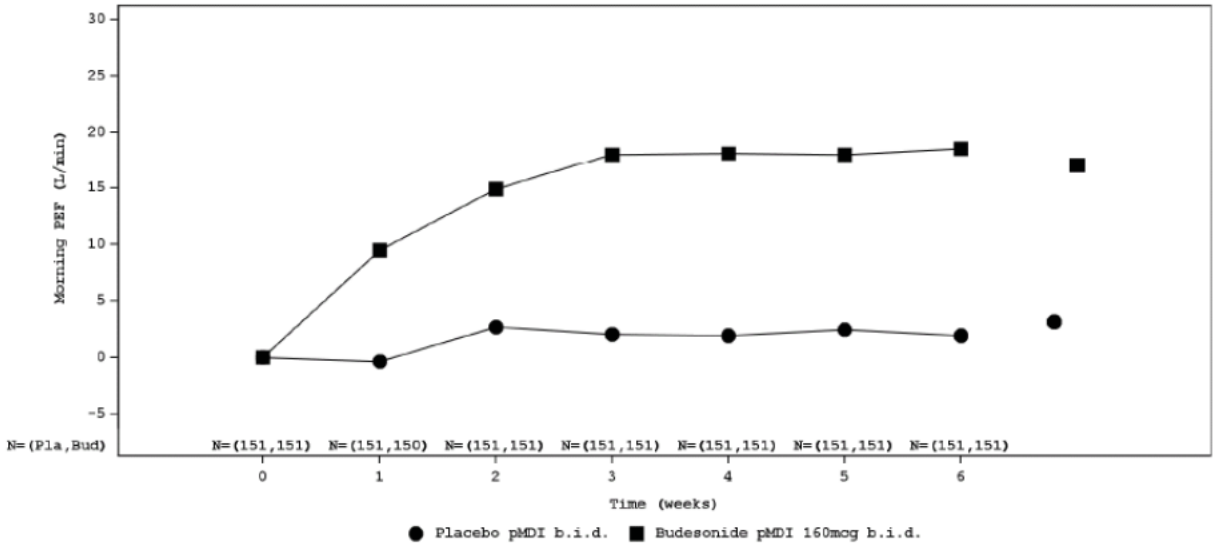
Source: Reviewer

3.2.1.4 Results and Conclusions

3.2.1.4.1 Primary Endpoint

The primary endpoint was the change in pre-dose morning PEF from baseline to the treatment period average. As shown in Figure 2, a greater improvement from baseline in mean morning PEF for the budesonide group was observed compared with placebo, beginning at Week 1 and continuing throughout the 6-week treatment period. In Chase 1, patients receiving budesonide had statistically significantly higher improvement compared to placebo (Table 4). The treatment effect (13.6 L/min) was in favor of budesonide and was statistically significant ($p<0.0001$). The results were based on the efficacy analysis dataset (EAS).

Figure 2 Change from baseline in pre-dose morning PEF weekly means (EAS)



Data points are means of the individual patient weekly mean change from baseline (including LOCF) values. Treatment Period Averages (excluding LOCF values) are also plotted (at end) for each treatment group.

Source: Chase 1 study report Figure 11.2.1.1.2.2

Table 4 Primary Analysis: Pre-dose morning PEF from patient diaries (EAS)

Statistics	Placebo (N=152)	Bud 160 (N=152)	Treatment Difference (Budesonide – Placebo)
Baseline mean	207.5	205.2	
Treatment period average	210.7	222.2	
LS mean change			
Estimate	4.1	17.8	13.6
95% CI			(7.5, 19.7)
p-value			<0.0001

Source: Reviewer

As noted in Section 3.2.1.3, there was a substantial amount of missing data in the Chase 1 study attributable to the fact that it was a placebo-controlled trial and there were patient withdrawals due to asthma worsening by design. The study discontinuation rate was 39.5% in the placebo group and 20.4% in the budesonide group, respectively. The applicant examined the impact of patient withdrawal on the primary endpoint by analyzing morning PEF from baseline to end of treatment average and from baseline to LOCF treatment average. Results were consistent with the analysis for treatment period average (Table 5).

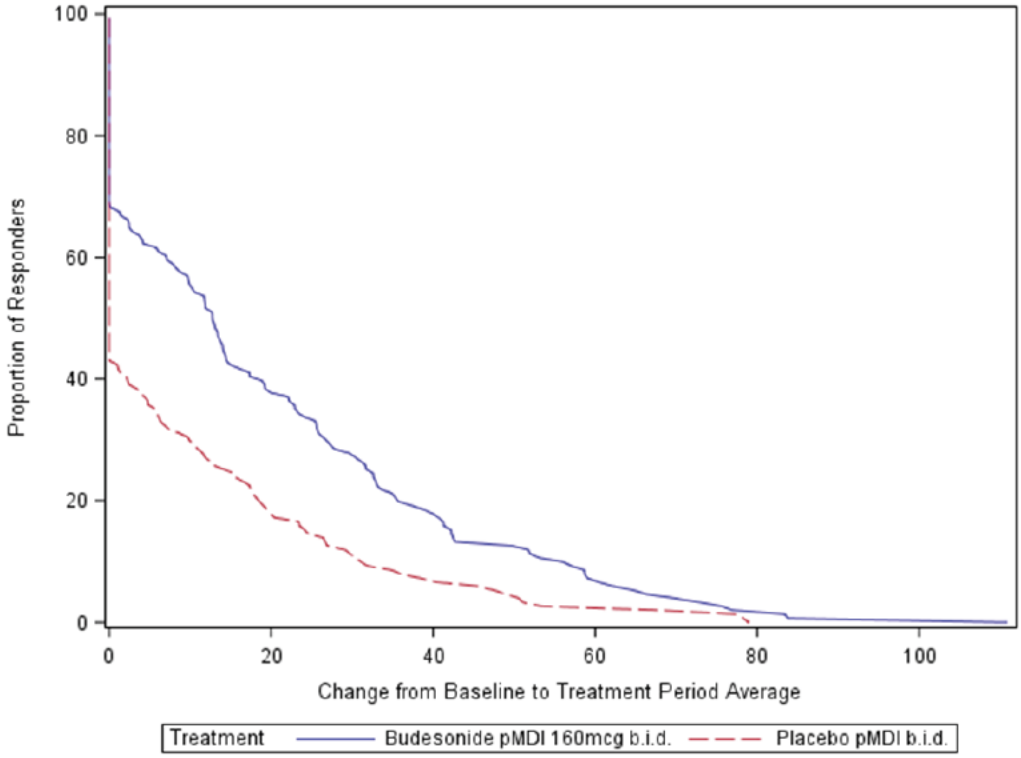
Table 5 Sensitivity analyses: Pre-dose morning PEF from patient diaries (EAS)

Statistics	Placebo (N=152)	Bud 160 (N=152)	Treatment Difference (Budesonide – Placebo)
Baseline mean	207.5	205.2	
End of Treatment average	209.9	224.1	
LS mean change			
Estimate	3.3	19.4	16.2
95% CI			(7.9, 24.5)
p-value			0.0001
LOCF Treatment average	209.2	221.7	
LS mean change			
Estimate	2.2	16.8	14.6
95% CI			(8.1, 21.0)
p-value			<0.0001
Treatment period average (assuming no change for dropouts)	210.7	222.2	
LS mean change			
Estimate	9.5	20.1	10.6
95% CI			(5.7, 15.5)
p-value			<0.0001

Source: Reviewer

To further investigate the potential impact of missing data on the treatment comparison, I conducted a cumulative proportion of responder analysis for the primary efficacy endpoint, change in pre-dose morning PEF from baseline to treatment period average. In this analysis, patients who discontinued from the study regardless of reason are considered as having the least favorable outcome. The worst value is imputed to missing post-baseline observations. This approach seems reasonable, especially because most patients who discontinued treatment did so because of asthma worsening and therefore did not benefit from the study therapy. Figure 3 provides a visual display of the range of different levels of PEF response and the corresponding percentage of patients achieving that level of response. Compared with placebo treatment, there is clear evidence that a higher proportion of patients treated with budesonide responded better in terms of pre-dose morning PEF change from baseline to treatment period average.

Figure 3 Pre-dose morning PEF response profile (EAS)



3.2.1.4.2 Secondary and Other Endpoints

Similar results were seen for the key secondary variable, change from baseline in pre-dose FEV1 (Table 6). Budesonide was superior to placebo in improving FEV1 from baseline to treatment period average. The treatment effect was 0.06L and was statistically significant (p-value=0.0047) according to the pre-specified multiple testing procedure. Results for change of FEV1 from baseline to end of treatment average and from baseline to LOCF treatment average were also consistent with the analysis for treatment period average (data not shown here).

Table 6 Pre-dose FEV1 (L) from clinical visits (EAS)

Statistics	Placebo (N=152)	Bud 160 (N=152)	Treatment Difference (Budesonide – Placebo)
Baseline mean	1.71	1.69	
Treatment period average	1.73	1.77	
LS mean change			
Estimate	0.00	0.06	0.06
95% CI			(0.02, 0.11)
p-value			0.0047

Source: Reviewer

Analyses of other secondary variables were summarized in Table 7. With the exception of forced vital capacity (FVC), there were nominally statistically significant differences between the budesonide group and the placebo group in favor of budesonide.

Table 7 Summary of secondary variables (EAS)

		Statistics	Placebo (N=152)	Bud 160 (N=152)	Treatment Difference (Budesonide – Placebo)
FVC	Baseline	Mean	2.18	2.18	
	Change from baseline to treatment period average	Estimate	0.00	0.04	0.04
		(95% CI)			(0.00, 0.08)
		p-value			0.0673
FEF25_75	Baseline	Mean	1.59	1.55	
	Change from baseline to treatment period average	Estimate	0.01	0.11	0.10
		(95% CI)			(0.01, 0.19)
		p-value			0.0216
Evening PEF	Baseline	Mean	221.0	217.2	
	Change from baseline to treatment period average	Estimate	4.0	14.7	10.8
		(95% CI)			(4.9, 16.7)
		p-value			0.0004
Daytime asthma symptom scores	Baseline	Mean	1.3	1.3	
	Change from baseline to treatment period average	Estimate	-0.2	-0.4	-0.2
		(95% CI)			(-0.31, -0.09)
		p-value			0.0004
Nighttime asthma symptom scores	Baseline	Mean	1.2	1.1	
	Change from baseline to treatment period average	Estimate	-0.3	-0.4	-0.1
		(95% CI)			(-0.26, -0.04)
		p-value			0.0079
Total daily asthma symptom scores	Baseline	Mean	2.4	2.4	
	Change from baseline to treatment period average	Estimate	-0.5	-0.8	-0.3
		(95% CI)			(-0.55, -0.13)
		p-value			0.0015
Nighttime awakenings (%)	Baseline	Mean	20.7	23.3	
	Change from baseline to treatment period average	Estimate	-9.8	-14.5	-4.7
		(95% CI)			(-8.2, -1.1)
		p-value			0.0095
Nighttime awakenings with reliever use (%)	Baseline	Mean	14.0	12.4	
	Change from baseline to treatment period average	Estimate	-6.1	-10.0	-3.9
		(95% CI)			(-6.2, -1.7)
		p-value			0.0007
Daytime reliever use	Baseline	Mean	0.8	0.8	
	Change from baseline to treatment period average	Estimate	-0.1	-0.4	-0.3
		(95% CI)			(-0.4, -0.1)
		p-value			0.0001
Nighttime reliever use	Baseline	Mean	0.6	0.6	
	Change from baseline to treatment period average	Estimate	-0.1	-0.4	-0.2
		(95% CI)			(-0.3, -0.1)
		p-value			<0.0001
Total reliever use	Baseline	Mean	1.4	1.3	
	Change from baseline to treatment period average	Estimate	-0.3	-0.7	-0.5
		(95% CI)			(-0.7, -0.2)
		p-value			<0.0001

Source: Reviewer

Table 8 presents a summary of pre-defined asthma events in Chase 1 study. A total of 94 patients developed 98 pre-defined asthma events during the treatment period; more in the placebo group (61 patients, 40.1%) than in the budesonide group (33 patients, 21.7%). Of the 94 patients with pre-defined asthma events, 50 (32.9%) placebo patients and 25 (16.4%) budesonide patients discontinued the study due to meeting the study-specific withdrawal criteria of pre-defined asthma event. The other 19 remained in the study after having asthma event(s) and 15 eventually completed the study.

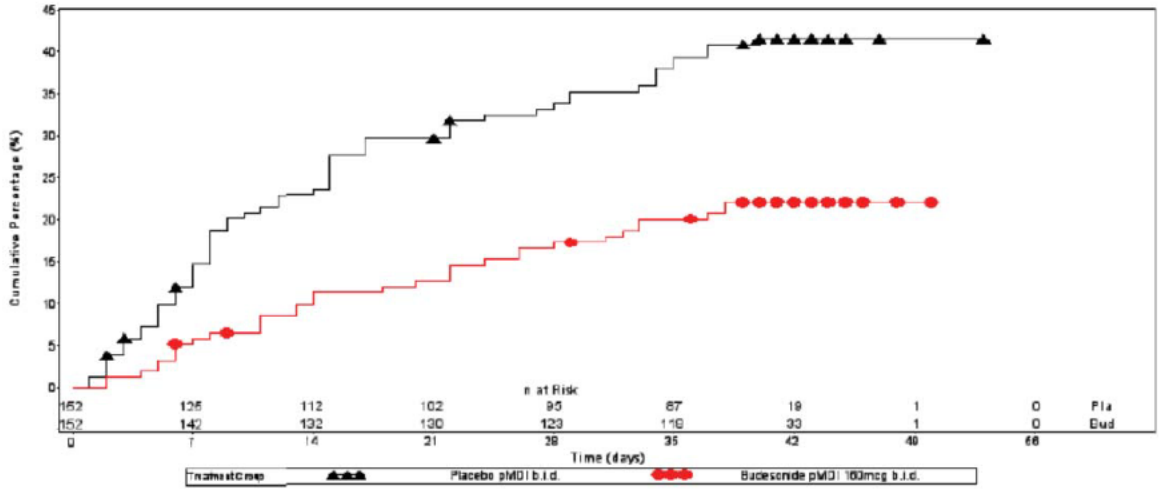
Table 8 Summary of pre-defined asthma events (EAS)

	Placebo (N=152)	**Bud 160 (N=152)**	**Total (N=304)**
Number of pre-defined asthma events	63	35	98
Patients with at least one pre-defined asthma event	61 (40.1%)	33 (21.7%)	94 (30.9%)
with 1 event	59	32	91
with 2 events	2	0	2
with 3 events	0	1	1
Patients withdrew due to a pre-defined asthma event	50 (32.9%)	25 (16.4%)	75 (24.7%)
Patients with pre-defined asthma event but not withdrew	11 (7.2%)	8 (5.3%)	19 (6.3%)
Complete the study	8	7	15
Not complete the study	3	1	4

Source: Reviewer

Time to the first pre-defined asthma event and time to withdrawal due to a pre-defined asthma event are plotted in Figures 4 and 5, respectively. A log-rank test comparing treatment groups showed a statistically significant difference in favor of budesonide although the p-values were considered nominal.

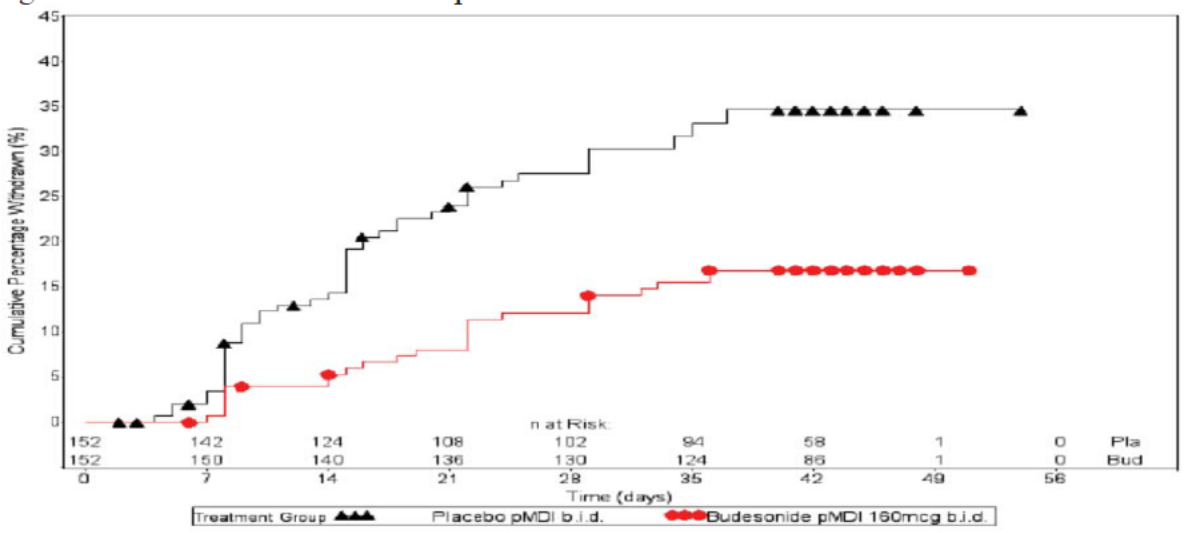
Figure 4 Time to first pre-defined asthma event



For patients who complete the study without a pre-defined asthma event, time to first pre-defined asthma event is censored at the day of study completion up to a maximum of the last randomized dose day.
The symbols on each line indicate patients who were censored.

Source: Chase 1 study report Figure 11.2.2.2.

Figure 5 Time to withdrawal due to pre-defined asthma event



For patients who complete the study time to withdrawal is censored at the day of study completion.
For patients who withdraw from the study for reasons other than a pre-defined asthma event, time to withdrawal is censored at the last day of treatment.
The symbols on each line indicate patients who were censored.

Source: Chase 1 study report Figure 11.2.2.1.

3.2.2 Study D589GC00002 (Chase 2)

3.2.2.1 Study Design and Endpoints

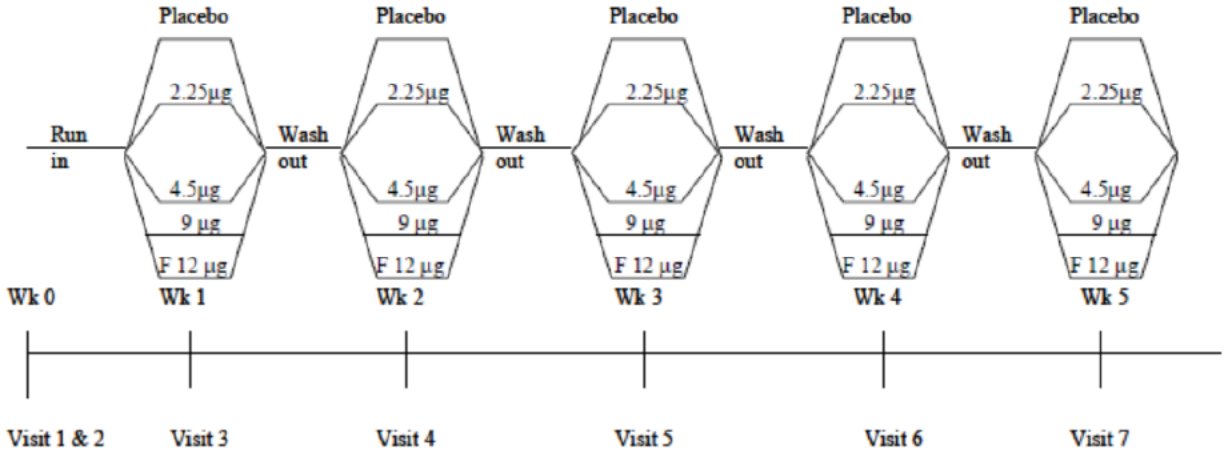
The Chase 2 study was a Phase 2, single-dose, randomized, double-blind, 5-way crossover, active- and placebo-controlled, multicenter study in pediatric asthmatic patients who were stable on a medium dose range of ICS therapy. The primary objective was to evaluate the bronchodilating effects of 3 doses of formoterol given in combination with budesonide as SYMBICORT pMDI. Single-dose treatments of inhaled formoterol 2.25 µg, 4.5 µg, and 9.0 µg delivered in combination with budesonide via SYMBICORT were compared with placebo in combination with budesonide pMDI. In addition, Foradil Aerolizer (12 µg, metered dose), the US approved formoterol product for pediatric patients ≥5 years of age, was included as an active control arm (in combination with budesonide).

After the run-in period, eligible patients were randomized in a 1:1:1:1:1 ratio to receive one of five single-dose treatments (4 blinded and 1 partially blinded):

- The blinded single-dose treatments (each delivered in 3 inhalations):
  - 2.25 µg formoterol (as 80/2.25 µg SYMBICORT pMDI ×1 inhalation) + 40 µg budesonide HFA pMDI × 2 inhalations, referred to as SYM 80/2.25 or Bud 160/FM 2.25;
  - 4.5 µg formoterol (as 80/2.25 µg SYMBICORT pMDI × 2 inhalations) + placebo HFA pMDI × 1 inhalation, referred to as SYM 80/4.5 or Bud 160/FM 4.5;
  - 9.0 µg formoterol (as 80/4.5 µg SYMBICORT pMDI × 2 inhalations) + placebo HFA pMDI × 1 inhalation, referred to as SYM 80/9 or Bud 160/FM 9.0;
  - 80 µg budesonide HFA pMDI × 2 inhalations + placebo HFA pMDI × 1 inhalation, referred to as Bud 160 or Bud 160/Placebo;
- The partially blinded treatment arm was delivered as:
  - 80 µg budesonide HFA pMDI × 2 inhalations + Foradil Aerolizer 12 µg × 1 inhalation, referred to as Bud 160 / Foradile 12.0;

Following randomization and administration of the first study medication, each patient had 4 further visits to receive cross-over treatments and monitoring tests. These visits were separated by approximately 7-day (minimum 3 days; maximum 14 days) washout periods as shown in the study flow chart (Figure 6). The study duration for each patient was 4 to 8 weeks.

Figure 6 Chase 2 study design



Source: Chase 2 study report Figure 1

The primary efficacy endpoint was average FEV1 over 12 hours (calculated through an area under curve determination and divided by time, FEV1 AUC_{0-12}). The AUC was defined as the area between the x-axis (FEV1=0) and the FEV1-over-time curve from the serial spirometry maneuvers, after the administration of study medication at each visit. Area was calculated using the trapezoidal method using the actual times of measurements. The secondary efficacy endpoints included:

- Maximum 12-hour FEV1: defined as the largest observed FEV1 value recorded during each 12-hour serial spirometry procedure
- FEV1 value at each time point (3, 9, 15, 60, 120, 180, 240, 360, 480, 600, and 720 minutes during 12-hour serial spirometry)
- FEV1 value at 12- hours after dosing
- Estimation of time to 15% improvement in FEV_1 during 12-hour serial spirometry
- PK parameters

3.2.2.2 Statistical Methodologies

The following analysis datasets were defined in the protocol:

- Efficacy analysis set (EAS): consisted of all patients who were randomized, took at least 1 dose of study medication, and contributed sufficient data for at least 1 efficacy endpoint to be calculated.
- Per-Protocol analysis set: included all patients in the full analysis set except those with protocol deviations, as described in the statistical analysis plan. An analysis of the Per-Protocol analysis set was to be performed only if 20% or more of the patients were excluded.
- Safety analysis set: included all randomized patients who took at least one dose of study medication.

The primary variable of average FEV1 from 12-hour serial FEV_1 measurements was analyzed with an analysis of covariance (ANCOVA) model for a crossover design, adjusting for the fixed factors of patient, period, and treatment, and for the covariate of pre-dose FEV_1 from each visit. Treatment comparisons were made by formulating contrasts within the context of this model. The analysis was based on the efficacy analysis dataset and used the last observation carried forward (LOCF) method of extrapolation if FEV1 values were missing as described below.

FEV1 values were interpolated and/or extrapolated for use in the calculation of the AUC if data were missing within an individual set of serial spirometric measurements at a visit, according to the following algorithm:

- For patients with "bounded" missing data, interpolated the missing value(s) with a straight line connecting the 2 points bounding the missing data.
- For patients with "unbounded" missing data, the following extrapolation techniques were used:
  - Carry forward the FEV1 value from the last non-missing time point to all successive time points at that visit, hereafter referred to as 'LOCF',
  - Carry forward the pre-dose FEV1 value from that visit to all successive time points at that visit, hereafter referred to as 'Pre-CF'.

Both bounded and unbounded methods were used simultaneously within a visit to complete any missing 12-hour serial spirometry measurements; AUC itself was not carried forward to subsequent visits for any reason.

The secondary efficacy variables, FEV1 at 12 hours and maximum FEV1 over 12 hours, were analyzed in the same way as the primary endpoint. For FEV_1 values at each time point, descriptive statistics were presented to show the pattern of FEV1 responses over time from the 12-hour serial FEV1 assessments. For estimation of time to 15% improvement in FEV1 during 12-hour serial spirometry, descriptive statistics were used to summarized the data along with Kaplan-Meier curves.

To control the overall Type I error rate in the primary analysis, a hierarchical testing procedure was employed in the following order. First, there was a comparison of Bud 160/FM 9.0 vs. Bud 160/Placebo for average 12-hour FEV1. If significant at α=0.05, then there was a comparison of Bud 160/FM 4.5 vs. Bud 160/Placebo at α=0.05. If also significant, there was a comparison of Bud 160/FM 2.25 vs. Bud 160/Placebo at α=0.05. If statistical significance was not reached at the 0.05 level for a given comparison, formal statistical testing would stop. P-values from all other comparisons were considered nominal. No multiplicity adjustment was made in the analysis of secondary endpoints.

The applicant performed several sensitivity analyses on the primary efficacy endpoint, including:

1) Repeat the primary analysis with the LOCF imputation method and exclude selected assessments that were identified as unsuitable following a blinded review of FEV1 profile;
2) Repeat the primary analysis with the LOCF imputation method and exclude assessments at visits incorrect medication was administered;
3) Repeat the primary analysis using the Pre-CF method of extrapolation for missing data

4) Repeat the primary analysis with the Pre-CF imputation method and exclude selected assessments that were identified as unsuitable following a blinded review of FEV1 profile;
5) Repeat the primary analysis with the Pre-CF imputation method and exclude assessments at visits incorrect medication was administered.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 54 subjects were randomized to the study, all subjects received at least one study treatment (Table 9). Fifty patients (92.6%) received all 5 treatments and completed the study. Two patients discontinued due to adverse events, and another 2 discontinued due to patient or caregiver decision.

Table 9 Patient disposition in the Chase 2 study (All randomized patients)

	Total N (%)
Randomized	54 (100%)
Never dosed	0 (0.0%)
Treated	54 (100%)
Completed treatment	50 (92.6%)
Discontinued treatment	4 (7.4%)
Completed study	50 (92.6%)
Discontinued study	4 (7.4%)
Analysis Datasets	
All Randomized Analysis Set	54
Efficacy Analysis Set	54
Safety Analysis Set	54
Per-protocol set	51

Source: Reviewer

Selected demographic features for all randomized patients are shown in Table 10. The study enrolled more boys than girls and approximately 80% of patients (43 patients) were between 8 to <12 years of age. The majority were either white (57.4%) or black/African American (40.7%). Patients had on average a 73.2-month history of asthma.

Table 10 Study demographics and baseline characteristics (All randomized patients)

	Total (N=54)
Age (years)	
Mean	9.2
SD	1.79
Median	10.0
Age group, n (%)	
6-<8 years	11 (20.4%)
8-<12 years	43 (79.6%)
Gender, n (%)	
Male	31 (57.4%)
Female	23 (42.6%)
Race, n (%)	
White	31 (57.4%)
Black /African American	22 (40.7%)
Other	1 (1.9%)
Months since asthma diagnosis	
Mean	73.2
SD	39.16
Median	72.7

Source: Chase 2 clinical study report Table 9.

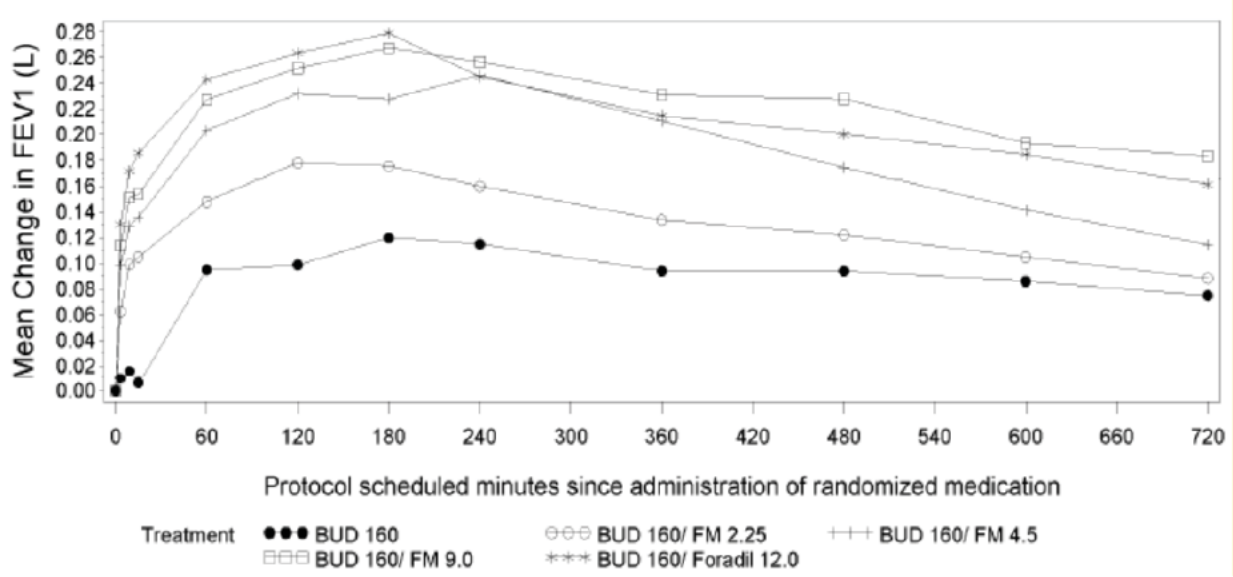
3.2.2.4 Results and Conclusions

3.2.2.4.1 Primary Endpoint

The primary efficacy assessment was based on the average FEV1 over the 12-hour time period. Results are shown in Figure 7 and Table 11. Compared to placebo, mean 12-hour FEV1 was statistically significantly improved with formoterol 9 µg or 4.5 µg given as single doses via SYMBICORT pMDI (p-values<0.0001). Formoterol 2.25 µg administered as a single dose via SYMBICORT pMDI was also superior to placebo in improving average FEV1 over the 12-hour time period (p-value=0.0001). While not in the framework of hierarchical testing, the 9 µg and 4.5 µg formoterol doses were statistically significantly superior to the 2.25 µg formoterol dose, but the 9 µg and 4.5 µg formoterol doses were not statistically significantly different from each other.

Compared to the active comparator Foradil Aerolizer (Bud 160/Foradil 12.0), the formoterol 2.25 µg dose was inferior and there was no difference for either 9 µg or 4.5 µg formoterol dose in increasing average 12-hour FEV1. Again, these comparisons were not in the hierarchical testing structure and all p-values were considered nominal.

Figure 7 Mean change from baseline in FEV1 over time (Efficacy analysis set)



BUD = budesonide; FM = formoterol.
Patients were included on only one treatment line for each week.

Source: Chase 2 study report Figure 3

Table 11 Treatment means and comparison for average 12-hour FEV1 (EAS)

Average 12-hour FEV1(L)	N	Pre-dose Value Mean	Observed Value Mean	From ANCOVA			
					Treatment Comparison vs Bud 160/Placebo		
				LS Mean	LS Mean	95% CI	p-value
Bud 160 / FM 9.0	53	1.534	1.587	1.603	0.114	(0.087, 0.142)	<0.0001
Bud 160 / FM 4.5	53	1.568	1.592	1.594	0.105	(0.078, 0.133)	<0.0001
Bud 160 / FM 2.25	54	1.581	1.558	1.546	0.058	(0.030, 0.085)	0.0001
Bud 160 / Placebo	51	1.546	1.482	1.489	--	--	--
Bud 160 / Foradil 12.0	51	1.538	1.593	1.603	0.114	(0.086, 0.142)	<0.0001

Source: Reviewer

Similar results were seen from various sensitivity analyses, such as using the Pre-CF imputation method, excluding selected unsuitable assessments or assessments at visits when incorrect medication was administered.

3.2.2.4.2 Secondary Endpoints

The analyses of secondary endpoints are shown in Table 12. Both the formoterol 4.5 µg and 9.0 µg doses resulted in significant improvements in FEV1 values at 12 hours after study medication inhalation compared to placebo (p-value=0.0092 and p-value<0.0001 respectively). At 12 hours, the formoterol 2.25 µg dose was not statistically different from placebo (p-value=0.5509). For maximum FEV1 during the 12-hour study period, all 3 formoterol doses led to significantly greater maximal FEV1 values when compared with placebo. The between-treatment comparisons showed numerically favorable results for formoterol 9.0 µg over 4.5 µg as well as superiority of the formoterol 4.5 µg and 9.0 µg doses over 2.25 µg (data not presented here).

Table 12 Treatment means and comparison for secondary endpoints (Efficacy Analysis Set)

				From ANCOVA			
					Treatment Comparison vs Bud 160/Placebo		
	N	Pre-dose Observed Value Mean	Value Mean	LS Mean	LS Mean	95% CI	p-value
FEV1(L) at 12th hour							
Bud 160 / FM 9.0	53	1.534	1.710	1.731	0.105	(0.056, 0.155)	<0.0001
Bud 160 / FM 4.5	53	1.568	1.686	1.692	0.066	(0.017, 0.116)	0.0092
Bud 160 / FM 2.25	54	1.581	1.653	1.641	0.015	(-0.035, 0.065)	0.5509
Bud 160 / Placebo	51	1.546	1.616	1.626	--	--	--
Bud 160 / Foradil 12.0	51	1.538	1.697	1.709	0.083	(0.034, 0.133)	0.0011
Maximum FEV1 over 12-hour							
Bud 160 / FM 9.0	53	1.534	1.866	1.884	0.107	(0.073, 0.140)	<0.0001
Bud 160 / FM 4.5	53	1.568	1.885	1.889	0.112	(0.078, 0.146)	<0.0001
Bud 160 / FM 2.25	54	1.581	1.844	1.833	0.057	(0.023, 0.090)	0.0011
Bud 160 / Placebo	51	1.546	1.767	1.777	--	--	--
Bud 160 / Foradil 12.0	51	1.538	1.880	1.892	0.115	(0.081, 0.149)	<0.0001

Source: Reviewer

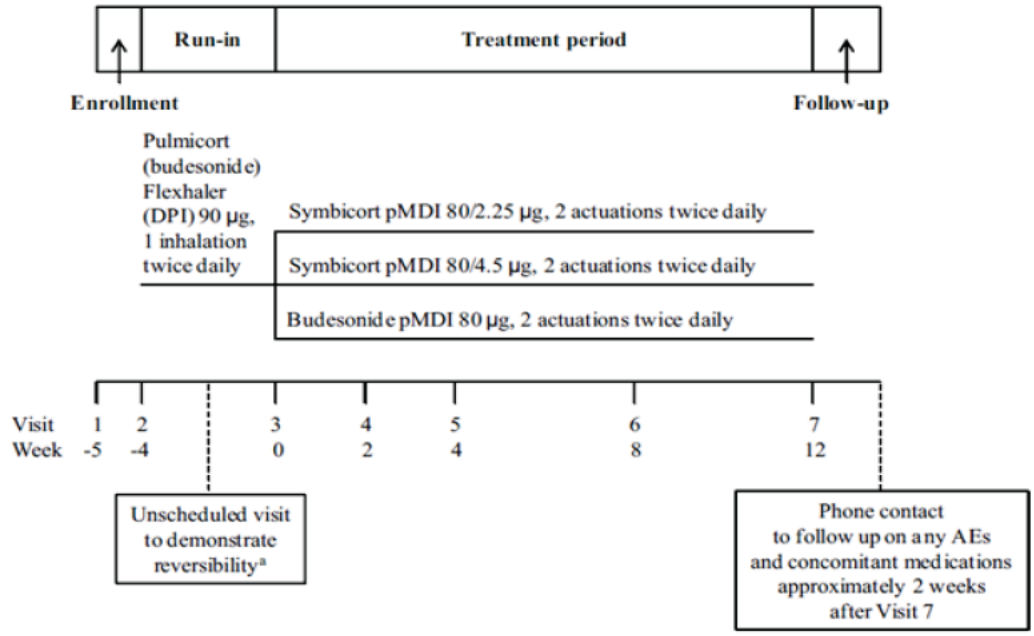
3.2.3 Study D589GC00003 (Chase 3)

3.2.3.1 Study Design and Endpoints

The Chase 3 study was a 12-week, randomized, double-blind, parallel-group, active-controlled, multicenter, Phase 3 study involving pediatric patients 6 to <12 years of age, with a documented clinical diagnosis of asthma for at least 6 months prior to study entry and a requirement for daily medium-dose range ICS therapy or fixed combination of ICS and LABA therapy and having symptoms when treated with low-dose ICS during run-in. The primary objective of the study was to demonstrate the efficacy of two doses of SYMBICORT, 80/4.5 µg (referred to as SYMBICORT 80/4.5 or SYM 80/4.5) and 80/2.25 µg (referred to as SYMBICORT 80/2.25 or SYM 80/2.25), compared with budesonide 80 µg x 2 actuations (referred to as budesonide 160 or Bud 160 or BUD 80). The secondary objective of the study was to compare the efficacy of the two SYMBICORT dosing regimens, SYM 80/4.5 versus SYM 80/2.25.

After a 2 to 4 week run-in period, eligible patients were randomly assigned in a blinded fashion (1:1:1) to one of the following three treatment groups: SYM 80/4.5, SYM 80/2.25, or Bud 160. Randomization was stratified by age group (children under 9 years of age versus children 9 years and older), with approximately 50% of patients under the age of 9. Patients took study drug by oral inhalation in the morning and evening (2 actuations twice daily) for 12 weeks and returned for clinical visits at Weeks 2, 4, 8, and 12. Patients were followed according to study protocol until study closure even if study medication had been discontinued. The overall study flow chart for the CHASE 3 study is shown in Figure 8.

Figure 8 Chase 3 study design



[a] Unscheduled visit is only for patients who failed to demonstrate reversibility but met all other inclusion and none of the exclusion criteria at Visit 2.

Source: Chase 3 clinical study report Figure 1.

The primary efficacy variable was change from baseline to Week 12 in 1-hour post-dose FEV1 measured at the clinic. It was defined as the 1-hour post-dose measurement taken at Week 12 minus the pre-dose measurement taken at randomization. If the pre-dose value was missing at randomization then the latest non-missing pre-bronchodilator measurement prior to randomization was used instead.

The secondary variables included additional clinical measurements of lung function, lung function and symptom-related variables recorded by electronic diary (eDiary), exacerbations, and quality of life measures as follows:

- Change from baseline to treatment period average and change from baseline to end of study (Withdrawal from study or Week 12):
    - Pre-dose and 15-minute post-dose clinic FEV1 (L)
    - Pre-dose, 15-minute post-dose and 1-hour post-dose clinic FVC (L)
    - Pre-dose, 15-minute post-dose and 1-hour post-dose clinic FEF25-75 (L/s)
    - Pre-dose, 15-minute post-dose and 1-hour post-dose clinic PEF (L/min)
    - Morning and evening FEV1 (L) and PEF (L/min) (eDiary)
    - Nighttime, daytime, and total daily asthma symptom scores (eDiary)
    - Nighttime awakenings due to asthma symptoms requiring reliever use (eDiary)
    - Nighttime, daytime, and total daily reliever medication use (eDiary)
    - Pediatric Asthma Quality of Life Questionnaire with Standardized Activities (PAQLQ[S]) scores
- Time to occurrence of first protocol defined asthma exacerbation defined as any of the following events:
    - Emergency room treatment for asthma.
    - In-patient hospitalization for asthma.
    - Use of systemic steroids (oral or parenteral) for asthma.
    - Exacerbation that required a change in maintenance asthma therapy (increases in ICS dose or additional daily medications to treat exacerbation).
- Time to discontinuation of treatment

3.2.3.2 Statistical Methodologies

The following analysis datasets were defined in the protocol:

- All randomized patients set: contained patients who were randomized and were used for summarizing the demographic and patient characteristics data.
- Efficacy analysis set (EAS): consisted of all patients who were randomized, received at least one dose of study medication and contributed post-baseline data for at least one efficacy endpoint. Patients were accounted for according to the treatment to which they were randomized, regardless of whether they were administered the incorrect treatment or terminated use of the investigational product (IP).
- Safety analysis set: included patients who received at least one dose of study medication and had data collected after randomization. Patients would be accounted for according to the treatment they actually received, regardless of their randomized treatment group.

The primary variable, change from baseline to Week 12 in 1-hour post-dose clinic FEV1, was analyzed using a mixed model repeated measures (MMRM) with terms for treatment, age group (6 to <9 years and 9 to <12 years of age), and region (US and non-US), visit, treatment-by-visit interaction as factors, and with baseline clinic FEV1 as a covariate. Baseline was the latest non-missing pre-dose assessment prior to first dose of investigational product (typically at randomization (Visit 3). An unstructured covariance matrix was used for the within-patient correlation modeling. In case of a convergence problem, a compound symmetric variance-covariance matrix would be assumed instead. The primary analysis was based on the efficacy analysis set and included all data collected during the study period, from the date of first dose of IP up to and including Week 12 (end of study assessment or withdrawal from study).

The overall treatment effect for each SYMBICORT dose was compared to Budesonide using a 2-sided test at the significance level of 0.05. A hierarchical testing procedure was used to control the overall Type I error rate and adjust for the two comparisons of SYMBICORT to Budesonide. Statistical significance would be declared in the order of SYM 80/4.5 first and SYM 80/2.25 second. Specifically, the comparison of SYM 80/4.5 versus Bud 160 would be performed first. If the result was statistically significant at the 0.05 level of significance, then SYM 80/2.25 would be compared to Bud 160 at α=0.05.

A similar MMRM procedure to the one described for the primary analysis was used to analyze the secondary lung function variables including change from baseline to Week 12 in 1-hour post-dose and pre-dose clinical FEV1, FVC, FEF25-75, and PEF. The model included terms for treatment, region (US and non-US), age group (6 to <9 years and 9 to <12 years of age), visit, treatment-by-visit interaction as factors and the respective baseline lung function variable as a covariate. Other variables, such as change from baseline to study period average (1-hour post-dose clinical FEV1, PAQLQ(S) score) and change from baseline to Week 12 (15 minutes post dose clinical FEV1), were analyzed using an analysis of covariance (ANCOVA) model. The model had terms for treatment, region (US and non-US), and age group (6 to <9 years and 9 to <12 years of age) as factors, and the corresponding baseline value as a covariate. Additionally the proportion of patients achieving clinically relevant improvement (change $\geq$ 0.5 points from baseline to Week 12) in PAQLQ(S) score was analyzed using a Cochran-Mantel-Haenszel (CMH) test, adjusting for region and age group (6 to <9 years and 9 to <12 years of age). For time to occurrence of the first protocol defined asthma exacerbation or time to treatment discontinuation, a log-rank test was used to compare treatment effect between each SYMBICORT dose and Budesonide dose, as well as between the two SYMBICORT dose groups. All eDiary variables including asthma symptom scores, nighttime awakenings, and reliever medication use were summarized using descriptive statistics only. Testing of the secondary variables was performed at the significance level of 0.05. There was no adjustment for multiplicity for the secondary endpoints.

In order to assess the robustness of study results, the following sensitivity analyses were conducted on the primary endpoint of change from baseline to Week 12:

- The primary analysis was repeated using all on-treatment data which were collected between the date of first dose of IP up to and including the last dose of study medication +7 days.

- The primary analysis was repeated incorporating all data collected during the study period except for data recorded after patients switched to maintenance therapy with a bronchodilator containing product.
- The primary analysis was repeated incorporating all data collected during the study period except for spirometry data from patients with percent predicted normal FEV1 ≥ 150% at any time point, besides run-in assessments.
- Performed a "jump to the reference" approach assuming missing not at random data. Specifically, it was assumed that post withdrawal FEV_1 in subjects from the experimental arms would immediately change to have the mean of the control group at the relevant time point, conditional only on baseline values, while missing data on the placebo arm would be missing at random. This assumption was implemented by a multiple imputation method so that subjects who withdrew from the SYMBICORT arms at any visit would have a mean close to that of the Budesonide arm for that visit.

3.2.3.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 279 patients were randomized in Chase 3, all but 6 subjects received at least 1 dose of study drug and were included in the efficacy or safety analysis set. Twenty-four (8.8%) subjects stopped medication early and 20 (7.3%) discontinued from the study prematurely. The proportion of patients that completed treatment or study was similar across treatment groups. The most frequent cause for treatment discontinuation or withdrawal from the study was patient decision, occurring in 15 (5.4%) subjects. Patient disposition is shown in Table 13.

Table 13 Patient disposition in the Chase 3 study

	SYM 80/4.5 N (%)	SYM 80/2.25 N (%)	Bud 160 N (%)	Total N (%)
Randomized	92	95	92	279
Never dosed	2	2	2	6
Treated	90 (100)	93 (100)	90 (100)	273 (100)
Completed treatment	83 (92.2)	83 (89.2)	83 (92.2)	249 (91.2)
Discontinued treatment	7 (7.8)	10 (10.8)	7 (7.8)	24 (8.8)
Completed study	85 (94.4)	84 (90.3)	84 (93.3)	253 (92.7)
Discontinued study	5 (5.6)	9 (9.7)	6 (6.7)	20 (7.3)
Analysis Datasets				
All Randomized Analysis Set	92	95	92	279
Efficacy Analysis Set	90	93	90	273
Safety Analysis Set	90	93	90	273

Source: Reviewer

Selected demographic and clinical features for all randomized patients are shown in Table 14. Baseline demographics were generally well-balanced across the treatment groups, with some small differences for sex and race. Among the randomized patients, 113 (40.5%) were female and 166 (59.5%) were male. The majority were White (62.4%); 27.2% were Black or African American and 0.7% were Asians. A total of 106 (38.0%) were of Hispanic or Latino ethnicity. Approximately one third were 6 to <9 years of age and two thirds were 9 to <12 years of age. The distributions of clinical characteristics including pulmonary function, asthma duration, and severity, were similar across all treatment groups. The average time since asthma diagnosis was 6 years and the mean clinical FEV1 at baseline was 1.64 L.

Table 14 Chase 3 Study demographics and baseline characteristics (All Randomized Analysis Set)

	SYM 80/4.5 (N=92)	**SYM 80/2.25 (N=95)**	**Bud 160 (N=92)**	**Total (N=279)**
Age (years)	n=92	n=95	n=92	n=279
Mean	9	9	9	9
SD	1.6	1.6	1.4	1.5
Median	9	9	9	9
Age group, n (%)				
6-<9 years	30 (32.6)	36 (37.9)	32 (34.8)	98 (35.1)
9-<12 years	62 (67.4)	59 (62.1)	60 (65.2)	181 (64.9)
Gender, n (%)				
Male	42 (45.7)	34 (35.8)	37 (40.2)	113 (40.5)
Female	50 (54.3)	61 (64.2)	55 (59.8)	166 (59.5)
Race, n (%)				
American Indian or Alaska Native	2 (2.2)	3 (3.2)	3 (3.3)	8 (2.9)
Asian	0	0	2 (2.2)	2 (0.7)
Black or African American	24 (26.1)	26 (27.4)	26 (28.3)	76 (27.2)
Native Hawaiian or Other Pacific Islander	1 (1.1)	0	0	1 (0.4)
Other	4 (4.3)	4 (4.2)	7 (7.6)	15 (5.4)
Unknown	0	2 (2.1)	1 (1.1)	3 (1.1)
White	61 (66.3)	60 (63.2)	53 (57.6)	174 (62.4)
Ethnicity, n (%)				
Hispanic or Latino	38 (41.3)	36 (37.9)	32 (34.8)	106 (38.0)
Non-Hispanic or non-Latino	54 (58.7)	59 (62.1)	60 (65.2)	173 (62.0)
Region, n (%)				
US	75 (81.5)	76 (80.0)	75 (81.5)	226 (81.0)
Non-US	17 (18.5)	19 (20.0)	17 (18.5)	53 (19.0)
Weight (kg)	n=91	n=95	n=92	n=278
Mean	38	38	40	39
SD	12.9	12.9	13.6	13.1
Median	36	35	38	37
Years since asthma diagnosis	n=92	n=95	n=92	n=279
Mean	5.75	5.92	6.16	5.94
SD	3.004	3.227	3.055	3.092
Median	5.82	6.78	6.25	6.15
FEV1 (L)	n=89	n=93	n=90	n=272
Mean	1.62	1.60	1.69	1.64
SD	0.423	0.347	0.387	0.387
Median	1.61	1.60	1.66	1.62

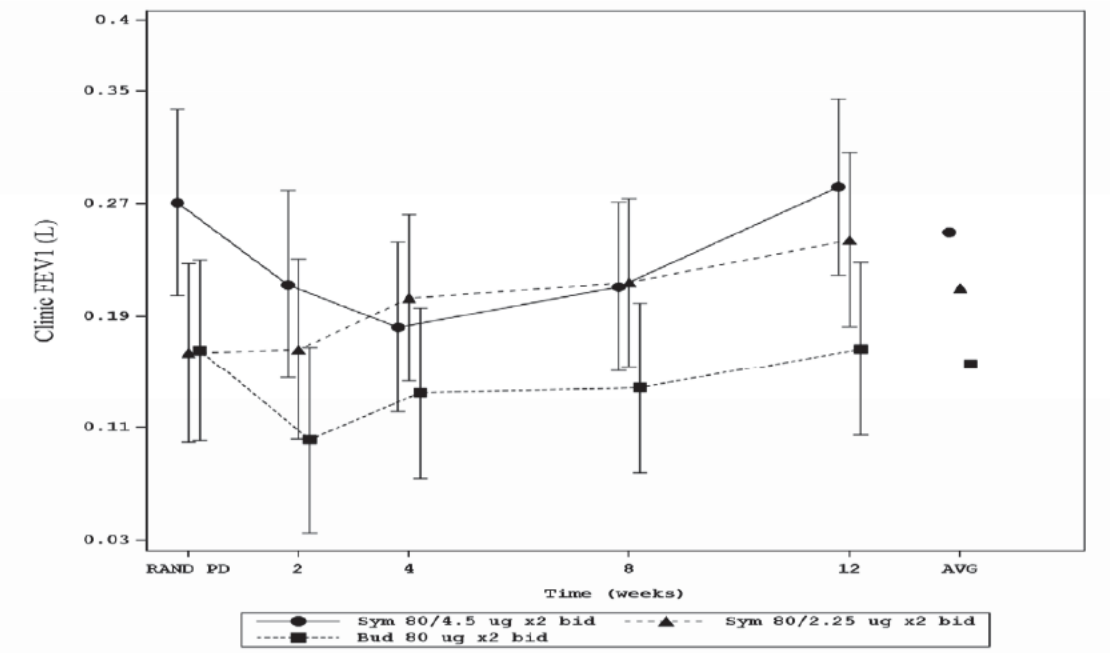
Source Reviewer

3.2.3.4 Results and Conclusions

3.2.3.4.1 Primary Endpoint

The primary endpoint was the change from baseline to Week 12 in 1-hour post-dose clinical FEV1. In Chase 3, patients receiving SYMBICORT had higher increases in 1-hour post-dese FEV1 from baseline compared to Budesonide (Figure 9 and Table 15). The increase was statistically significant for SYM 80/4.5 compared to budesonide 160, with an estimated difference of 0.12L (p-value=0.006). The improvement was numerically greater with SYM 80/2.25 versus budesonide 160, but the difference was not statistically significant (p-value=0.063). A numerical yet not statistically significant difference was also observed between the two SYMBICORT doses in favor of SYMBICORT 80/4.5. Additional analysis of 1-hour post-dose clinic FEV1 based on the change from baseline to the study period average produced results also in line with the results for the primary analysis.

Figure 9 Mean change from baseline in 1-hour post-dose clinic FEV1 (L) over time



RAND PD=Randomization post-dose assessment.

Source: Chase 3 clinical study report Figure 3

Table 15 Clinic FEV1 (L) 1-hour post-dose change from baseline (EAS)

					Treatment Difference		
	Statistics	SYM 80/4.5 (N=90)	SYM 80/2.25 (N=93)	Bud 160 (N=90)	SYM 80/4.5 vs Bud 160	SYM 80/2.25 vs Bud 160	SYM 80/4.5 vs SYM 80/2.25
Baseline	Mean	1.58	1.58	1.61			
Primary Endpoint:							
Change from baseline to Week 12	Estimate	0.28	0.24	0.17	0.12	0.08	0.04
	(95% CI)	(0.22, 0.34)	(0.18, 0.31)	(0.10, 0.23)	(0.03, 0.20)	(0.00, 0.16)	(-0.05, 0.12)
	p-value				0.006	0.063	0.373
Change from baseline to study period average	Estimate	0.23	0.19	0.14	0.09	0.05	0.04
	(95% CI)	(0.18, 0.28)	(0.14, 0.24)	(0.09, 0.19)	(0.03, 0.15)	(-0.01, 0.11)	(-0.02, 0.10)
	p-value				0.006	0.108	0.237

Source: *Reviewer*

Table 16 lists sensitivity analyses conducted by the applicant. The "Jump to the reference" approach is considered the most useful of these analyses, since it includes all observed data and evaluates an alternative missing data assumption in which patients who dropped out on SYMBICORT were assumed to have similar Week 12 outcomes to the observed outcomes on the control budesonide arm. Therefore, this analysis does not carry forward benefit in patients who discontinued treatment. There was significant improvement in 1-hour post-dose clinical FEV_1 for SYM 80/4.5 treatment compared with budesonide in this and the other sensitivity analyses, consistent with the findings from the primary analysis. These results provide additional confidence that the conclusions are reliable despite the missing data.

Table 16 Consistency between primary and sensitivity analyses

Change from baseline to Week 12 for 1-hour post-dose FEV_1[a]	Estimated difference (L)	95% CI	P-value
Primary analysis	**0.12**	**0.03, 0.20**	**0.006**
On-treatment data	0.12	0.03, 0.20	0.006
Excluding data after patients switched to maintenance therapy	0.12	0.03, 0.20	0.006
Excluding patients with FEV_1 ≥150% of predicted normal	0.11	0.03, 0.18	0.006
"Jump to the reference" analysis	0.11	0.03, 0.20	0.011

CI confidence interval; FEV_1 forced expiratory volume in 1 second.
[a] The comparison is SYMBICORT 80/4.5, 2 inhalations bid vs budesonide 80 µg, 2 inhalations bid.

Source: *Chase 3 clinical study report Table 3.*

3.2.3.4.2 Secondary Endpoints

In general, trends toward improvement (more with SYMBICORT 80/4.5 than 80/2.25) over budesonide was observed in the majority of secondary clinic and eDiary lung function variables which supported the findings for the primary endpoint. However, treatment comparisons between SYM 80/4.5 and Bud 160 reached nominal statistical significance (p-value<0.05) only in change from baseline to Week 12 for 1-hour post-dose FEF25_75, PEF, and 15-minute post-dose FEV1. In addition, for symptom-related variables and health-related quality of life measures, there was no statistical significant difference (nominal p-value<0.05) between each SYMBICORT dose and budesonide. There were trends for slightly greater improvement on SYMBICORT than budesonide for some but not all of these endpoints. There also were no statistically significant differences between treatment groups for time to first asthma exacerbation or time to discontinuation of treatment with IP. Comparisons in secondary efficacy endpoints were not controlled for multiplicity and were considered exploratory.

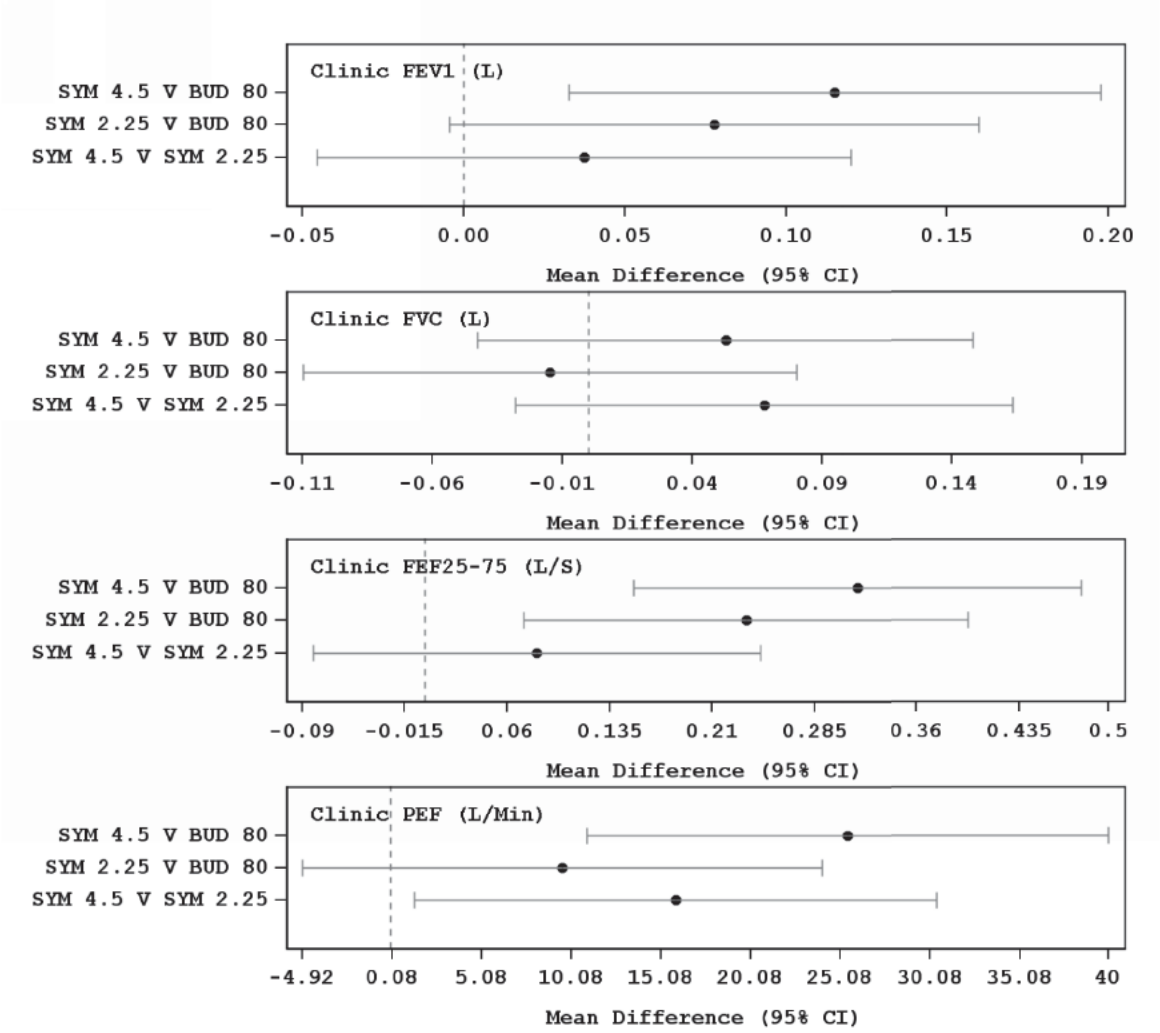
Analyses of the secondary clinic lung function variables are presented in Table 17 and Figure 10 for post-dose measurements as well as Table 18 and Figure 11 for pre-dose measurements, respectively. For post-dose clinical assessment, results were consistent with the primary analysis for 1-hour post-dose clinical FEV1. SYM 80/4.5 led to overall improvement as measured by 1-hour post-dose clinical lung function (FEF25_75 and PEF) and 15-miniute post-dose FEV1. Of note there were no statistically significant differences between each SYMBICORT dose and Budesonide for 1-hour post-dose FVC. With regard to pre-dose clinic measurements (change from baseline to Week 12 for pre-dose values for FEV1, FEF25_75, FVC, and PEF), while some numerical improvement was observed with both SYMBICORT doses than with budesonide, there were no statistically significant differences between treatment groups. A descriptive summary of FEV1 and PEF assessed pre-dose morning and evening by patients at home were generally consistent with the findings observed for clinic FEV1 and clinic PEF (data not shown here).

Table 17 Secondary post-dose clinic lung function endpoints (EAS)

					Treatment Difference		
	Statistics	SYM 80/4.5 (N=90)	SYM 80/2.25 (N=93)	Bud 160 (N=90)	SYM 80/4.5 vs Bud 160	SYM 80/2.25 vs Bud 160	SYM 80/4.5 vs SYM 80/2.25
FVC							
1-hour post-dose							
Baseline	mean	2.06	2.11	2.12			
Change from baseline to Week 12	Estimate	0.22	0.16	0.17	0.05	-0.01	0.07
	(95% CI)	(0.15, 0.30)	(0.09, 0.23)	(0.10, 0.24)	(-0.04, 0.15)	(-0.11, 0.08)	(-0.03, 0.16)
	p-value				0.276	0.759	0.165
FEF25_75							
1-hour post-dose							
Baseline	mean	1.42	1.38	1.36			
Change from baseline to Week 12	Estimate	0.55	0.47	0.23	0.32	0.23	0.08
	(95% CI)	(0.43, 0.67)	(0.35, 0.59)	(0.11, 0.35)	(0.15, 0.48)	(0.07, 0.40)	(-0.08, 0.25)
	p-value				<0.001	0.005	0.326
PEF							
1-hour post-dose							
Baseline	mean	233.9	222.3	235.6			
Change from baseline to Week 12	Estimate	57.0	41.1	31.6	25.5	9.6	15.9
	(95% CI)	(46.1, 68.0)	(30.3, 52.0)	(20.8, 42.4)	(10.9, 40.0)	(-4.9, 24.1)	(1.3, 30.5)
	p-value				0.001	0.195	0.032
FEV1							
15-min post-dose							
Baseline	mean	1.58	1.58	1.61			
Change from baseline to Week 12	Estimate	0.25	0.19	0.15	0.10	0.04	0.06
	(95% CI)	(0.18, 0.31)	(0.12, 0.25)	(0.08, 0.21)	(0.02, 0.18)	(-0.04, 0.12)	(-0.02, 0.15)
	p-value				0.015	0.342	0.138

Source: Reviewer

Figure 10 Clinic lung function post-dose change from baseline to Week 12 (EAS)



SYM 4.5=SYMBICORT pMDI 80/4.5 µg, 2 inhalations bid. SYM 2.25=SYMBICORT pMDI 80/2.25 µg, 2 inhalations bid. BUD 80=budesonide pMDI 80 µg, 2 inhalations bid.

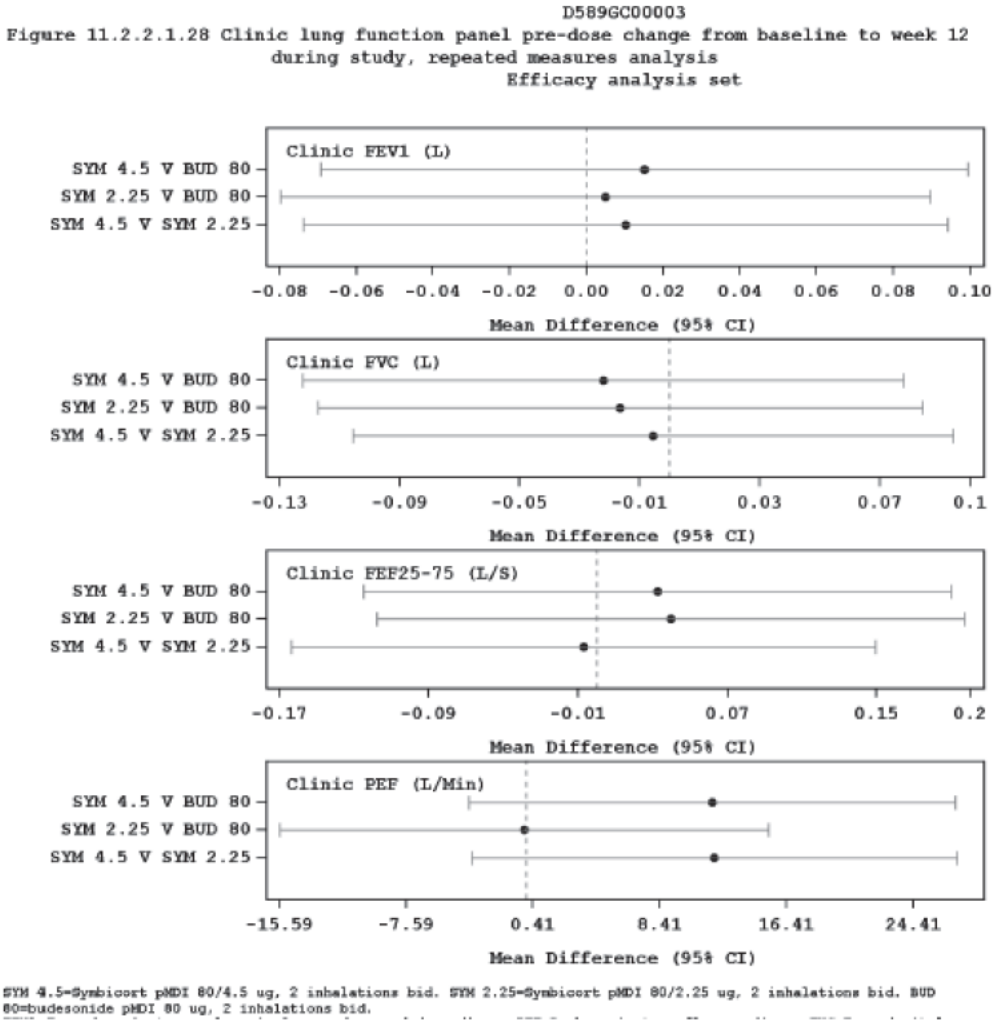
Source: Chase 3 study report Figure 5

Table 18 Secondary pre-dose clinic lung function endpoints (EAS)

					Treatment Difference		
	Statistics	SYM 80/4.5 (N=90)	SYM 80/2.25 (N=93)	Bud 160 (N=90)	SYM 80/4.5 vs Bud 160	SYM 80/2.25 vs Bud 160	SYM 80/4.5 vs SYM 80/2.25
FEV1 pre-dose							
Baseline	Mean	1.58	1.58	1.61			
Change from baseline to Week 12	Estimate	0.11	0.10	0.09	0.02	0.00	0.01
	(95% CI)	(0.04, 0.17)	(0.03, 0.16)	(0.03, 0.15)	(-0.07, 0.10)	(-0.08, 0.09)	(-0.07, 0.09)
	p-value				0.724	0.909	0.811
FVC pre-dose							
Baseline	Mean	2.06	2.11	2.12			
Change from baseline to Week 12	Estimate	0.11	0.11	0.13	-0.02	-0.02	-0.01
	(95% CI)	(0.03, 0.18)	(0.04, 0.19)	(0.05, 0.20)	(-0.12, 0.08)	(-0.12, 0.08)	(-0.11, 0.09)
	p-value				0.664	0.747	0.913
FEF25_75 pre-dose							
Baseline	Mean	1.42	1.38	1.36			
Change from baseline to Week 12	Estimate	0.12	0.13	0.09	0.03	0.04	-0.01
	(95% CI)	(0.01, 0.24)	(0.01, 0.25)	(-0.03, 0.21)	(-0.12, 0.19)	(-0.12, 0.20)	(-0.16, 0.15)
	p-value				0.684	0.621	0.929
PEF pre-dose							
Baseline	Mean	233.9	222.3	235.6			
Change from baseline to Week 12	Estimate	27.7	15.9	16.0	11.7	-0.15	11.87
	(95% CI)	(16.4, 39.1)	(4.4, 27.3)	(4.5, 27.5)	(-3.6, 27.1)	(-15.6, 15.3)	(-3.4, 27.2)
	p-value				0.134	0.985	0.128

Source: Reviewer

Figure 11 Clinic lung function pre-dose change from baseline to Week 12 (EAS)



SYM 4.5=SYMBICORT pMDI 80/4.5 µg, 2 inhalations bid. SYM 2.25=SYMBICORT pMDI 80/2.25 µg, 2 inhalations bid. BUD 80=budesonide pMDI 80 µg, 2 inhalations bid.

Source: Chase 3 study report Figure 11.2.2.1.28

Table 19 shows symptom scores, reliever use, and night-time awakenings due to asthma symptoms recorded by patients in the eDiary. An improvement from baseline in all symptom-related variables was observed in all treatment groups and with a tendency for a slightly greater improvement in the SYMBICORT 80/2.25 group on most of the endpoints, although differences were not statistically significant.

Table 19 Mean values for symptom-related variables (EAS)

Efficacy variable	SYM 80/4.5		SYM 80/2.25		Bud 160		SYM 80/4.5 vs Bud 160	SYM 80/2.25 vs Bud 160
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	Mean (95% CI)	Mean (95% CI)
Nighttime symptom score								
Baseline	89	0.2 (0.27)	93	0.2 (0.28)	90	0.2 (0.25)		
Change from baseline to Week 11-12 mean	78	-0.2 (0.27)	81	-0.2 (0.30)	80	-0.1 (0.22)	-0.02 (-0.09, 0.22)	-0.06 (-0.14, 0.24)
Daytime symptom score								
Baseline	88	0.9 (0.42)	93	0.8 (0.55)	90	0.8 (0.50)		
Change from baseline to Week 11-12 mean	76	-0.4 (0.53)	79	-0.4 (0.56)	79	-0.3 (0.48)	-0.02 (-0.18, 0.45)	-0.06 (-0.23, 0.47)
Total symptom score								
Baseline	87	1.1 (0.51)	92	1.0 (0.68)	89	1.0 (0.58)		
Change from baseline to Week 11-12 mean	73	-0.5 (0.66)	75	-0.6 (0.73)	74	-0.5 (0.53)	-0.06 (-0.26, 0.54)	-0.17 (-0.38, 0.58)
Nighttime awakenings due to asthma symptoms (%)								
Baseline	89	18.9 (26.70)	93	21.0 (28.44)	90	16.5 (25.16)		
Change from baseline to Week 11-12	78	-15.0 (26.56)	81	-19.3 (30.29)	80	-13.4 (21.55)	-1.56 (-9.15, 21.75)	-5.87 (-14.06, 23.71)
Nighttime awakenings due to asthma symptoms requiring reliever medication (%)								
Baseline	89	12.2 (22.16)	93	13.8 (23.60)	90	12.0 (22.44)		
Change from baseline to Week 11-12	78	-9.4 (21.23)	81	-13.5 (26.35)	80	-10.0 (19.58)	0.56 (-5.85, 18.38)	-3.53 (-10.76, 20.94)
Nighttime reliever medication								
Baseline	89	0.5 (0.70)	93	0.7 (1.09)	90	0.5 (0.86)		
Change from baseline to Week 11-12 mean	78	-0.3 (0.83)	81	-0.4 (0.98)	80	-0.3 (0.65)	-0.02 (-0.25, 0.67)	-0.10 (-0.36, 0.75)
Daytime reliever medication								
Baseline	88	0.7 (0.81)	93	1.0 (1.42)	90	0.7 (1.05)		
Change from baseline to Week 11-12 mean	76	-0.4 (0.89)	79	-0.5 (1.36)	79	-0.4 (1.06)	-0.02 (-0.34, 0.88)	-0.15 (-0.53, 1.10)
Total reliever medication								
Baseline	87	1.2 (1.43)	92	1.8 (2.46)	89	1.2 (1.52)		
Change from baseline to Week 11-12 mean	73	-0.7 (1.65)	75	-0.9 (2.42)	74	-0.6 (1.35)	-0.09 (-0.58, 1.35)	-0.28 (-0.91, 1.76)

Source: Reviewer

The health-related quality of life PAQLQ(S)) score was analyzed in terms of change from baseline to study period average (Table 20). The PAQLQ(S) score was also categorized for change from baseline to Week 12 by clinically relevant improvement (change ≥ 0.5 points), no change in score (change between >-0.5 and <0.5) or clinically relevant deterioration (change ≤ -0.5). The proportion of responders, i.e., patients achieving clinically relevant improvements, is summarized in Table 21. There were no statistically significant differences between treatment groups, and there was actually a slight trend toward greater improvement on budesonide than the SYMBICORT treatment arms.

Table 20 Overall PAQLQ(S) scores (EAS)

					Treatment Difference		
	Statistics	**SYM 80/4.5 (N=81)**	**SYM 80/2.25 (N=81)**	**Bud 160 (N=84)**	**SYM 80/4.5 vs Bud 160**	**SYM 80/2.25 vs Bud 160**	**SYM 80/4.5 vs SYM 80/2.25**
Baseline	Mean	5.36	5.61	5.53			
Change from baseline to study period average	Estimate	0.46	0.53	0.62	-0.17	-0.09	-0.08
	(95% CI)	(0.30, 0.62)	(0.38, 0.69)	(0.47, 0.78)	(-0.36, 0.03)	(-0.29, 0.11)	(-0.27, 0.12)
	p-value				0.098	0.367	0.449

Source: Reviewer

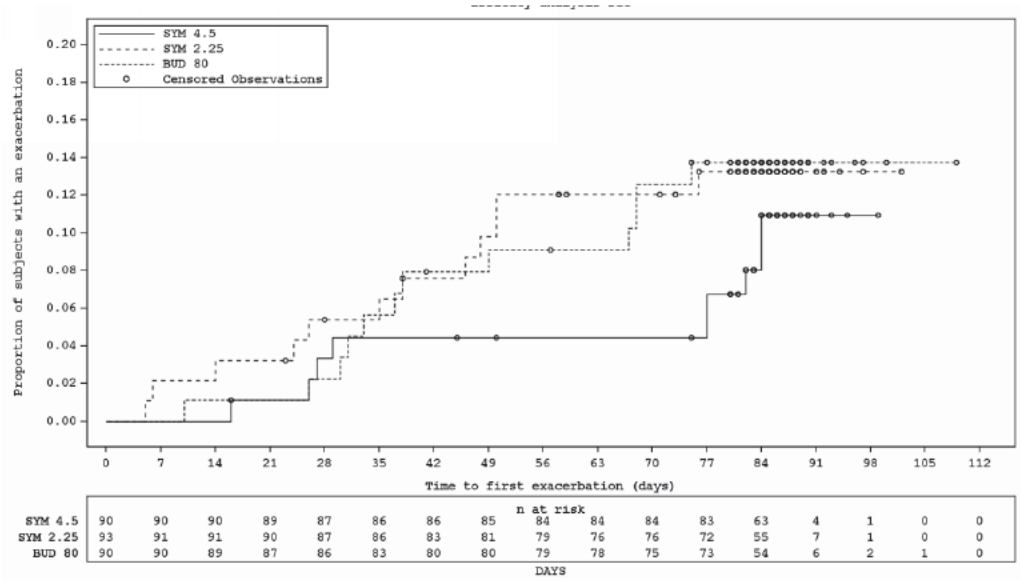
Table 21 Proportion of PAQLQ(S) responders (EAS)

	SYM 80/4.5 N (%)	**SYM 80/2.25 N (%)**	**Bud 160 N (%)**	**Treatment Comparison**		
				SYM 80/4.5 vs Bud 160	**SYM 80/2.25 vs Bud 160**	**SYM 80/4.5 vs SYM 80/2.25**
N	79	80	82			
Number (%) of patients						
with clinically relevant deterioration (change ≤ -0.5)	10 (12.66)	8 (10.00)	5 (6.10)			
with no change in score (change between >-0.5 and <0.5)	36 (45.57)	37 (46.25)	39 (47.56)			
with clinically relevant improvements(change ≥ 0.5 points)	33 (41.77)	35 (43.75)	38 (46.34)			
Odds ratio for clinically relevant improvements						
Estimate				0.82	0.89	0.96
(95% CI)				(0.44, 1.54)	(0.48, 1.65)	(0.52, 1.79)
p-value				0.540	0.719	0.903

Source: Reviewer

Figures 12 and 13 are Kaplan-Meier plots for time to first exacerbation and time to discontinuation from treatment with investigational product, respectively. There were no statistically significant differences between treatment groups. There were 9 (10.0%), 12 (12.9%) and 12 (13.3%) patients with exacerbation events in the SYM 80/4.5, SYM 80/2.25 and Bud 160 groups, respectively. The number of patients who discontinued treatment was slightly higher for the SYM 80/2.25 group (10.5%) compared with the SYM 80/4.5 and Bud 160 groups (both groups, 7.6%)

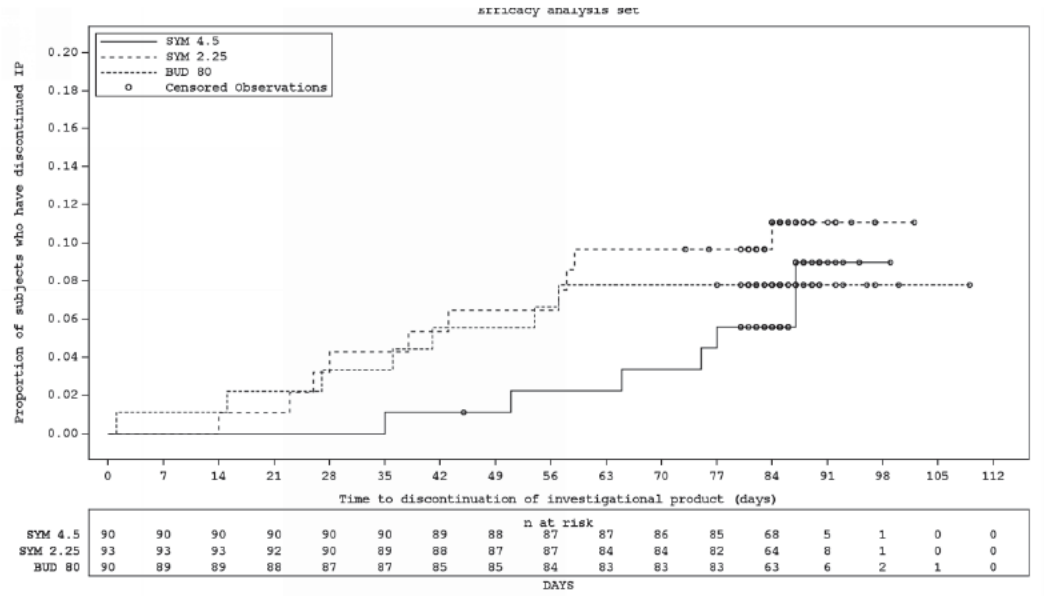
Figure 12 Time to occurrence of the first protocol defined asthma exacerbation (EAS)



SYM 4.5=SYMBICORT pMDI 80/4.5 µg, 2 inhalations bid. SYM 2.25=SYMBICORT pMDI 80/2.25 µg, 2 inhalations bid. BUD 80=budesonide pMDI 80 µg, 2 inhalations bid.

Source: Chase 3 study report Figure 19

Figure 13 Time to discontinuation of investigational product (EAS)



SYM 4.5=SYMBICORT pMDI 80/4.5 µg SYM 2.25=SYMBICORT pMDI 80/2.25 µgBUD 80=budesonide pMDI 80 µg, 2 inhalations bid.

Source: Chase 3 study report Figure 20

3.3 EVALUATION OF SAFETY

The original pediatric sNDA (21-929/S-013) included safety data and summaries for SYMBICORT pMDI from one Phase 1 and six Phase 3 studies. The current submission provides additional safety information primarily from the Phase 3 study since this was the only new Phase 3 study that evaluated treatment with SYMBICORT pMDI in pediatric patients 6 to <12 years of age.

No deaths were reported in the Chase 3 study. There were 2 serious adverse events (AEs) including acute lymphocytic leukemia and asthma exacerbation, both in the budesonide group. There were 5 patients who discontinued treatment due to AEs, 1 in each SYMBICORT group and 3 in the budesonide group. Most common AEs (frequency ≥3%) were evenly distributed across groups. However, the following were reported more frequently in the SYMBICORT groups than the budesonide group: upper respiratory tract infection, pharyngitis, headache, and vomiting. There were few potentially ICS-related AEs: 2 (dysgeusia and candida infection) in the SYMBICORT 80/2.25 group and 2 (oral candidiasis and upper limb fracture) in the budesonide 80 µg group. The only potentially β2-agonist-related adverse event reported was headache (4 patients in each SYMBICORT group and none in the budesonide group). Laboratory, vital signs, ECG, and physical examination findings did not raise any safety concerns.

Readers are referred to the review by the Medical Officer, Dr. Peter Starke, for a more detailed discussion of safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses for the primary efficacy endpoint were conducted to assess the consistency of treatment effects across demographic subgroups including age, gender, race, and region. The treatment effects were evaluated in each subgroup using the same model as used for the primary analysis. Since these were descriptive analyses, overall Type I error was not controlled. Results from Chase 1 and Chase 3 studies are presented in this section. Subgroup analysis was not performed for the Chase 2 study due to the small number of subjects.

The conclusions were generally consistent with those from the overall study population. The efficacy of budesonide over placebo and SYMBICORT 80/4.5 over budesonide 80 bid (Bud 160) were supported by most subgroup analyses. Interpretation of subgroup results, however, should be treated with caution due to small number of subjects in some subgroups.

4.1 Gender, Race, Age, and Geographic Region

Chase 1 Study

The similar ANCOVA model described for the primary analysis was used to explore the effect of age group (<8 years and ≥ years), gender, race, and region (US and non-US), on the change in pre-dose morning PEF from baseline to the treatment period average. Results are shown in Table 22 and are supportive of budesonide efficacy over placebo. There was no statistical significance for treatment differences across any subgroup for the primary endpoint. The estimated treatment effect was numerically greater in patients who were at least 8 years of age, males, White, and US patients, but estimates trended in the direction of benefit in all subgroups. Interpretation is limited due to the small number of patients in some subgroups.

Table 22 Subgroup analysis of the primary efficacy endpoint (Chase 1 study)

	Statistics	Placebo	Bud 160	Treatment Difference (Bud 160 – Placebo)
Age				
<8 years (n=66)	Estimate (95% CI) p-value	8.98	16.3	7.33 (-7.8, 22.4) 0.335
≥8 years (n=238)	Estimate (95% CI) p-value	5.63	21.7	16.0 (9.34, 22.7) <0.0001
Sex				
Male (n=192)	Estimate (95% CI) p-value	4.09	20.7	16.6 (9.15, 24.1) <0.0001
Female (n=112)	Estimate (95% CI) p-value	-3.6	7.96	11.6 (1.04, 22.1) 0.032
Race				
White (n=270)	Estimate (95% CI) p-value	4.28	19.5	15.2 (8.79, 21.7) 0.000
Other (n=34)	Estimate (95% CI) p-value	5.89	6.93	1.04 (-20, 21.90) 0.920
Region				
US (n=110)	Estimate (95% CI) p-value	-3.9	16.0	19.9 (9.13, 30.6) <0.0001
Non-US (n=194)	Estimate (95% CI) p-value	6.80	17.9	11.1 (3.64, 18.5) 0.004

Source: Reviewer

Chase 3 Study

The similar MMRM procedure described for the primary analysis was used to explore the effect of age group (6 to <9 years and 9 to <12 years), gender, race (White, Black/African American, or Other), and region (US and non-US) on the change from baseline in 1-hour morning post-dose FEV1 at Week 12. Results are in line with the overall study population (Table 23). There was no statistically significant interaction for subgroups of age category, sex, race, and region for the primary endpoint. Estimates trended in favor of SYMICORT over budesonide in all subgroups. The estimated treatment effect was numerically greater in the non-US region than in the US and also numerically greater in male than female patients. Since the numbers of patients were small, no firm conclusions can be drawn from these analyses.

Table 23 Subgroup analysis of the primary efficacy endpoint (Chase 3 study)

					Treatment Difference		
	Statistics	**SYM 4.5**	**SYM 2.25**	**Bud 160**	**SYM 4.5 vs Bud 160**	**SYM 2.25 vs Bud 160**	**SYM 4.5 vs SYM2.25**
Age							
6-<9 years (n=98)	Estimate	0.31	0.25	0.19	0.12	0.06	0.06
	(95% CI)	(0.19, 0.43)	(0.14, 0.36)	(0.08, 0.30)	(-.03, 0.28)	(-.09, 0.21)	(-.10, 0.21)
	p-value				0.124	0.417	0.452
9-<12 years (n=181)	Estimate	0.28	0.27	0.17	0.11	0.09	0.01
	(95% CI)	(0.21, 0.35)	(0.19, 0.34)	(0.10, 0.25)	(0.01, 0.20)	(-.01, 0.19)	(-.08, 0.11)
	p-value				0.033	0.067	0.764
Sex							
Male (n=113)	Estimate	0.31	0.26	0.14	0.17	0.11	0.05
	(95% CI)	(0.23, 0.39)	(0.18, 0.33)	(0.07, 0.22)	(0.06, 0.27)	(0.01, 0.21)	(-.05, 0.16)
	p-value				0.002	0.029	0.320
Female (n=166)	Estimate	0.25	0.23	0.21	0.05	0.02	0.02
	(95% CI)	(0.16, 0.35)	(0.12, 0.34)	(0.11, 0.31)	(-.09, 0.18)	(-.12, 0.17)	(-.12, 0.17)
	p-value				0.494	0.749	0.742
Race							
White (n=174)	Estimate	0.23	0.23	0.14	0.09	0.09	0.00
	(95% CI)	(0.15, 0.32)	(0.15, 0.32)	(0.05, 0.23)	(-.02, 0.21)	(-.02, 0.21)	(-.11, 0.11)
	p-value				0.104	0.115	0.984
Black or African American (n=76)	Estimate	0.28	0.23	0.21	0.08	0.03	0.05
	(95% CI)	(0.18, 0.39)	(0.13, 0.34)	(0.10, 0.31)	(-.06, 0.21)	(-.11, 0.16)	(-.08, 0.19)
	p-value				0.260	0.705	0.445
Other (n=29)	Estimate	0.49	0.25	0.17	0.32	0.07	0.25
	(95% CI)	(0.32, 0.67)	(0.12, 0.38)	(0.06, 0.29)	(0.12, 0.52)	(-.10, 0.24)	(0.03, 0.46)
	p-value				0.003	0.384	0.027
Region							
US (n=226)	Estimate	0.27	0.25	0.18	0.09	0.07	0.02
	(95% CI)	(0.20, 0.34)	(0.18, 0.32)	(0.11, 0.25)	(-.01, 0.19)	(-.02, 0.17)	(-.08, 0.12)
	p-value				0.065	0.142	0.697
Non-US (n=53)	Estimate	0.34	0.22	0.12	0.22	0.10	0.12
	(95% CI)	(0.25, 0.44)	(0.13, 0.31)	(0.03, 0.21)	(0.09, 0.35)	(-.03, 0.23)	(-.01, 0.25)
	p-value				0.002	0.126	0.074

Source: Reviewer

4.2 Other Special/Subgroup Population

This section is not applicable.

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

This submission contains two Phase 2 studies intended to determine the appropriate dose(s) of budesonide (Chase 1) and formoterol (Chase 2) as well as one Phase 3 confirmatory study (Chase 3) which evaluated the efficacy and safety of SYMBICORT, a fixed dose combination product containing budesonide 160 µg (an ICS) and formoterol 4.5 µg (a LABA). The contribution of each component to the claimed effects must be demonstrated according to the combination rule (21 CFR Section 300.50: Fixed-combination Prescription Drugs for Humans). As such the Chase 3 study was designed to evaluate the contribution of formoterol to the efficacy of the combination. While the contribution of budesonide could not be directly examined due to safety concerns with giving LABA as a monotherapy in asthma patients, its contribution can be reasonably inferred from earlier studies and the Chase 1 study, as well as from the general medical consensus that LABA/ICS products may be safer than LABA monotherapies in asthma.

In Chase 1 study, budesonide 160 µg bid (80 µg x 2 inhalations bid) was superior to placebo in improving morning PEF (primary endpoint) and in-clinic morning pre-dose FEV1(key secondary endpoint) from baseline to treatment period average. The treatment effects of 13.6 L/min for PEF (p-value<0.0001) and 0.06L for FEV1 (p-value=0.0047) were in favor of budesonide and were statistically significant. Other secondary variables were numerically supportive, including measures of lung function, asthma symptom scores, nighttime awakenings, reliever medication use, and withdrawals. There was a relatively high discontinuation rate (approximately 30%) attributable to inclusion of the placebo group and mandatory withdrawal due to pre-defined asthma events. Additional sensitivity analyses and a cumulative proportion of responder analysis supported the efficacy of budesonide over placebo. The study thus established an appropriate dose of budesonide as a single ingredient product for the treatment of asthma in patients 6 to <12 years old.

In Chase 2 study, all 3 formoterol doses given in combination with budesonide (ie, 160/2.25 µg, 160/4.5 µg, and 160/9 µg) provided statistically significant improvements in lung function compared with placebo (budesonide 160 µg), as assessed by the primary endpoint of FEV_1 averaged over 12 hours post-dose and the secondary endpoint of maximum FEV1 over the 12-hour assessment period. However, only the 4.5 µg and 9 µg formoterol doses provided improvements in FEV1 at the end of the 12-hour dosing period that were statistically significantly greater than the placebo treatment. Statistically significant improvements were observed when comparing 9 µg and 4.5 µg with 2.25 µg but not between the 9 µg and 4.5 µg doses. This study supported formoterol doses of 4.5 µg and 9 µg in the combination product with the 9.0µg dosage strength showing numerically similar results compared to the active control.

In Chase 3 study, treatment with SYMBICORT 80/4.5 led to statistically significant improvement in lung function as measured by the primary endpoint of change from baseline to Week 12 in 1-hour post-dose clinical FEV1. In patients receiving SYMBICORT 80/4.5, 1-hour post-dose FEV1 improved by 0.28 L from baseline to Week 12, as compared with 0.24 L for those receiving SYMBICORT 80/2.25 and 0.17 L for those receiving budesonide 80. The improvement was statistically significant for SYMBICORT 80/4.5 compared to budesonide 80, with an estimated difference of 0.120 L (p-value=0.006), whereas the difference between SYMBICORT 80/2.25 and budesonide was not statistically significant (p-value=0.063). A numerical yet not statistically significant difference was also observed between the two SYMBICORT doses in favor of SYMBICORT 80/4.5. Findings from additional analyses of change from baseline to study period average and various sensitivity analyses were consistent with the primary results.

It should be noted that while improvement of SYMBICORT 80/4.5 over budesonide was observed in the majority of secondary lung function variables, treatment comparisons reached nominal statistical significance (p-value<0.05) only in a few post-dose measurements, such as change from baseline to Week 12 for 1-hour post-dose FEF25_75, PEF, and 15-minute post-dose FEV1. There were no statistically significant differences between SYMBICORT 80/4.5 and budesonide in change from baseline to Week 12 for 1-hour post-dose FVC or any of the pre-dose lung function tests. Furthermore, there were no major differences between treatment groups for health-related quality of life and symptom-related variables. There also were no statistically significant differences between treatment groups for time to first asthma exacerbation or time to discontinuation of treatment with IP. Exacerbation events were noted in 9 (10.0%) and 12 (13.3%) patients in the SYMBICORT 80/4.5 and budesonide groups, respectively.

The Chase 3 study confirmed the efficacy of SYMBICORT 80/4.5, 2 inhalations bid in comparison with budesonide 80 µg, 2 inhalations bid, demonstrating the added benefit of the formoterol component.

5.2 CONCLUSIONS AND RECOMMENDATIONS

Three studies conducted in accordance with the data requested in the complete response letter supported the use of SYMBICORT pMDI 80/4.5 µg, 2 inhalations bid, for the treatment of children 6 to <12 years old whose asthma is not adequately controlled with low-dose ICS.

The 6-week, randomized, double-blind, placebo-controlled study (Chase 1) showed that a budesonide dose of 160 µg is efficacious as a single ingredient product and provided support for the chosen dose to include in the SYMBICORT inhalation aerosol combination product. The single dose, 5-way cross-over study (Chase 2) demonstrated the effect of formoterol given in addition to 160 µg of budesonide, supporting formoterol doses of 4.5 µg and 9 µg in the combination product. The 12-week randomized, double-blind, parallel group study (Chase 3) evaluated the added benefit of formoterol in combination with budesonide and justified the use of SYMBICORT 80/4.5 as an effective treatment of asthma in pediatric patients aged 6 to <12 years old.

5.3 LABELING RECOMMENDATIONS

The focus of the labeling review will be on the later part of Section 14.1 Clinical Studies Asthma: Patients aged 6 to <12 years old. Based on the preliminary review of the proposed labeling, I have the following comments for discussion.

- Add brief description of the Chase 1 and Chase 2 studies since these two determined the appropriate doses of budesonide and formoterol, respectively, to include in the combination product.
- For Chase 3 study, should the SYMBICORT 80/2.25 dose group be reported? Would it be helpful to include a graph showing mean change from baseline in 1-hour post-dose clinic FEV1 (L) over time?
- For Chase 3 study, provide a brief summary on patient reported outcomes or quality of life measures, given the lack of difference seen for these measures, which are more direct measures of how patients function and feel in daily life than the primary spirometry-based lung function endpoint.

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/s/

LAN ZENG
01/09/2017

GREGORY P LEVIN
01/09/2017