4.

b(4)

9.2.1. Proposed Draft of Letter to Sponsor:

b(5)

b(5)

9.3. Recommendation on Postmarketing Actions

9.3.1. Risk Management Activity

In regard to educational activities to avoid confusion between the use of Foradil Aerolizer and Foradil Certihaler, the applicant has submitted a plan for differentiation in use of these two products which is not acceptable (v5. a51) (see description of applicant's plan below). It is important that practicing physicians and patients not use these products interchangeably. The Foradil Aerolizer is approved for treatment of COPD and exericise-induced asthma but the Certihaler is not. The Certihaler is a breath-actuated device that requires intensive education about appropriate use.

b(4)

9.3.2. Required Phase 4 Commitments

5 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

b(4)

9.5 Comments to Applicant

See section 9.2.1. above.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1. Patient Use Study CFOR258F2304 (v1, pgs9-13, a4, a5):

Two identical *patient use studies* were performed (*studies 2304 and 2306*). The objective of these studies was to evaluate the function of the Cerihaler device during and after patient use by collecting patient observation data on potential device failure and conducting an in-vitro technical assessment of the devices at the conclusion of the study, i.e. after three weeks of use. Analysis was descriptive for device functionality and safety (adverse events) only. No formal statistical analysis was done. *(NOTE: Study 2306 was performed subsequent to study 2304. In study 2304, there were 3 devices that had confirmed device malfunction based on in-vitro studies. Specifically, there was misalignment of the dosing bar and the sliding shelter of the device which led to failure of the dosing mechanism to move so that the dose could not be delivered. This defect had not been observed prior to that time, was not reproducible in the laboratory and was attributed by the applicant to the fact that study 2304 was performed with devices manufactured in 2002 without studs on the guiding rail. Study 2306 was performed using devices that included studs on the guiding rail.)*

10.1.1.1. Study Design:

Studies 2304 and 2306 were 3 week, open label, uncontrolled, multi-center studies in patients with asthma (FEV-1 40% or greater) who were 5-74 years of age. Patients received 10 mcg (1 inhalation) of formoterol delivered by Certihaler twice a day approximately 12 hours apart. Albuterol was used as rescue medication. Patients kept a diary that recorded counter number after each use and responded to specific questions about the function of the device. The devices were collected, sent back to Novartis and then shipped to SkyePharma for technical in-vitro assessment. The expected number of actuations by patients was 42 (twice a day for 21 days). Since 60 actuations are delivered by the Certihaler, there were doses left in returned devices. Devices from patients who discontinued the study prior to completion of the three week treatment period were collected and sent to SkyePharma and all unused devices were also collected and returned to Novartis. If the patient considered that the device was not functioning correctly, the patient contacted the study site. If it was determined that the device was malfunctioning, the patient was to be withdrawn from the study. The dataset obtained from the in-vitro technical assessment at the conclusion of the study was considered the primary data for the identification of device function but the results of the in-vitro assessment were to be considered in conjunction with the data recorded daily by the patient in the patient diary.

Study 2304 was a 3 week open label uncontrolled multi-center study in 157 patients with asthma (FEV-1 40% or greater) who were 5-74 years of age who received 10 mcg (1 inhalation) of formoterol delivered by Certihaler bid approximately 12 hours apart with albuterol as rescue medication.

All Certihaler devices were assessed after the patient treatment period by SkyePharma and given a rating of 0 = device functioning or 1 = device failure. Device assessment included: 1) visible appearance and weight of the returned MDDPI; 2) counter position function; 3) digital photography; 4) functionality of the protective cap and mouthpiece, as reflected in any inconsistencies during opening or bending movements of the protective cap and during removal of the mouthpiece; 5) actuation flow rate (flow rate required to trigger the valve shield); 6) dose counter function test; and 7) lock-out mechanism.

Assessment of AFR was initiated at 30 L/min with increases of 5 L/min if the valve shield failed to move (flow rate was not adequate to trigger the valve shield). Any AFR above 50 L/min was rated a device failure. If the dose counter was not functioning correctly in any way, it was considered a device failure. After the AFR testing, waste shots were made at a flow rate of 60 L/min. After the last dose (counter display 00) an additional waste shot was performed and recorded to confirm that the counter display changed to the final '999' reading and the device lock out mechanism engaged. If the lock-out failed it was considered a device failure

The initial technical assessment of the devices was conducted without reference to the information recorded in the patient diaries. However, at the final evaluation, the technical results were considered in conjunction with the data recorded daily by the patient in the diary so that any device identified as a problem device either from the technical assessment or by the patient was assessed and a narrative prepared discussing functionality of the given device.

Patient Diary: Patients kept a diary that recorded counter number after each use and patients responded to the following questions: "Did the dose counter decrease by one?"; "Did you get the dose?; and "Did you notice any difference in triggering the device?" "If yes, please comment." At the end of the treatment period, at least 14 doses were required to be left in the Certihaler. The devices were collected, send back to Novartis and then shipped to SkyePharma for technical assessment. Devices from patients who discontinued the study prior to completion of the three week treatment period were collected and sent to SkyePharma and all unused devices were also collected and returned to Novartis. If the patient considered that the device was not functioning correctly, the patient contacted the site. If it was determined that the device was malfunctioning, the patient was to be withdrawn from the study.

Post Treatment Assessment: All Certihaler devices were assessed after the patient treatment period by SkyePharma and given a rating of 0 = device functioning or 1 = device failure. Device assessment included: 1) visible appearance and weight of the returned MDDPI; 2) counter position (number); 3) digital photography; 4) functionality of the protective cap and mouthpiece, as reflected in any inconsistencies during opening or bending movements of the protective cap and during removal of the mouthpiece; 5) actuation flow rate (flow rate required to trigger the valve shield); 6) dose counter function test; and 7) lock-out mechanism.

Visible properties and weight of returned inhaler: The inhaler was inspected for visual appearance and the weight of the inhaler was recorded to determine the approximate amount of powder released during the in vitro tests of device functioning.

Counter position: The counter position was noted as an indicator of the number of inhalations remaining and whether the counter was functioning and the alignment of the counter figures was checked.

Function of the protective cap and mouthpiece: The moving parts of the inhaler were tested. Any inconsistencies during the opening or bending downward movements of the protective cap and during the removal of the mouthpiece were noted.

Actuation Flow Rate: The flow rate required to trigger the value shield was performed in incremental steps of 5 L/min up to the actuation point beginning at an actuation flow rate of 30 L/min. The minimum flow rate needed to actuate an inhaler was recorded as the average of three consecutive actuations. If the valve shield failed to move during three attempts, the flow rate was increased by 5 L/min and the test repeated. Actuation flow rates above the release specification of 50 L/min were rated as a "failure" and devices were identified where actuation occurred at 40, 45, 50, and 55 L/min. The simulated inhalation was actuated for a duration of 8 seconds to reach a total simulated inspiration volume of 4 liters.

Dose Counter Function: The counter number noted during the initial identification of the returned device was compared to the counter number after actuating each number of doses in the determination of the actuated flow rate. The counter display should have been the same as the calculated difference of the initial counter reading minus the number of effective actuations. After the last dose (counter display 00) an additional waste shot was recorded to confirm that the

counter display changed to the final "999" reading and the device lockout mechanism functioned.

The initial technical assessment of the devices was conducted without reference to the information recorded in the patient diaries. However, at the final evaluation, the technical results were considered in conjunction with the data recorded daily by the patient in the diary so that any device identified as a problem device either from the technical assessment or by the patient was assessed and a narrative prepared discussing functionality of the given device.

Safety Monitoring: adverse events were monitored.

10.1.1.2. Study Results (v2, a6, pgs12-32):

In *patient use study 2304*, 157 patients entered the study and 150 patients completed the study. There were 2 patients who discontinued because of adverse events and 5 patients who discontinued because of device malfunction or failure (confirmed in 3 patients; see below) (v6, p58-59). In the patient diary, the patient was asked to respond to 3 specific questions: 1) "Did the dose counter decrease by one?"; 2) "Did you get the dose?"; and 3) "Did you notice any difference in triggering the device?". A difference in device triggering was the major complaint by patients. Of the 81 patients (52%) who noted a difference in triggering the device, 17 (21%) of these patients also reported that the dose counter did not decrease and 17 (21%) reported that they did not get a dose of study medication. There were 8 patients who noted both that the dose counter did not decrease and that they did not get a dose of study medication. The remainder of the patients who gave a positive response, EITHER noted that the dose counter did not decrease OR that they did not get the dose. In-vitro data at the end of the study showed that most of the devices perceived by patients to be malfunctioning in some way were functioning normally without an increase in actuation flow rate or dose counter malfunction. Of 157 assessed devices, 153 worked without malfunction during in-vitro assessment, i.e. the dose counter functioned, the lock-out worked, and the actuation flow rates were expected given a 5 L/min increase with the use of the device. Of the 4 devices that malfunctioned during in-vitro testing, 3 were devices used by patients who discontinued because of device malfunction. These devices were found to have misalignment of the dosing bar and the sliding shelter of the device resulting in failure of the dosing mechanism to move so that the dose could not be delivered. One device was accidentally damaged in the lab and removed from the testing program while all of the other 153 returned devices functioned normally without mechanical failure.

In vitro device assessment that was done at the completion of the study confirmed that there was a mechanical failure in 3 of the 5 devices (2%) used by patients who discontinued because of device problems. The device functioned normally in the other 2 patients. There was a misalignment of the dosing bar and the sliding shelter of the device in the 3 malfunctioning devices that resulted in failure of the dosing mechanism to move so that the dose could not be delivered. This was a device failure that had not been observed in any of the previous clinical studies or during technical testing. This jamming of the sliding shelter and dosing bar could not be reproduced in the laboratory and was not a result of permanent deformation of the Certihaler.

Potential inconsistencies during the manufacturing process were retrospectively re-checked and no deviations for the production process of the sliding shelter, dosing bar and guiding rail were observed. All Certihalers showing misaligned position of the dosing bar and sliding shelter were from the same manufacturing period on the assembly line. The applicant attributes this particular device failure to the fact that the study was performed with devices manufactured in 2002 without studs on the guiding rail. The applicant repeated the study (study 2306; see below) with devices that contained the studs. One device was accidentally damaged in the lab and removed from the testing program while all of the other 153 returned devices functioned normally without mechanical failure.

There were another 9 devices that did not actuate at 40 L/min or less but did actuate at 45 L/min and one device actuated at 50 L/min after failing to actuate at 40 and 45 L/min. Of these, 4 patients did not comment on any problem in their diary, 4 patients commented about device function at some point during the study but did not indicate a problem at the last recorded visit and one patient indicated in the diary on the morning of the last day that it was hard to get a dose. At all visits, the dose counter had decreased as expected. There were no dose counter failures, or failure in lock-out.

There were 22 patients (14%) who responded negatively to the question "Did the dose counter decrease by one?", 21 patients (13%) who responded negatively to the question "Did you get the dose?", and 76 patients (48%) who responded negatively to the question "Did you notice any difference in triggering the device?"(v6, p61). Patient comments in this study and study 2306 discussed below included but were not limited to the following: "Device jammed, had to inhale twice, device sticks, delay in the click, would not work at all, counter would not move, breath in longer before holes opened, numbering system is messed up, had to breath twice before holes opened, device difficult to open, took 3 breathes, needed to breath in faster, hard to open, device would not release the dose, tried 4 times, it took 5 breaths, nothing came out, counter decreased by 2, device not working after 4 attempts, dosed much later in the breath cycle, took 20 puffs to activate, no rollover, holes never opened, difficult to open, tried 5 times before it opened, had to close and reopen the inhaler to work".

There were another 8 devices that did not actuate at 40 L/min or less but did actuate at 45 L/min and one device actuated at 50 L/min after failing to actuate at 40 and 45 L/min. Of these, 4 patients did not comment on any problem in their diary, 4 patients commented about device function at some point during the study but did not indicate a problem at the last recorded visit and one patient indicated in the diary on the morning of the last day that it was hard to get a dose. At all visits, the dose counter had decreased as expected. There were no dose counter failures, or failure in lock-out (v2, pgs 13-17).

There were 26 patients (16.6%) in study 2304 who reported an adverse event. There were 2 patients who had severe adverse events suspected of being related to Foradil administration – insomnia and feeling jittery. There were 2 patients who were discontinued from the study; one developed moderate tremor which went away when Foradil was discontinued; the other patient developed exacerbation of asthma not suspected of being related to the study medication. There were no serious adverse events reported. *In general, the adverse events that were reported were*

those frequently seen after administration of an inhaled beta agonist and were not serious or unexpected. No safety issues are raised from the data in this study.

10.1.1.3. COMMENTS: *There was a failure rate of 2% of the Certihaler devices characterized by a failure of the dose being delivered. This was recognized by the patient and is clinically acceptable for a drug product proposed for maintenance administration in the treatment of asthma. However, there was a significant incidence of patient inability to use the device correctly associated either with real or perceived malfunction of the device. This is a serious deficiency for this drug product and must be addressed by the applicant before Foradil Certihaler can be approved (see comments to applicant). There was no safety signal from the adverse events reported in this study.*

10.1.2 Patient Use Study CFOR258F2306 (v1, p13-15)(v2, a7)

Two identical *patient use studies* were performed (*studies 2304 and 2306*). The objective of these studies was to evaluate the function of the Cerihaler device during and after patient use by collecting patient observation data on potential device failure and conducting an in-vitro technical assessment of the devices at the conclusion of the study, i.e. after three weeks of use. Analysis was descriptive for device functionality and safety (adverse events) only. No formal statistical analysis was done. *(NOTE: Study 2306 was performed subsequent to study 2304. In study 2304, there were 3 devices that had confirmed device malfunction based on in-vitro studies. Specifically, there was misalignment of the dosing bar and the sliding shelter of the device which led to failure of the dosing mechanism to move so that the dose could not be delivered. This defect had not been observed prior to that time, was not reproducible in the laboratory and was attributed by the applicant to the fact that study 2304 was performed with devices manufactured in 2002 without studs on the guiding rail. Study 2306 was performed using devices that included studs on the guiding rail.)*

10.1.2.1. Study Design: identical to study F2304 except that the patient diary card was revised by changing the third question in the patient diary from "Did you notice any difference in triggering the device?" to "Did you have to breathe in any harder to make the device work? If yes, please comment.". The rationale for this change is not given by the applicant. In addition, patients were asked to write in the diary when and how they cleaned the device to assess any unusual handling of the device and drawings in the patient instructions were improved.

10.1.2.2. Study Results (v2, a9, pgs7-30)

There were 154 patients entered into the study 5-74 years of age and 145 patients completed the study. There were 9 patients who discontinued prematurely: one due to an adverse event (headache), five because of malfunction of the device, one because the device was destroyed by a dog, one because the patient missed multiple doses because of device and counter malfunction (described by the applicant as "administrative") and one because the patient broke the device.

There were 73 patients (47%) who had some type of device malfunction at least once during the study. Of these patients, 28 (18%) indicated that the dose counter did not decrease by one. There

were 16 patients (10%) who indicated that they did not get the dose. There were 14 of these 16 patients (86%) who indicated that they had to breathe in harder to make the device work. There were 63 patients in all (41%) who indicated that they had to breathe in harder to make the device work. There were 19 of these patients (30%) who also indicated that the dose counter did not decrease and 14 (22%) who indicated that they did not get the dose. Patient comments in this study and study 2304 discussed above included but were not limited to the following: "Device jammed, had to inhale twice, device sticks, delay in the click, would not work at all, counter would not move, breath in longer before holes opened, numbering system is messed up, had to breath twice before holes opened, device difficult to open, took 3 breathes, needed to breath in faster, hard to open, device would not release the dose, tried 4 times, it took 5 breaths, nothing came out, counter decreased by 2, device not working after 4 attempts, dosed much later in the breath cycle, took 20 puffs to activate, no rollover, holes never opened, difficult to open, tried 5 times before it opened, had to close and reopen the inhaler to work".

In-vitro device assessment at the end of the study found only one device with a mechanical failure, while all other devices functioned normally. The one malfunctioning device had a malfunctioning dose counter where the dose counter failed to count the dose. The patient who had this device recorded that the dose counter did not decrease by one on several occasions and that he did not get the dose of study medication. The device was still actuating and providing medication yet the dose counter had stopped counting which was due to a damaged counter mechanism. A hole was drilled into the top shell of the device, an endoscope was inserted and it was noted that a transportation pinion of the dosing bar was not engaging with the tooth of the counter wheel.

There were 19 adverse events (12%) reported from this study. One patient developed a severe headache requiring discontinuation from the study that was suspected of being related to Foradil administration. There were no serious adverse events reported. *In general, the adverse events that were reported were those frequently seen after administration of an inhaled beta agonist and were not serious or unexpected. No safety issues are raised from the data in this study*

10.1.2.3.COMMENT: *Using devices with studs, the absence of which was felt by the applicant to be the cause for device malfunctioning in study 2304, there was only one device (0.6%) that had a malfunctioning dose counter. This incidence of malfunction is clinically acceptable for a drug product that is intended for the maintenance treatment of asthma. However, there was a significant incidence of patient inability to use the device correctly associated either with real or perceived malfunction of the device. This is a serious deficiency for this drug product and must be addressed by the applicant before Foradil Certihaler can be approved (see comments to applicant). No safety signals were apparent from the data in this study.*

10.2 Line-by-Line Labeling Review (only the sections that were changed with this submission are reviewed below)

10.2.1. Description section:

4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

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Richard Nicklas
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Eugene Sullivan
12/10/04 11:18:32 AM
MEDICAL OFFICER
Agree with recommendation. See my memorandum.

Foradil Certihaler
NDA 21,592

Application type: original NDA
Sponsor: Novartis
Product Name: Foradil Certihaler
USAN Established Name: formoterol fumarate
Category of Drug: beta adrenergic agonist
Route of Administration: oral inhalation (Certihaler)
Medical Reviewer: Richard A. Nicklas M.D.
Review Date: 7 October 2003
Document Date: 17 December 2002
Stamp Date: 20 December 2002

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Clinical Review for NDA 21,592

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The data submitted by the applicant demonstrate that Foradil Certihaler (formoterol fumarate) is efficacious for the maintenance treatment of asthma and the prevention of bronchospasm in adults and children 5 years of age and older with reversible obstructive airway disease. Foradil Certihaler has a built-in airflow threshold limitation that releases the dose at the optimum point in the patient's breathing cycle. The device also has a blocking mechanism that prevents dose emission below 30 l/min and has a dose counter that is actuated only by the patient's inhalation of a dose. The incidence of adverse effects, as well as changes in vital signs, ECGs and laboratory tests that were observed when formoterol was delivered by the Certihaler were generally similar to those seen after administration of placebo. The exception was tremor, which is a recognized side effect associated with the administration of an inhaled beta agonist. The data submitted, therefore, support the safety of Foradil Certihaler and there are no serious risks associated with this drug product. There is an acceptable benefit:risk profile for this drug product and therefore, the clinical recommendation is for Approval.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The studies done by the sponsor were appropriate and of adequate quality to assess the effectiveness and safety of Foradil Certihaler in children and adults; Although additional studies in elderly adults and adolescents would be helpful in providing further data on the benefits and risks in these patient populations, no formal phase 4 commitment should be required. In addition, the majority of patients in the key studies were Caucasian. Although the incidence of adverse events did not appear to be significantly different in non-Caucasian patients in these studies, further evaluation of Foradil Certihaler in non-Caucasian patients would help to better define the benefit: risk profile for this drug product. However, no formal phase 4 commitment should be required.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Foradil (formoterol fumarate) Certihaler is a long-acting relatively beta-2 selective beta adrenergic agonist bronchodilator delivered by oral inhalation by multiple dose dry powder inhaler (MDDPI). Formoterol is currently marketed as Foradil Aerolizer. The sponsor performed 3 key studies in adults with persistent asthma and 2 key studies in children with persistent asthma. These included in adults, two 12 week repetitive dose efficacy and safety studies and one dose-ranging study, and in children one 12 week repetitive dose efficacy and safety study and one dose-ranging study. There were 326 patients enrolled in the two pediatric studies, 204 of whom received Foradil Certihaler. There were 683 patients enrolled in the key adult studies, of whom 243 received Foradil Certihaler. These studies were performed to obtain an indication for the maintenance treatment of asthma and the prevention of bronchospasm in adults and children 5 years of age and older. Overall patient exposure included 1262 patients of whom 326 were 5-12 years of age.

B. Efficacy

Foradil Certihaler was shown to be efficacious for the maintenance treatment of asthma and the prevention of bronchospasm in adults and children 5 years of age and older with reversible obstructive airway disease.

The two key studies in children were: 1) a 12 week multicenter, randomized, double-blind, placebo controlled, parallel group study in children 5-12 years of age with persistent asthma who received 10 mcg bid of formoterol delivered by Certihaler (MDDPI)(study 604). The primary efficacy variable was the 12 hour AUC FEV-1 measured on day 1, and after 1, 2 and 3 months of treatment. Other efficacy variables included serial FEV-1 and FVC, number of asthma exacerbations, AM/PM PEF, asthma symptom scores, and use of rescue medication. Safety variables included adverse events, vital signs, laboratory tests, physical examination and ECGs. Patients who received Foradil Certihaler had a statistically significantly greater improvement in AUC FEV-1 over 12 hours throughout the 3 months of treatment than did patients who received placebo. Serial measurements of FEV-1 showed that the duration of effectiveness, based on statistical comparison with placebo on day 1 was 12 hours, after one month of treatment was 10 hours and after 3 months of treatment was 6 hours. In study 604, the mean change from baseline in AUC for 12 hour FEV-1 after 3 months of treatment with formoterol by MDDPI was 2.45 L/hr compared with 1.45 L/hr after treatment with placebo. Based on serial measurements of FEV-1 over this 12 hour period, there was a peak mean improvement in the formoterol MDDPI

group over the placebo group of 0.12 L (17% mean improvement from baseline) 15-60 minutes after administration of study drug.

COMMENT: *This treatment effect, although small, is probably clinically significant in terms of patient benefit. The relative mildness of asthma in the patient population studied (mean % predicted FEV-1 at baseline = 76%) may have contributed to the modest improvement seen in FEV-1 after treatment. A 17% improvement from baseline is consistent with the change seen after administration of other long-acting inhaled beta adrenergic agonist drug products (Verberne AAPH et al. J Allergy Clin Immunol 1993; 91:127). A 0.12 L treatment effect is also consistent with the change seen after administration of other long-acting inhaled beta adrenergic agonist drug products (see MOR NDA 20,236 S-005). Based on serial FEV-1 measurements in study 604, there is a suggestion that tolerance develops with continued administration over 3 months in children 5-12 years of age. This is not, however, supported by other data from that study and may represent, in part, a small but significant and unexpected increase in placebo response after 3 months of treatment.*

2) a randomized, double-blind, placebo-controlled and active treatment controlled, crossover study in children 5-12 years of age who received 5, 10, 15 and 30 mcg bid of formoterol delivered by Certihaler as well as 12 mcg bid of formoterol delivered from the Aerolizer each for a period of one week (study 602). The primary efficacy variable was AUC for FEV-1 over 12 hours measured at the end of each week of treatment. Other efficacy variables included serial FEV-1 measurements, daily asthma symptom scores, and use of rescue medication. Safety parameters included adverse events, ECGs, vital signs, physical examination and laboratory tests. Unchanged and conjugated formoterol were measured in the urine. All doses of formoterol delivered by Certihaler as well as formoterol delivered by Aerolizer produced a statistically significantly greater improvement in FEV-1 AUC over 12 hours than did placebo. Based on pharmacokinetics and pharmacodynamics, an appropriate dose of 10 mcg bid was selected for administration in study 604.

The three key studies in adults were: 1) two 12 week randomized, multicenter, double-blind, double-dummy, placebo and active treatment controlled, parallel group studies in patients 13-85 years of age with persistent asthma who received 10 mcg bid of formoterol delivered by Certihaler (MDDPI) (studies 2302 and 2303). The active treatment control was albuterol MDI 180 mcg qid. The primary efficacy variable in both these studies was the 12 hour AUC FEV-1 after 3 months of treatment. Other efficacy variables were QOL assessment, serial FEV-1 and FVC measurements, number of asthma exacerbations, AM/PM PEF, symptoms scores and use of rescue medication. Safety variables included adverse events, laboratory tests, vital signs, physical examination and ECGs. In both studies, there was a statistically significantly greater improvement in FEV-1 AUC over 12 hours after treatment with Foradil Certihaler compared with placebo.

In *study 2302*, the mean AUC for 12 hour FEV-1 after 3 months of treatment with formoterol by MDDPI was 5.21 L/hr compared with 1.47 L/hr after treatment with placebo. Based on serial measurements of FEV-1 over this 12 hour period, there was a peak mean improvement in the formoterol MDDPI group over the placebo group of 0.41 L one hour after administration of study drug. In *study 2303*, the mean AUC for 12 hour FEV-1 after 3 months of treatment with formoterol by MDDPI was 4.45 L/hr compared with 2.79 L/hr after treatment with placebo. Based on serial measurements of FEV-1 over this 12 hour period, there was a peak mean improvement in the formoterol MDDPI group over the placebo group of 0.36 L 30 minutes after administration of study drug.

COMMENT: *These effect sizes are clinically significant and consistent with changes that have been seen with formoterol delivered by Aerolizer (see study 601; package insert for Foradil Aerolizer; NDA 20,236 Serevent MDI). There are no unresolved issues regarding the efficacy of Foradil Certihaler in adults.*

2) a randomized, multicenter, double-blind, double-dummy, placebo-controlled and active treatment controlled, incomplete block crossover study with pharmacokinetic evaluation in patients 20-73 years of age who received 5, 10, 15 and 30 mcg bid of formoterol delivered by Certihaler as well as 12 mcg bid of formoterol delivered from the Aerolizer each for a period of one week (study 601). The primary efficacy variable in this study was AUC for FEV-1 over 12 hours measured at the end of each week of treatment. Other efficacy variables included serial FEV-1 measurements, daily symptom scores, and use of rescue medication. Safety variables included adverse events, ECGs and vital signs. Conjugated and unchanged formoterol was measured in the urine. A statistically significantly greater improvement in FEV-1 AUC over 12 hours after treatment for one week was demonstrated for all doses of formoterol delivered by Certihaler as well as for formoterol delivered by Aerolizer compared to placebo. An appropriate dose, 10 mcg bid, was selected for studies 2302 and 2303, based on efficacy and safety assessments in study 601.

C. Safety

There were 558 patients who received formoterol by Certihaler (MDDPI), 204 of whom were children 5-12 years of age. For comparison, there were 215 patients who received formoterol by Aerolizer as an active treatment control, 167 patients who received albuterol MDI as an active treatment control and 512 patients who received placebo. There were 166 adults who received a dose of 10 mcg bid of formoterol by MDDPI for a period of 12 weeks and 127 pediatric patients who received 10 mcg bid of formoterol by MDDPI for the same period of time. In studies of varying length 506 patients received a total daily dose of 20 mcg (10 mcg bid), including 127 children 5-12 years of age.

COMMENT: *This provided an adequate database for safety evaluation, both from the standpoint of monitoring and follow-up.*

Serious adverse events occurred in 9 patients who received formoterol MDDPI (1.6%), 1 patient who received formoterol by Aerolizer at a dose of 12 mcg bid (0.5%), 5 patients who received 180 mcg qid of albuterol MDI (3%) and 4 patients who received placebo (0.8%). The serious adverse events seen after administration of formoterol MDDPI were femoral neck fracture, basal cell carcinoma, small cell lung cancer, asthma aggravated (3), bronchospasm, respiratory distress and appendicitis. None of these serious adverse events were seen in the placebo group. There was one patient in the formoterol Aerolizer group who had aggravated asthma (incidence was 0.5% in both formoterol groups). COMMENT: *Exacerbation of asthma has been recognized in patients receiving long-acting inhaled beta agonists and is difficult to conclusively link to use of this type of drug in patients who are at risk for such events because of their underlying disease.*

Adverse events that occurred in the formoterol MDDPI group with an incidence of 2% or more greater than in the placebo group included: 1) vomiting (2.9% in the formoterol MDDPI group, 1.4% in the placebo group); 2) pyrexia (3.6% in the formoterol MDDPI group, 2.1% in the placebo group); 3) nasopharyngitis (7% in the formoterol MDDPI group, 5% in the placebo group); and 4) tremor (7% in the formoterol MDDPI group, 1% in the placebo group). Adverse events in children 5-12 years of age that occurred in the formoterol MDDPI group with an incidence of 2% or more greater than in the placebo group included: 1) vomiting (6% of the formoterol MDDPI group and 2% of the placebo group; 2) pyrexia (7% of the formoterol MDDPI group and 4% of the placebo group; 3) URIs (11% of the formoterol MDDPI group and 8% of the placebo group; 4) headache (7% of the formoterol MDDPI group and 5% of the placebo group; and 5) tremor (6% of the formoterol MDDPI group and 1% of the placebo group).

COMMENT: *Tremor is a recognized adverse effect associated with administration of inhaled beta adrenergic agonist medications in humans and in other animals. The reason for the higher incidence of infections and/or manifestations of infection in patients who received formoterol by MDDPI is unclear but of doubtful clinical significance.*

In studies with formoterol MDDPI, the incidence of cardiovascular adverse events after administration of formoterol MDDPI was not significantly different than the incidence of cardiovascular adverse events seen after administration of active treatment controls or placebo. The incidence of tachycardia was 1% in adults who received formoterol MDDPI and formoterol by Aerolizer and 0.2% in patients who received placebo. In children, there was a 2% incidence of tachycardia in patients who received formoterol MDDPI and 1% incidence in patients who received placebo. In regard to palpitations, there was a 0.4%, 0.5%, 0% and 0% incidence after administration of formoterol MDDPI, formoterol Aerolizer, albuterol MDI, and placebo respectively in adults. In children, the incidence of palpitations was 1%, 0% and 0% in patients who received formoterol MDDPI, formoterol Aerolizer and placebo, respectively.

COMMENT: *Cardiovascular side effects are also commonly seen in patients and in animal that have received beta adrenergic agonist drugs.*

There were no drug interaction studies done with Foradil Certihaler. This is acceptable given the lack of any defined interactions between formoterol delivered by Aerolizer and other drugs. Patients were allowed to use short acting inhaled beta agonists as rescue medication during the key 12 week studies without any indication of any increased cardiovascular or other type of adverse effect when they were administered concomitantly with Foradil Certihaler. Formoterol, as with other beta agonists, should be administered with extreme caution to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants

because of the possible effect on the vascular system. Inhaled corticosteroids were used frequently in conjunction with formoterol without any indication that the safety profile of either type of drug was worsened. The concomitant administration of Foradil Certihaler and methylxanthines was not evaluated. Methylxanthines are used infrequently in the treatment of asthma at the present time. There is no reason to believe that Foradil Certihaler would produce any greater safety issue when administered concomitantly with methylxanthines than other inhaled long-acting beta agonist formulations.

The marketing exposure for Foradil Certihaler is difficult to predict. There are certain advantages of the Certihaler compared with the Aerolizer, but there is extensive use of Serevent (salmeterol). Marketing exposure to Foradil Certihaler will certainly be substantially greater than the 558 patients who received Foradil Certihaler in the studies submitted under this NDA. The patient exposure in terms of number of patients and duration of treatment in studies submitted under the NDA is, however, adequate to support more extensive use of this drug product once it is marketed.

Pregnant women were excluded from studies with Foradil Certihaler. Pregnant women with moderate to severe asthma will frequently be treated with long-acting inhaled beta agonists. The safety of long-acting inhaled beta agonists in pregnant patients has been reported in studies in the literature although based on animal studies this drug product is still labeled Pregnancy Category C. Exclusion of pregnant women from the studies of Foradil Certihaler does not change the safety profile for the marketed population.

Patients with significant medical illnesses such as cardiovascular disease, diabetes, or thyroid disease were excluded from the studies of Foradil Certihaler. Patients with these conditions who have concomitant asthma will be treated with long-acting inhaled beta agonists. There is sufficient experience with the use of long-acting inhaled beta agonists, such as Serevent and Foradil Aerolizer in patients with cardiovascular or endocrine disease to assure an acceptable benefit: risk ratio that supports the use of Foradil Certihaler in this patient population. Patients were excluded from studies with Foradil Certihaler who had a QTc interval > 460 msec. Patients might receive this drug product who have a QTc interval that is > 460 msec. Some of these patients could be at risk for adverse events. Excluding such patients from the clinical studies with Foradil Certihaler does not change the known potential for beta agonists to produce an effect on the QTc interval or the safety profile for the marketed population.

Patients who had a smoking history of more than 10 pack years or were current smokers were excluded from the studies with Foradil Certihaler. Such patients were intentionally excluded so that the study population better represented asthma and did not include patients with COPD. This exclusion does not change the safety profile for the marketed population. Also excluded from the studies of

Foradil Certihaler were patients who had a history of alcoholism, drug abuse or who were HIV positive. Their exclusion does not change the safety profile for the marketed population. Patients were excluded, as well, if they had taken parenteral or oral corticosteroids in the month prior to the first visit or required new therapy with these medications, if they had used inhaled or intranasal corticosteroids or changed the dose, dosing schedule or formulation in the month prior to the first visit and required institution of such therapy during the run-in period, or were on a total daily dose that exceeded the recommended dose, or who had taken inhaled beta agonists, theopylline, antihistamines, oral beta-2 agonists, oral or inhaled anticholinergics, antileukotrienes, cromolyn, or nedocromil within specified periods prior to the first visit, or who had started allergen immunotherapy within 3 months or were taking non-potassium sparing diuretics, beta adrenergic blocking agents, quinidine or quinidine-like medications tricyclic anti-depressants, monoamine oxidase inhibitors or other anti-depressants. None of these exclusions significantly change the safety profile for the expected marketing population.

Recommended Warnings include Warnings in the proposed labeling for this drug product that are appropriate for all drugs in this class and consistent with the labeling for Foradil Aerolizer, i.e. 1) that Foradil Certihaler should not be used if the patient has significantly worsening or acutely deteriorating asthma, which might be a life threatening condition; 2) that Foradil Certihaler is not a substitute for inhaled or oral corticosteroids and that corticosteroids should not be stopped or reduced when treatment with Foradil Certihaler is initiated; 3) that when initiating treatment with Foradil Certihaler, patients who have been taking short acting inhaled beta agonists on a regular basis should discontinue this practice and use them only for symptomatic relief of acute asthma, i.e. only PRN as rescue medication; 4) that paradoxical bronchospasm can occur with use of inhaled beta agonists; 5) that asthma may deteriorate rapidly which requires re-evaluation of the patient's management program and consideration of anti-inflammatory treatment and not increasing the dosage of Foradil Certihaler; 6) that inhaled beta agonists can produce a clinically significant cardiovascular effect; 7) that immediate hypersensitivity reactions can occur after administration of formoterol; and 8) that fatalities have been reported after excessive use of inhaled beta agonists.

The data presented in this NDA does not indicate that Foradil Certihaler would be any less safe than other drugs available for the maintenance treatment of asthma and prevention of bronchospasm. The safety profile of Foradil Certihaler is not significantly different than the safety profile for Foradil Aerolizer or Serevent. Inhaled corticosteroids and leukotriene antagonists have a different safety profile than long-acting inhaled beta agonists but a benefit:risk ratio similar to that of Foradil Certihaler. Methylxanthines are rarely used clinically at the present time for the treatment of asthma but are recognized as having a very narrow therapeutic index.

There are no unresolved safety issues for Foradil Certihaler.

D. Dosing

Two double-blind, double-dummy, randomized, placebo-controlled and active treatment controlled, incomplete block crossover studies, one in children 5-12 years of age (study 602) and the other in adolescents and adults (study 601), were conducted to determine the dose to be used in 12 week efficacy and safety studies in these two patient populations. There were 77 patients randomized to treatment in study 602 (children) and 67 patients randomized to treatment in study 601 (adults). Patients in these studies received 4 of 6 treatments, that included 5, 10, 15 and 30 mcg bid of formoterol delivered by Certihaler (MDDPI), formoterol 12 mcg bid delivered by Aerolizer and placebo.

In *study 601,* in terms of the primary efficacy variable, i.e. standardized AUC FEV-1 over 12 hours after drug administration measured at the end of each week of treatment, all doses of formoterol delivered by MDDPI and 12 mcg bid delivered by Aerolizer produced a statistically significant degree of improvement compared to placebo ($p<0.0001$). The mean difference from placebo was 0.16 after 5 mcg bid of formoterol MDDPI, 0.20 after 12 mcg of formoterol Aerolizer, 0.22 after 10 mcg bid of formoterol MDDPI, 0.23 after 15 mcg bid of formoterol MDDPI and 0.24 after 30 mcg bid of formoterol MDDPI. Serial measurements of FEV-1 over 12 hours after drug administration showed that a statistically significant difference between the active drug and placebo was reached throughout the dosing interval for formoterol by MDDPI at doses of 10 mcg bid, 15 mcg bid and 30 mcg bid, as well as for formoterol by Aerolizer at a dose of 12 mcg bid, but only for 10 hours with the 5 mcg bid dose. There was no significant difference between treatments in regard to any of the safety parameters evaluated in this study (see discussion under section IIIA of this review and Biopharmaceutics review in regard to assessment of PK data obtained in this study).

COMMENT: *Based on the effectiveness of 10 mcg bid of formoterol delivered from MDDPI in adults throughout the dosing interval with somewhat less effectiveness of the 5 mcg bid dose, as indicated by effectiveness on serial FEV-1 determinations for only 10 hours after drug administration and no significantly greater effectiveness at higher doses delivered by MDDPI, in conjunction with a lack of safety concerns, the dose selected for administration to adults, 10 mcg bid delivered by MDDPI is appropriate.*

In *study 602*, in terms of the primary efficacy variable, i.e. standardized AUC FEV-1 over 12 hours after drug administration measured at the end of each week of treatment, all doses of formoterol delivered by MDDPI and 12 mcg bid delivered by Aerolizer produced a statistically significant degree of improvement compared to placebo ($p<0.0001$ for a dose of 10 mcg bid). The mean difference from placebo was 0.12 after 5 mcg bid of formoterol MDDPI and 12 mcg bid of formoterol by Aerolizer, 0.14 after 15 mcg bid of formoterol MDDPI, 0.16 after 10 mcg bid of formoterol MDDPI and 0.18 after 30 mcg bid of formoterol MDDPI. Serial measurement of FEV-1 over the 12 hours after drug administration showed that there was a statistically significant difference between the active drug and placebo after 10, 15, and 30 mcg bid of formoterol delivered from the MDDPI, while there was no statistically significant difference between 5 mcg bid of formoterol delivered by MDDPI and placebo at the 11 hour time point and no statistically significant difference between formoterol delivered by Aerolizer and placebo at any time point beyond 7 hours. There was a significantly greater incidence of adverse events in patients after receiving formoterol by MDDPI (22% after 5 mcg bid, 18% after 10 mcg bid, 21% after 15 mcg bid and 23% after 30 mcg bid) than was seen in patients after receiving formoterol by Aerolizer (8%). However, the incidence in patients after administration of placebo was 19%. The incidence of tremor, severe adverse events and drug-related adverse events were higher after administration of doses of formoterol delivered from the MDDPI at dosages greater than 10 mcg bid than after administration of 10 mcg bid. In contrast to the response after other treatments, the percentage of patients who had abnormal ECG findings after administration of 10 mcg bid of formoterol by MDDPI increased from 17% to 31% after administration of the first dose and from 8% to 12% 2 hours after administration when formoterol at a dose of 10 mcg bid by MDDPI had been given for one week. However, none of these abnormal ECG findings was considered to be clinically significant.

COMMENT: *Since efficacy was demonstrated with a dose of 10 mcg bid of formoterol delivered by MDDPI in children 5-12 years of age comparable to higher doses delivered from the MDDPI and comparable to 12 mg bid delivered from the Aerolizer (a dose that is approved for administration to children 5 years of age and older), the selection of a dose of 10 mcg bid for administration to children is appropriate.*

E. Special Populations

The studies done by the sponsor were appropriate and of adequate quality to assess the effectiveness and safety of formoterol MDDPI in children and adults, although more data in elderly adults and adolescents would provide a better database for use of this drug product in those patient populations. There were only 13 adolescent patients in the two key 12 week studies (studies 2302 and

2303) who received formoterol MDDPI. Elderly adults may be at increased risk from administration of inhaled beta agonists because of polypharmacy and underlying cardiovascular disease. Adequate numbers of males and females were entered into studies of this drug product. The majority of patients in the key studies were Caucasian, although the incidence of adverse events did not appear to be significantly different in non-Caucasian patients.

COMMENT: *Further studies evaluating formoterol MDDPI in adolescents and elderly patients, as well as non-Caucasian patients would provide a better understanding of the benefit:risk ratio in these patient populations. The performance of such studies should be strongly recommended to the sponsor but is not a requirement for approval of this drug product.*

1. Gender:

   a. Biopharmaceutical consideration: There was no formal gender analysis of the pharmacokinetic data submitted by the sponsor.
   b. safety:
      1) exposure:

Gender	Formoterol MDDPI	Formoterol Aerolizer	Albuterol MDI	Placebo
All studies	N = 558	N = 215	N = 167	N = 512
Male	290 (52%)	99 (46%)	67 (40%)	237 (46%)
Female	268 (48%)	116 (54%)	100 (60%)	275 (54%)
Pediatric studies	N = 204	N = 48	N = 0	N = 176
Male	139 (68%)	28 (58%)	-----	104 (59%)
Female	65 (32%)	20 (42%)	-----	72 (41%)

2) adverse events:

There were no adverse events that occurred with a 3% or greater incidence in one gender over the other, in patients who received Foradil Certihaler, based on evaluation of data from all studies. Those adverse events that occurred with an incidence of >3% in one gender compared to the other in patients who received Foradil Certihaler in pediatric studies can be seen in the table below.

Executive Summary Section

All studies	Male	Male	Female	Female
	MDDPI N = 290	Placebo N = 237	MDDPI N = 268	Placebo N = 275
Total adverse events all studies	149 (51.4%)	107 (45.1%)	152 (56.7%)	126 (45.8%)
Adverse events 20 mcg per day dose all studies	116 (45.8%)		130 (51.4%)	
Pediatric studies	N = 139	N = 104	N = 65	N = 72
Total pediatric adverse events	59.0%	41.3%	55.4%	45.8%
Vomiting	7.2%	2.9%	3.1%	1.4%
Nasopharyngitis	7.2%	3.8%	3.1%	5.6%
Headache	9.4%	5.8%	1.5%	2.8%
Asthma aggravated	10.1%	15.4%	6.2%	9.7%
Cough	5.8%	3.8%	1.5%	0%

3) There was no gender analysis provided by the sponsor for vital signs, ECGs or laboratory tests.

c. effectiveness:

12 hour AUC FEV-1 imputed after 3 months of treatment

Combined studies 2302 and 2303	Mean (L x hour) MDDPI	Mean (L x hour) albuterol	Mean (L x hour) Placebo	P value MDDPI vs. placebo
Males	5.75 (n = 69)	4.07	1.18	< 0.0001
Females	3.79 (n = 97)	2.69	1.77	0.0004
Study 604				
Males	2.41	-----	1.15	0.01
Females	2.79	-----	1.76	0.11

COMMENT: *In terms of the primary efficacy variable as well as other efficacy variables, there was no statistically significant difference seen when formoterol was delivered via MDDPI and placebo in adults based on gender. However, in study 604 which evaluated children 5-12 years of age, a statistically significant difference from placebo in terms of the primary efficacy parameter was seen in males but not in females (v33, p235). Despite this finding, there is no reason to believe that this type of drug product would produce a clinically significant effect in female children that was different than that seen in male children.*

2. Ethnic/Racial:

a. Biopharmaceutical consideration: There was no formal analysis of the pharmacokinetic data submitted by the sponsor in regard to ethnicity/race.

b. safety:

1) exposure:

Race	Formoterol MDDPI	Formoterol Aerolizer	Albuterol MDI	Placebo
All studies	N = 558	N = 215	N = 167	N = 512
Caucasian	441 (79%)	175 (81%)	145 (87%)	404 (79%)
Black	55 (10%)	2 (1%)	13 (8%)	45 (9%)
Oriental	4 (1%)	1 (1%)	1 (1%)	7 (1%)
Other	58 (10%)	37 (17%)	8 (4%)	56 (11%)
Pediatric studies	N = 204	N = 48	N = 0	N= 176
Caucasian	143 (70%)	36 (75%)	-----	129 (73%)
Black	33 (16%)	None	-----	21 (12%)
Oriental	1 (1%)	None	-----	3 (2%)
Other	27 (13%)	12 (25%)	-----	23 (13%)

2) Adverse events: The table below contains adverse events that occurred in 5% or more of the Black, Caucasian or Other patient populations after administration of formoterol MDDPI as well as 5% or more of the Caucasian population who received formoterol Aerolizer or placebo. The number of non-Caucasian patients is so small that it is difficult to draw any conclusions about adverse events in other ethnic groups compared to Caucasians.

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Adverse events	Black	Caucasian	Oriental	Other
Formoterol MDDPI ••••••••••	N = 55	N = 441	N = 4	N = 58
Total number of patients with AEs	30 (55%)	234 (53%)	3 (75%)	34 (59%)
Pyrexia	4 (7%)	12 (3%)	3 (25%)	3 (5%)
Nasopharyngitis	2 (4%)	36 (8%)	2 (50%)	1 (2%)
URI	1 (2%)	32 (7%)	None	4 (7%)
Tremor	1 (2%)	36 (8%)	None	1 (2%)
Headache	5 (9%)	31 (7%)	None	3 (5%)
Asthma aggravate	11 (20%)	27 (6%)	None	10 (17%)
Allergic rhinitis	4 (7%)	6 (1%)	None	1 (2%)
Nasal congestion	4 (7%)	5 (1%)	None	1 (2%)
Formoterol Aerolizer ••••••••	N = 2	N = 175	N = 1	N =37
Total number of patients with AEs	2	39 (22%)	None	18 (49%)
Asthma aggravate	1	12 (7%)	0	6 (16%)
Placebo •••••••••	N = 45	N = 404	N =7	N =56
Total number of patients with AEs	21 (47%)	181 (45%)	4 (57%)	27 (48%)
URI	4 (9%)	26 (6%)	0	2 (4%)
Nasopharyngitis	2 (4%)	21 (5%)	2 (29%)	1 (2%)
Headache	3 (7%)	23 (6%)	0	8 (14%)
Asthma aggravate	7 (16%)	44 (11%)	1 (14%)	10 (18%)

3) There was no analysis provided by the sponsor for vital signs, ECGs or laboratory tests based on ethnicity/race.

c. efficacy:

12 hour AUC FEV-1 imputed after 3 months of treatment

	Mean (L/hour) MDDPI	Mean (L/hour) Albuterol	Mean (L/hour) Placebo	P value MDDPI vs. placebo
Combined studies 2302 and 2303				
Caucasian	4.98 (n=137)	3.30 (n=145)	1.50 (n=141)	< 0.0001
Black	3.12 (n=19)	3.53 (n=13)	1.22 (n=22)	0.002
Other	5.40 (n=10)	2.93 (n=9)	3.36 (n=8)	0.0005
Study 604				
Caucasian	2.28 (n=81)	-----	1.57 (n=84)	< 0.0001
Black	2.72 (n=33)	-----	1.90 (n=21)	0.0002
Other	2.52 (n=13)	-----	0.90 (n=15)	0.004

COMMENT: *The majority of patients in the key studies were Caucasian. Although the incidence of adverse events did not appear to be significantly different in non-Caucasian patients in these studies, further evaluation of formoterol MDDPI in non-Caucasian patients as well as adolescents and elderly patients, would help to better define the benefit: risk profile for this drug product. The use of this drug product in pregnancy should follow the same guidelines established for Foradil Aerolizer, i.e. "Because there are no adequate and well controlled studies in pregnant women, Foradil Certihaler should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."*

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Foradil (formoterol fumarate) is approved for use with the Aerolizer device for long-term morning and evening administration for the maintenance treatment of asthma, in the prevention of bronchospasm in adults and children 5 years of age and older with reversible obstructive airway disease, for adults and adolescents 12 years of age and older for the prevention of exercise-induced bronchospasm and for the maintenance of chronic obstructive pulmonary disease (NDA 20-831). The Aerolizer is a dry powder inhaler (DPI) that delivers a single dose as a capsule containing 12 mcg of Foradil which must be placed in the device in order to deliver each dose. The recommended dose of formoterol when delivered from the Aerolizer for asthma and COPD is 12 mcg every 12 hours and for the prevention of exercise-induced bronchospasm, 12 mcg at least 15 minutes prior to exercise. The delivery of formoterol from the Aerolizer depends on inspiratory flow rate and the time of inspiration. A post-marketing commitment was made to conduct a large placebo-controlled study to further evaluate the safety and efficacy of regular, twice daily administration of one or more dose levels of Foradil Aerolizer above that of the approved dose comparing the results to the safety and efficacy of the approved dose.

The sponsor (Novartis) has now submitted on 18 December 2002, data to support the use of Foradil in a device called a Certihaler, with an action date of 18 October 2003. The Certihaler is a multiple dose dry powder inhaler, that contains, in addition to a [redacted] formoterol in a dry powder mixture, magnesium stearate and lactose monohydrate. It delivers a dose of 10 mcg from the valve and 8.5 mcg from the actuator using in-vitro testing at a fixed flow rate of 60 L/min for 2 seconds. This was the dose used in pivotal studies with this drug product, based on the findings in two dose ranging studies. Each inhaler contains 60 doses. The Certihaler, a breath-actuated medium resistance device, cannot be activated unless it is held in the horizontal position. It has a built-in airflow threshold limitation that releases the dose at the optimum point in the patient's breathing cycle in order to better ensure the correct delivery of the drug since activation is only possible when the device is held in the correct position and ensure that the dose is delivered at the correct point in the patient's breathing cycle. It has a blocking mechanism that prevents dose emission below 30 L/min. The mean peak inspiratory flow rate through the Certihaler was 63 L/min (range 45-80 L/min) in adults (38 patients), 70 L/min (range 56-95 L/min) in adolescents (17 patients), and 63 L/min (range 44-79 L/min) in children (27 patients). It also has a dose counter that is actuated only by the patient's inhalation of a dose.

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Formoterol fumarate is a formylamino-substituted catecholamine derivative.

Formoterol, like salmeterol, is a long-acting beta-2 selective adrenergic agonist bronchodilator that is used in the treatment of asthma and other lower respiratory conditions which includes bronchospasm. It is not indicated for patients whose asthma can be controlled by the use of short-acting inhaled beta agonists and should be used on a regular, not a PRN, basis.

Foradil Certihaler has not been approved for marketing in any country.

B. State of Armamentarium for Indication(s)

The proposed indication for Foradil Certihaler is long-term administration as maintenance treatment for asthma and the prevention of bronchospasm. Drugs that are currently used extensively for the maintenance treatment of asthma are other long-acting inhaled beta adrenergic agonist drugs, e.g. Serevent (salmeterol), short-acting inhaled beta adrenergic agonist drugs, e.g. albuterol, leukotriene antagonists, e.g. Singulair (montelukast) and corticosteroids, particularly inhaled corticosteroids, e.g. Flovent (fluticasone). Medications labeled for the prevention of bronchospasm or as prophylactic management of asthma include the same drugs listed above.

C. Important Milestones in Product Development

The formoterol Aerolizer (NDA 20-831) is currently marketed in the United States, Europe, South American and other countries. There is no foreign marketing history with the formoterol Certihaler. This NDA was submitted on 17 December 2002. It was approved for asthma on 16 February 2001 and for COPD on 25 September 2001.

A pre-NDA meeting was held with the sponsor on 10 May 2002 to discuss the non-clinical, clinical and clinical pharmacology portions of the application. A separate pre-NDA meeting on CMC issues was held on 25 April 2002. At the meeting of 10 May 2002, the Division stated that the Foradil Certihaler should have a separate package insert from the Foradil Aerolizer. The Division also stated that if study 603 was submitted after the NDA as part of the 120 day safety update, it might not be reviewed as part of the first review cycle, that individual studies should be analyzed separately, that the content of the proposed Summary of Clinical Efficacy was acceptable, and that the sponsor should include all safety data in two major categories, controlled and uncontrolled studies. In addition, the Division recognized the difficulty experienced by the sponsor with the electronic diary and recognized that the sponsor had not broken the blind before they changed endpoints in study 605. Pooling of data in the ISE was felt to be acceptable and that it was important to consider the clinical significance of scores in the QOL instrument as well as statistical comparisons.

D. Other Relevant Information

Foradil Certihaler has not been approved in any other country. There has not been any non-approval of Foradil Certihaler in any country. Inhaled formoterol has been approved in the United States as Foradil Aerolizer. This application is for the purpose of providing a device that more effectively delivers formoterol to the lower respiratory tract.

E. Important Issues with Pharmacologically Related Agents

The use of long-acting inhaled beta agonists has been associated with deterioration of asthma in a small number of patients. This phenomenon was also noted with the 24 mcg dose of Foradil Aerolizer and has been the basis for proposed changes in the labeling for Serevent Inhaler. Patients at risk for such events have not been defined. There is no reason to believe, based on the data submitted in this NDA, that there is any greater risk of this development associated with the use of Foradil Certihaler than with the use of already marketed long-acting inhaled beta agonists. The labeling for Foradil Certihaler, as does the labeling for already marketed long-acting inhaled beta agonists, addresses this issue under the Warnings section.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Foradil multidose DPI (Certihaler) is a breath-actuated multi-dose dry powder inhaler that delivers a dose of 10 mcg from the valve and 8.5 mcg from the actuator. The active drug is formoterol fumarate dihydrate and the excipients are lactose monohydrate and magnesium stearate. The device is designed to deliver 60 actuations and contains a counter that counts down from "60" for each individual actuation. Counting takes place after the dose is delivered. After the last dose is delivered, the device will lock preventing further use.

The updated report of 17 March 2003 included complaints on inhalers returned from studies 603, 604, 2302 and 2303 which used 10,000-15,000 of the > 36,000 inhalers sent to clinical sites (see CMC review). Out of 173 complaints, 111 were characterized as device failure. There were 101 inhalers that exceeded the maximum actuation flow rate of [redacted] L/min. The sponsor states that the "problem with the increased actuation flow rate cannot be completely avoided because it is related to the generation of powder residues during device use on gliding parts of the device mechanism, which might result in increased friction." Although the sponsor has made changes in the [redacted] that reduce the increase in the needed actuation flow rate by reducing air leakage around the mouthpiece and increasing smoothness of moving parts, the inhalers used in the clinical studies were all produced using the [redacted] and therefore do not include

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improvements made to prevent the defects found in the inhalers that were returned. The second greatest complaint on returned devices was defective counters, which occurred in 15 of the 173 returned inhalers (0.1-0.2% of the inhalers used in the clinical studies).

Chemistry has asked the sponsor to provide data to demonstrate that the improvements in the [redacted] devices will reduce the magnitude of the actuation flow rate increase and the numbers of defective counters. Chemistry has determined that the Foradil Certihaler is approvable but that approval is dependent on resolution of several issues, including provision of more information on the product prepared with [redacted] tooling, so that a link can be made between the data on primary stability of clinical lots that were manufactured with [redacted] devices exclusively and the data for the proposed marketed design prepared in slightly modified form from [redacted] tools. b(4) b(4)

There are minimal Toxicology issues that relate to the approval of Foradil Certihaler. The sponsor submitted toxicology data for the excipient magnesium stearate, since its GRAS status did not cover inhalation exposure and there has not been use of this chemical by the inhaled route in approved drug products. The studies submitted by the sponsor were reviewed by Pharmacology and supported the safe administration of magnesium stearate in this drug product (see Pharmacology/Toxicology Review).

The Statistical Reviewers have concluded that the efficacy of Foradil Certihaler was demonstrated in adults in studies 2302 and 2303 and that Foradil Certihaler significantly improved pre-dose (on-study baseline) FEV-1 in these studies. However, the statisticians conclude that there was "limited efficacy" demonstrated after use of Foradil Certihaler in children for 3 months, as reflected in the pre-dose FEV-1 and decreased efficacy at the end of the 12 hour dosing interval after 3 months of treatment. The statisticians also point out that study 605 was underpowered because the sponsor changed the primary efficacy variable from the average of the last seven daily morning pre-dose PEF to the morning pre-dose FEV-1 at the final visit, in the middle of the study and chose not to adjust the sample size. Possibly as a result, this study did not demonstrate any statistically significant difference between Foradil Certihaler and placebo. The statisticians point out that subgroup analysis of studies 2302 and 2303 in adults showed a numerical superiority in terms of treatment effect in males, that was not seen in the pediatric study.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The pharmacokinetics of multiple doses of formoterol delivered by MDDPI for one week were evaluated in adults and adolescents (*study 601*), as well as in children 5-12 years of age (*study 602*).

All doses of formoterol are expressed in terms of formoterol fumarate but all plasma and urine concentrations and PK parameters are expressed in terms of formoterol free base. One ng of formoterol fumarate is equivalent o 0.819 ng of formoterol free base and 1 ng of formoterol free base = 2.38 nmol of formoterol free base. One mol of formoterol fumarate contains 2 mol of formoterol free base. Formoterol fumarate contains two asymmetric carbon atoms. The preparation used in clinical studies is a b(4)

Systemic exposure measured as the amount of formoterol excreted in the urine was consistent with dose proportionality in adults and children following administration of 5-30 mcg of formoterol delivered by MDDPI. The data from measurement of formoterol in the urine suggest that systemic exposure is not substantially different when 10 mcg of formoterol is delivered from the MDDPI and when 12 mcg of formoterol is delivered by Aerolizer in adults and children.

Based on previous data after administration of formoterol by Aerolizer, absorption is rapid and extensive. After a single dose of 120 mcg, the peak plasma concentration is observed 5 minutes after inhalation. At least 65% of an oral dose is absorbed. Urinary excretion data indicate that unchanged racemic formoterol and the R and S enantiomers increase in a linear fashion with increasing dose. Formoterol is bound to plasma to a high degree (61-64%) in vitro. Formoterol is metabolized primarily by direct glucuronidation with the most prominent metabolite being phenolic O-glucuronide formoterol. Multiple CYP450 isozmes catalyze O-demethylation. In-vitro data at pharmacologically relevant doses showed that "formoterol would not be expected to inhibit the metabolism of drugs by any of the major human P450 isozymes". After a single oral dose, 59-62% of the dose is recovered in the urine and 32-34% in the feces. Formoterol is eliminated primarily by metabolism. After inhalation of 12-120 mcg of formoterol fumarate approximately 6-9% of the dose is recovered from the urine as unchanged formoterol. There is biphasic elimination with a terminal ½ life of 10 hours. The only drug interaction study performed with formoterol showed that there was no interaction with theophylline.

The absolute amount of unchanged formoterol excreted following administration of 10 mcg bid of formoterol by MDDPI in *study 601* in adolescents and adults was 24% higher than that excreted after administration of 12 mcg bid of formoterol by Aerolizer. Overlap of the 95% confidence intervals of the geometric means for these two drug deliveries suggest that systemic exposure of formoterol whether delivered as 10 mcg bid from the MDDPI or 12 mcg bid delivered from the Aerolizer were not substantially different (see detailed review of study 601 below and Biopharm review) .

Excretion of unchanged and total formoterol following administration of doses of 5-30 mcg bid by MDDPI and 12 mcg bid by Aerolizer as a percent of dose were similar for all doses in *study 602* in children 5-12 years of age. Based on urinary

excretion of unchanged formoterol as a measure of systemic exposure, a 10 mcg dose of formoterol by MDDPI produced a systemic exposure that was 25% higher than that produced by a 12 mcg dose of formoterol delivered by Aerolizer. Overlap of the 95% confidence intervals of the geometric means for these two drug deliveries suggest that systemic exposure was not substantially different (see detailed review of study 602 below and Biopharm review).

There was no significant difference in urinary excretion between adults and children. With the 10 mcg dose delivered from the MDDPI, the 95% confidence intervals of the geometric mean for urinary excretion of both unchanged and total formoterol almost completely overlapped between children and adults. The amount of accumulation at steady state, which was approximately 60% in adults and children after receiving formoterol by MDDPI, was similar to that seen in previous studies with the Aerolizer in adults (62-74%) and children (18-84%).

Pharmacokinetic data from a subgroup of adult asthmatic patients (16 patients who received formoterol and 51 patients total from 4 predetermined centers) in *study 2303* included plasma samples taken over 12 hours after drug administration after the first dose and after 12 weeks of treatment with 10 mcg bid of formoterol from a MDDPI and urine samples collected after the first dose and 12 weeks of treatment. Peak plasma concentrations were reached within the first 10 minutes after drug administration. Trough plasma levels were very close to the limit of quantitation. Accumulation of approximately 60% at steady state was seen in the urine compared with 63-73% in studies where formoterol was delivered by Aerolizer. The mean renal clearance was 19.8 L/h compared to 18 L/h seen in healthy volunteers with a single dose of 12 mcg of formoterol delivered by Aerolizer (see detailed review of study 2303 below).

In *study 604* in asthmatic children 5-12 years of age, unchanged formoterol was measured in the plasma for up to 12 hours after drug administration for 8 weeks and prior to drug administration over the 12 weeks of the study. Urine samples over 12 hours after drug administration on day 1 and after 12 weeks of treatment were analyzed in a subgroup of patients (38 patients from 3 pre-selected centers of whom 19 received 10 mcg bid of formoterol by Aerolizer). Peak concentrations of formoterol were reached within 10 minutes after drug administration. Average trough plasma levels were very close to the limit of quantitation. An accumulation of approximately 60% at steady state was seen in the urine compared to 18-84% after administration of formoterol from the Aerolizer (see detailed review of study 604 below)

In *study 701*, 36 mcg tid of formoterol was inhaled from an Aerolizer for 3 days in patients with type 2 diabetes who did not have asthma. Unchanged formoterol was measured in pre-dose plasma samples and 24 hour urine samples collected from 16 patients over intervals of 0-12 and 12-24 hours on day 1 and day 3 of the study. On day 3, the pre-dose concentrations of the second and third daily dose

was on average higher (1.6 and 1.8 fold, respectively) than the corresponding pre-dose concentrations on day 1. There was an increase (1.4 fold) in urine unchanged formoterol on day 3 compared to day 1.

PK parameters were not significantly different in males and females. No PK studies of specific ethnic groups have been done. PK was evaluated in a very small number of patients > 65 years of age with COPD in a previous study where 12 mcg bid of formoterol was delivered by Aerolizer. In this subset of patients, there was an average increase of 4% in 12 hour urinary unchanged formoterol compared to patients < 65 years of age. No studies were performed in patients with renal or hepatic impairment.

COMMENT: *No safety concerns were raised based on the pharmacokinetics of formoterol when delivered by inhalation nor, where data exists, in regard to delivery of formoterol by MDDPI.*

B. Pharmacodynamics

Following inhalation of 36 mcg of formoterol by Aerolizer tid for 3 days in patients with persistent asthma (*study 701*), hypokalemia, hyperglycemia, increased QTc interval, and increased pulse rate were produced. The mean maximum QTc interval was 428.8 msec during treatment with formoterol and 417.4 msec during treatment with albuterol. The effect seen was slightly greater than that seen after administration of 600 mcg of albuterol in the same study (see detailed review of study 701 below).

The mean plasma glucose concentration 2 hours after a standardized meal in patients with type 2 diabetes (*study 2301*) was 208 mg/dL after 24 mcg of formoterol delivered by Aerolizer compared to 182 mg/dL after placebo administration. The difference between placebo and formoterol for the 4 hour plasma glucose AUC was not statistically significant (see detailed review of study 2301 below).

A dose-dependent increase in plasma cyclic AMP was seen following doses from 12 to 96 mcg of inhaled formoterol fumarate. The beta adrenergic effects of formoterol are believed to result from increased production of intracellular cyclic AMP caused by activation of the enzyme adenyl cyclase after binding to beta adrenergic receptors on smooth muscle and effector cells, such as mast cells.

Dose ranging studies 601 (adults and adolescents) and 602 (children) demonstrated that a dose of 10 mcg bid of formoterol delivered from the MDDPI (Certihaler) produced a degree of efficacy comparable to higher doses of 15 and 30 mcg bid (see detailed review of these studies below).

Previous submission of data regarding formoterol fumarate included: 1) following inhalation of 12-96 mcg in 10 healthy volunteers, urinary formoterol excretion was related in a linear fashion to decrease in serum potassium levels and increased heart rate. The increase in QTc interval was related to the square of the urinary excretion of formoterol; and 2) after inhalation of a single 120 mcg dose of formoterol fumarate delivered by Aerolizer, formoterol levels were highly correlated with reduction in plasma potassium concentration.

IV. Description of Clinical Data and Sources

A. Overall Data

The sponsor has submitted 6 key studies: two dose ranging studies (studies 601 and 602), three large pivotal efficacy studies (studies 2302, 2303, and 604) and a safety study (study 605). A total of 1262 patients were entered into these studies, of whom 558 received Foradil.

Study 2302 is a 12 week, randomized, multi-center, double-blind, double-dummy, placebo and active treatment controlled, parallel group study evaluating the safety and efficacy of formoterol delivered by the DPI compared to placebo and albuterol MDI in patients with persistent asthma. There were 22 centers in the United States enrolling 265 patients 13 years of age or older, of whom 86 were randomized to treatment with formoterol DPI, 88 were randomized to receive albuterol MDI and 91 were randomized to the placebo arm.

Study 2303 is a 12 week, randomized, multi-center, double-blind, double-dummy, placebo and active treatment controlled parallel group study evaluating the safety, efficacy and pharmacokinetics of formoterol DPI compared with placebo and albuterol MDI in patients with persistent asthma. There were 18 centers in the United States enrolling 239 patients, 13 years of age and older, of whom 80, 79, and 80 patients were randomized to the formoterol DPI, albuterol MDI and placebo arms, respectively.

Study 604 is a 12 week, randomized, multi-center, double-blind, placebo-controlled, parallel group study in children 5-12 years of age with persistent asthma evaluating the safety, efficacy and pharmacokinetics of formoterol compared to placebo in an outpatient setting. There were 22 centers in the United States that enrolled 249 patients, of whom 127 were randomized to receive formoterol DPI and 122 received placebo.

Study 605 is a 12 week, randomized, multi-center, double-blind, double-dummy, placebo-controlled, parallel group study evaluating the efficacy and safety of formoterol DPI compared to formoterol Aerolizer and placebo. This study was conducted at 28 centers in 6 countries and enrolled 365 patients, 13 years of age

and older with persistent asthma. There were 121 patients randomized to receive formoterol DPI, 121 to receive formoterol Aerolizer, and 123 to receive placebo.

Study 601 is a multi-center, randomized, double-blind, placebo-controlled, crossover repetitive dose study of 1 week duration in adults and adolescents with persistent asthma. Four doses of formoterol DPI (5, 10, 15 and 30 mcg bid) were compared to 12 mcg of formoterol Aerolizer bid. This study was conducted at one site in Denmark and 6 sites in the Netherlands. There were 67 patients 20-73 years of age enrolled into the study, of whom, 42, 45, 43, 46, 41 and 46 received placebo, 5 mcg of formoterol DPI, 10 mcg of formoterol DPI, 15 mcg of formoterol DPI, 30 mcg of formoterol DPI and 12 mcg of formoterol Aerolizer, respectively. There was a one week washout period between treatments.

Study 602 is a multi-center, randomized, double-blind, placebo-controlled, crossover repetitive dose study of 1 week duration in children 5-12 years of age with persistent asthma designed to demonstrate an optimal effective dose formoterol DPI in this age group. There were 11 centers in 4 countries that enrolled 77 patients, of whom 54 received placebo, 51 received 5 mcg of formoterol DPI, 49 received 10 mcg of formoterol DPI, 48 received 15 mcg of formoterol DPI, 52 received 30 mcg of formoterol DPI and 53 received 12 mcg of formoterol Aerolizer. There was a one week washout period between treatments.

Study 2301 is a pharmacodynamic study in healthy volunteers that enrolled 17 patients 30-75 years of age with type 2 diabetes in a randomized, double-blind, placebo-controlled, multiple dose, two period crossover study to effect of bid administration of formoterol when delivered by Aerolizer at a dose of 24 mcg on glucose control.

Study 701 is a pharmacodynamic study in patients with mild persistent asthma comparing high doses of formoterol when delivered by Aerolizer with high doses of albuterol in 16 patients.

B. Tables Listing the Clinical Trials

Study	Study design	Drug administration	Patients	Parameters
2302 (v18-24)	12 week, randomized, multi-center, double-blind, double-dummy, placebo and active treatment controlled, parallel group; active control is albuterol MDI; 265 patients; safety and efficacy evaluation	Formoterol 10 mcg bid (n=86) Albuterol 180 mcg qid (n=88) Placebo (n=91)	13 years of age and older; persistent asthma	Efficacy: 12 hour AUC for FEV-1; miniAQLQ; serial FEV-1, FVC; number asthma exacerbation; AM and PM PEFR; symptom scores; use of rescue medications Safety: AEs, labs, VS, ECGs, PE
2303 (v25-30)	12 week, randomized, multi-center, double-blind, double-dummy, placebo and active treatment controlled, parallel group, safety, efficacy and PK evaluation; active control is albuterol MDI	Formoteroal 10 mcg bid (n=80) Albuterol 180 mcg qid (n=77) Placebo (n=80)	13 years of age and older; persistent asthma	Efficacy: 12 hour AUC FEV-1; miniAQLQ, serial FEV-1, FVC; number of exacerbations; AM and PM PEFR, symptom scores, use of rescue medication Safety: AEs, labs, VS, ECGs PK:
604 (v12-14)	12 week, randomized, multicenter, double-blind, placebo-controlled, parallel group, safety, efficacy, PK	Formoterol 10 mcg bid (n=127) Placebo (n=122)	5-12 years of age persistent asthma	Efficacy: 12 hour AUC for FEV-1, serial FEV-1, FVC, PEF, symptom scores, rescue medication use Safety: Aes, labs, VS, ECGs, PE PK:
605	12 week, randomized, multicenter, double-blind, double-dummy, placebo-controlled, active treatment controlled, parallel group, efficacy, safety, foreign, 28 centers in 6 countries	Formoterol DPI 10 mcg bid (n=121) Formoterol Aerolizer 12 mcg bid (n=121) Placebo (n=123)	13 years of age and older, persistent asthma	Efficacy: AM predose FEV-1 during final visit Safety: Aes, labs, VS, ECGs
601 (v4-7)	1 week, randomized, double-blind, placebo-controlled, dose-finding, multicenter, crossover	Formoterol DPI 5, 10, 15 and 30 mcg bid Formoterol Aerolizer 12 mcg bid	67 patients, 20-73 years of age, persistent asthma	Efficacy: AUC of FEV-1 over 12 hours, FEV-1, pulmonary function testing 5, 15, 30 minutes, 1 hour and hourly 3-12 hours after drug administration, symptom scores, rescue medication Safety: Aes, ECGs, VS, unchanged and total formoterol levels in urine over 12 hours
602 (v8-11)	One week, randomized, double-blind, placebo-controlled, dose-finding, multicenter, crossover, foreign; 11 centers in 4 countries	Formoterol DPI5, 10, 15, and 30 mcg bid Formoterol Aerolizer 12 mcg bid	N = 77 5-12 years of age, persistent asthma	Efficacy: AUC for FEV-1 over 12 hours, and 5, 15, 30 minutes and one hour and hourly up to 3-12 hours after drug administration, symptom scores, rescue medication, safety: AEs, ECGs, labs
2301 (v55-56)	Randomized, double-blind, placebo-controlled, repetitive dose, two-period crossover, effect on glucose control	Formoterol Aerolizer 24 mcg bid	N = 17 30-75 years of age, type 2 diabetes	Safety: VS, ECGs, labs, Aes plasma glucose, serum fructosamine on days 1 and 21
701 (v52-54)	Randomized, double-blind, double-dummy, active treatment controlled, 2-way crossover, safety and tolerability, high doses, repetitive dose	Formoterol Aerolizer 36 mcg tid Albuterol 600 mcg tid	N = 16 18-65 years mild persistent asthma	Safety: VS, ECG, Holter, FEV-1, labs. Aes, blood for trough plasma levels, urine analysis for PK

C. Postmarketing Experience

Foradil Certihaler has not been approved for marketing in any country and as of 25 November 2002, no marketing applications for Foradil Certihaler had been submitted in any country. Foradil Aerolizer and Foradil aerosol solution have been approved in a number of other countries. No post-marketing data is available for Foradil Certihaler and no post-marketing data was submitted for other Foradil formulations.

C. Literature Review

The sponsor submitted 27 articles or abstracts from the literature dealing with the pharmacology of formoterol, the mechanism of action of long-acting inhaled beta agonists, published randomized, blinded, controlled studies and validation of testing methods, such as quality of life questionnaires. These articles were reviewed. The data presented in them did not change the conclusions reached based on the data from the key studies submitted by the sponsor. No additional review of the literature was done.

V. Clinical Review Methods

A. How the Review was Conducted

The review was initiated with a review of the key studies to support the efficacy and safety of Foradil Certihaler. This consisted of studies 601, 2302 and 2303 in adults and studies 602 and 604 in patients 5-12 years of age. Each study was reviewed separately and is described separately in the appendix to this review. Each study was reviewed as intensely as possible in terms of summaries submitted by the sponsor and line listings, with review of case report forms if necessary to clarify issues in the summary reports of studies submitted by the sponsor. Following this, the ISE and ISS were reviewed and linked, where necessary to individual study reports. Finally, the labeling was reviewed in regard to justification for claims made based on the data submitted by the sponsor.

B. Overview of Materials Consulted in Review

The labeling for other long-acting inhaled beta agonists was reviewed to insure consistency and for comparison with claims for Foradil Certihaler and previously approved long-acting inhaled beta agonists. INDs and other documents not submitted to the NDA were not evaluated. Electronic materials were used to assess specific issues related to individual patients through case report forms.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

There were no DSI Audits of studies submitted under this NDA. Case report forms and detailed analysis of the database based on type of study, patient age, patient gender, race/ethnic background, length of exposure, and dosage were used to double-check the data submitted by the sponsor.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The studies submitted in this NDA were performed in accordance with accepted ethical standards.

D. Evaluation of Financial Disclosure

There was only one investigator who had a disclosable financial arrangement, Dr — at center — in study 2302 who had $100,000 in stock with Novartis. There was no evaluation of the data by individual center and the data was not analyzed with and without inclusion of this study site. There were — patients evaluated at this site out of a total of 265 patients in this study. It is not likely that bias was introduced into the database for this drug product based on the potential conflict of interest at this study site. b(6)

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Foradil Certihaler was shown to be efficacious for the maintenance treatment of asthma and the prevention of bronchospasm in adults and children 5 years of age and older with reversible obstructive airway disease. The data support the labeling claims made by the sponsor with certain exceptions, such as the sponsor's claim that in the key adult and pediatric studies there was "— b(4)

— These and other proposed changes to the labeling are discussed below.

B. General Approach to Review of the Efficacy of the Drug

The two key studies in children were: 1) a 12 week multicenter, randomized, double-blind, placebo controlled, parallel group study in children 5-12 years of age with persistent asthma who received 10 mcg bid of formoterol delivered by Certihaler (MDDPI)(study 604). The primary efficacy variable was the 12 hour AUC FEV-1 measured on day 1, and after 1, 2 and 3 months of treatment. Other efficacy variables included serial FEV-1 and FVC, number of asthma exacerbations, AM/PM PEF, asthma symptom scores, and use of rescue medication. Safety variables included adverse events, vital signs, laboratory tests and ECGs. Patients who received Foradil Certihaler had a statistically significantly greater improvement in AUC FEV-1 over 12 hours throughout the 3 months of treatment than did patients who received placebo; and

2) a randomized, double-blind, placebo-controlled and active treatment controlled, crossover study in children 5-12 years of age who received 5, 10, 15 and 30 mcg bid of formoterol delivered by Certihaler as well as 12 mcg bid of

formoterol delivered from the Aerolizer each for a period of one week (study 602). The primary efficacy variable was standardized AUC for FEV-1 over 12 hours measured at the end of each week of treatment. Other efficacy variables included serial FEV-1 measurements, daily asthma symptom scores, and use of rescue medication. Safety parameters included adverse events, ECGs, vital signs and laboratory tests. Unchanged and conjugated formoterol were measured in the urine. All doses of formoterol delivered by Certihaler as well as formoterol delivered by Aerolizer produced a statistically significantly greater improvement in FEV-1 AUC over 12 hours than did placebo. Serial measurements of FEV-1 showed that the duration of effectiveness on day 1 was 12 hours, after one month of treatment was 10 hours and after 3 months of treatment was 6 hours.

In study 604, the mean change from baseline in AUC for 12 hour FEV-1 after 3 months of treatment with formoterol by MDDPI was 2.45 L/hr compared with 1.45 L/hr after treatment with placebo. Based on serial measurements of FEV-1 over this 12 hour period, there was a peak mean improvement in the formoterol MDDPI group over the placebo group of 0.12 L (17% mean improvement from baseline) 15-60 minutes after administration of study drug.

COMMENT: *This treatment effect, although small, is probably clinically significant in terms of patient benefit. The relative mildness of asthma in the patient population studied (mean % predicted FEV-1 at baseline = 76%) may have contributed to the modest improvement seen in FEV-1 after treatment. A 17% improvement from baseline is consistent with the change seen after administration of other long-acting inhaled beta adrenergic agonist drug products (Verberne AAPH et al. J Allergy Clin Immunol 1993; 91:127). A 0.12 L treatment effect is also consistent with the change seen after administration of other long-acting inhaled beta adrenergic agonist drug products (see MOR NDA 20,236 S-005).*

The three key studies in adults were: 1) two 12 week randomized, multicenter, double-blind, double-dummy, placebo and active treatment controlled, parallel group studies in patients 13-85 years of age with persistent asthma who received 10 mcg bid of formoterol delivered by Certihaler (MDDPI) (studies 2302 and 2303). The primary efficacy variable in both these studies was the 12 hour AUC FEV-1 after 3 months of treatment. Other efficacy variables were QOL assessment, serial FEV-1 and FVC measurements, number of asthma exacerbations, AM/PM PEF, symptoms scores and use of rescue medication. Safety variables included adverse events, laboratory tests, vital signs and ECGs. In both studies, there was a statistically significantly greater improvement in FEV-1 AUC over 12 hours after treatment with Foradil Certihaler compared with placebo; and 2) a randomized, multicenter, double-blind, double-dummy, placebo-controlled and active treatment controlled, incomplete block crossover study with pharmacokinetic evaluation in patients 20-73 years of age who received 5, 10, 15 and 30 mcg bid of formoterol delivered by Certihaler as well as

12 mcg bid of formoterol delivered from the Aerolizer each for a period of one week (study 601). The primary efficacy variable in this study was standardized AUC for FEV-1 over 12 hours measured at the end of each week of treatment. Other efficacy variables included serial FEV-1 measurements, daily symptom scores, and use of rescue medication. Safety variables included adverse events, ECGs and vital signs. Conjugated and unchanged formoterol was measured in the urine. A statistically significantly greater improvement in FEV-1 AUC over 12 hours after treatment for one week was demonstrated for all doses of formoterol delivered by Certihaler as well as for formoterol delivered by Aerolizer compared to placebo.

In *study 2302*, the mean AUC for 12 hour FEV-1 after 3 months of treatment with formoterol by MDDPI was 5.21 L/hr compared with 1.47 L/hr after treatment with placebo. Based on serial measurements of FEV-1 over this 12 hour period, there was a peak mean improvement in the formoterol MDDPI group over the placebo group of 0.41 L one hour after administration of study drug. In *study 2303*, the mean AUC for 12 hour FEV-1 after 3 months of treatment with formoterol by MDDPI was 4.45 L/hr compared with 2.79 L/hr after treatment with placebo. Based on serial measurements of FEV-1 over this 12 hour period, there was a peak mean improvement in the formoterol MDDPI group over the placebo group of 0.36 L 30 minutes after administration of study drug. These effect sizes are clinically significant and consistent with changes that have been seen with formoterol delivered by Aerolizer (see study 601; package insert for Foradil Aerolizer; NDA 20,236 Serevent MDI). There are no unresolved issues regarding efficacy in adults.

Study 605 was a 12 week, randomized, multicenter, double-blind, double-dummy, placebo controlled, active treatment controlled parallel group foreign study involving 28 centers in 6 countries and comparing formoterol MDDPI 10 mcg bid with formoterol Aerolizer 12 mcg bid and placebo in 365 patients 13 years of age and older with persistent asthma. The data from this study was only included in the safety analysis for Foradil Certihaler because Foradil Certihaler did not produce a statistically significantly different response than placebo using a primary outcome variable that had been changed by the sponsor in a study not powered appropriately for that end point.

C. Detailed Review of Trials by Indication

The reader is referred to a detailed review of individual studies later in review. The tables below compare the primary efficacy variable in studies done by the sponsor.

Dose-ranging study 602 in children comparing response to placebo after one week of treatment and to change from baseline in terms of AUC FEV-1(v33, p108)

Treatment	N	Mean	P value *	P value **
Placebo	48	1.76	-----	0.03
MDDPI 5 mcg bid	48	1.89	0.002	< 0.0001
MDDPI 10 mcg bid	48	1.92	< 0.0001	< 0.0001
MDDPI 15 mcg bid	51	1.91	0.0002	< 0.0001
MDDPI 30 mcg bid	52	1.94	< 0.0001	< 0.0001
Aerolizer 12 mcg bid	47	1.88	0.03	< 0.0001

* p value comparison to placebo
** p value comparison to baseline

Study 604 in children comparing response to placebo over 3 months of treatment in terms of FEV-1 AUC over 12 hours after drug administration (v33, p120)

Treatment and time of treatment	N	Mean (L x hour)	P value *
Day 1 ■■■■■■■■■			
Formoterol MDDPI 10 mcg bid	120	2.2	< 0.0001
Placebo	127	0.6	-----
Month 1 ■■■■■■■■■■			
Formoterol MDDPI 10 mcg bid	114	2.2	< 0.0001
Placebo	121	1.2	-----
3 month ITTE population ■■■■■■			
Formoterol MDDPI 10 mcg bid	108	2.6	0.003
Placebo	116	1.5	-----
3 month imputed ■■■■■■■■■			
Formoterol MDDPI 10 mcg bid	120	2.5	0.01
Placebo	127	1.5	-----

* compared to placebo

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Comparison of studies 2302 and 2303 comparing response to placebo over 3 months of treatment in terms of 12 hour AUC for FEV-1 (v33, p122)

		study 2302			study 2303	
Treatment	N	Mean (L x hour)	P value	N	Mean (L x hour)	P value
Day 1 ■■■■■■						
Formoterol MDDPI	86	5.08	< 0.0001	80	4.80	< 0.0001
Albuterol	88	4.14	< 0.0001	79	3.53	< 0.0001
Placebo	90	1.34	-----	80	1.39	-----
One month ■■■■■■						
Formoterol MDDPI	80	4.60	< 0.0001	76	5.08	0.0001
Albuterol	84	3.38	0.001	72	2.83	0.35 ••••
Placebo	86	1.26	-----	72	2.11	-----
3 month (ITTE) ■■■						
Formoterol MDDPI	75	5.14	< 0.0001	70	4.42	0.003
Albuterol	78	3.78	0.004	72	2.88	0.33 ••••
Placebo	82	1.73	-----	67	2.14	-----
3 month imputed ■■						
Formoterol MDDPI	86	5.21	< 0.0001	80	4.45	0.0002
Albuterol	88	3.78	0.0005	79	2.80	0.15 ••••
Placebo	90	1.47	-----	80	1.79	-----

•••• = not statistically significantly different from placebo p > 0.05

Cross-study comparison of change in FEV-1 measured serially after formoterol administration for 3 months (v33, p152)

	Study 604			study 2302			study 2303		
Length of treatment and time of FEV-1 measurement	N	Mean (L)	P value	N	Mean (L)	P value	N	Mean (L)	P value
3 month imputed									
Pre-dose	127	1.82	0.27 ••	86	2.60	0.001	80	2.46	0.01
5 minutes	127	1.89	0.0006	86	2.74	< 0.0001	80	2.63	< 0.0001
15 minutes	127	1.92	< 0.0001	86	2.81	< 0.0001	80	2.66	< 0.0001
30 minutes	127	1.94	0.0002	86	2.84	< 0.0001	80	2.69	< 0.0001
1 hour	127	1.97	0.0002	86	2.89	< 0.0001	80	2.72	< 0.0001
2 hour	127	1.97	0.001	86	2.90	< 0.0001	80	2.73	< 0.0001
3 hour	127	1.97	0.001	86	2.91	< 0.0001	80	2.74	< 0.0001
4 hour	127	1.95	0.004	86	2.88	< 0.0001	80	2.70	< 0.0001
6 hour	127	1.93	0.02	86	2.81	< 0.0001	80	2.65	0.0004
8 hour	127	1.89	0.09 ••	86	2.81	< 0.0001	80	2.58	0.02
10 hour	127	1.88	0.10 ••	86	2.78	< 0.0001	80	2.54	0.04
11 hour	127	1.88	0.23 ••	86	2.77	< 0.0001	80	2.53	0.06
12 hour	127	1.88	0.24 ••	86	2.76	< 0.0001	80	2.55	0.03

•• = not statistically significantly greater than placebo p > 0.05

Cross-study comparison for secondary efficacy parameters comparing formoterol response with the response to placebo over the entire treatment period (v33, p163)

	Study 604			study 2302			study 2303		
Parameter	N	Mean (L/min)	P value	N	Mean (L/min)	P value	N	Mean (L/min)	P value
AM PEF	125	260	0.05	83	373	< 0.0001	77	376	< 0.0001
AM sx score	125	0.77	0.10 *	83	1.41	0.03 **	77	1.54	0.03 **
PM sx score	125	0.88	0.02	83	1.68	0.01	77	1.71	0.02 #
Nocturnal sx score	125	0.14	0.02	83	0.34	0.25 #	77	0.40	0.26 •
Night-time rescue medication (# puffs)	125	0.21	0.04	83	0.50	0.006	77	0.67	0.005
Daytime rescue medication	125	0.44	0.17 &	83	0.79	0.03 ##	77	1.04	0.006&
24 hour rescue meds	125	0.65	0.09 &&	83	1.29	0.01	77	1.70	0.002 &&

* albuterol vs. placebo p = 0.14
** albuterol vs. placebo p = 0.50
# albuterol vs. placebo p = 0.27
albuterol vs. placebo p = 0.23
& albuterol vs. placebo p = 0.52
&& albuterol vs. placebo p = 0.79

Study 605 is a 12 week randomized, multicenter, double-blind, double dummy, placebo controlled and active treatment controlled, parallel group study in adolescents and adults 13-74 years of age with persistent asthma who received 10 mcg bid of formoterol delivered by MDDPI or 12 mcg bid of formoterol delivered by Aerolizer. There were 28 centers in 6 countries (Brazil, Czech Republic, Germany, Mexico, Russia, and Turkey). There was randomization of 365 patients, of whom 121 received formoterol MDDPI, 121 received formoterol Aerolizer and 123 received placebo.

The original primary efficacy variable was AM PEF which was amended to AM pre-dose FEV-1 at the last visit. The original sample size estimate was based on AM PEF as the primary outcome variable, but because AM PEF was considered unreliable, the primary outcome variable was changed to pre-dose FEV-1 which was the only pulmonary function parameter not collected by electronic diary. By changing the primary outcome variable it is likely that the study was underpowered. The sponsor considered it reasonable to assume that a difference of 0.2 L in FEV-1 was clinically relevant for this type of study. For the purpose of re-assessing the power of the study, the blinded pooled common standard deviation was calculated to be approximately 0.6 L for FEV-1.

Secondary outcome variables included AM and PM PEF, daytime and nighttime symptom scores and use of rescue medication for efficacy and adverse events, laboratory tests, ECGs and vital signs for safety. All efficacy analyses were based on the ITTE population. No statistically significant difference from placebo was found for either formoterol delivered from the MDDPI or formoterol delivered from the Aerolizer in regard to the primary efficacy variable. There was a statistically significant difference from placebo in regard to daytime and nighttime asthma symptoms scores when formoterol MDDPI was compared to placebo and patients in both active treatment groups used less rescue medication than those in the placebo group. The majority of adverse events were mild to moderate and were similar in the three treatment groups. Mean QTc intervals were significantly higher after 8 weeks of treatment in the formoterol MDDPI group than in the Aerolizer group (mean 425.3 msec in the formoterol MDDPI group and 421.2 msec in the formoterol Aerolizer group).

Efficacy Conclusions:

1. Children: In a pediatric study of patients 5-12 years of age (study 604), based on statistical comparison with placebo, patients who received 10 mcg bid of formoterol delivered by MDDPI (Certihaler) had a significantly greater improvement in FEV-1 throughout 3 months of treatment than did patients who received placebo.

   In dose ranging study 602, there was no statistically significant difference between doses ranging from 5-30 mcg bid of formoterol delivered by MDDPI or between any dose of formoterol delivered by MDDPI and 12 mcg bid of formoterol delivered by Aerolizer in regard to FEV-1. All doses of formoterol delivered by MDDPI and Aerolizer produced a statistically significantly greater improvement in FEV-1 than did placebo, despite the fact that there was a statistically significant improvement in FEV-1 in the placebo group compared with baseline.

   Comment: *There was a suggestion of tolerance developing in this age group based on serial measurements of FEV-1, since a statistically significant difference from placebo was only demonstrated for 6 hours after administration of formoterol by MDDPI after 3 months of treatment, whereas such a difference was demonstrated for 10 hours after formoterol MDDPI administration after one month of treatment and for 12 hours after administration of formoterol MDDPI on day 1. In addition, there was a statistically significant difference between formoterol MDDPI and placebo prior to drug administration after one month of treatment (p=0.03) that was not seen after 3 months of treatment (p=0.27).*

A statistically significantly greater improvement in AM/PM PEF, nocturnal symptom score, and nighttime use of rescue medication was seen in children after administration of 10 mcg bid of formoterol from the MDDPI compared with placebo. No statistically significant difference was seen between formoterol 10 mcg bid by MDDPI and placebo for FVC, morning or evening symptoms, individual asthma symptoms or daytime or 24 hour rescue medication use in this pediatric study.

COMMENT: The efficacy of formoterol when delivered at a dose of 10 mcg bid from the Certihaler (MDDPI) has been demonstrated in patients 5-12 years of age. After administration over a period of 3 months, however, effectiveness was not demonstrated for greater than 6 hours after drug administration based on serial measurements of FEV-1 and comparison with placebo. However, evaluation of other parameters, such as mean % change in FEV-1 from baseline, and analysis of responders do not support the development of tolerance. Nevertheless, there will need to be modification of the labeling since the current statement in the labeling about the development of tolerance is too strongly worded to be consistent with the data.

2. Adults: Two studies of three months duration were performed in adult and adolescent patients 13-85 years of age. In both studies, there was a statistically significant improvement in FEV-1 after formoterol administration by MDDPI compared to placebo on day 1 and after 1 and 3 months of treatment. In one of these studies (study 2303), the active treatment control, albuterol, did not show a statistically significant improvement in FEV-1 compared to placebo. Unlike the study in children (study 604), a statistically significant improvement over placebo was maintained throughout the dosing interval after 3 months of treatment.

   Greater improvement after formoterol administration by MDDPI at a dose of 10 mcg bid in adults was also demonstrated in regard to other efficacy parameters, i.e. AM/PM PEF, FVC, and daytime, nighttime and 24 hour use of rescue medication. The results from the two studies differed in regard to QOL assessment which was statistically significantly greater than placebo in one study (study 2303) but not the other (study 2302), asthma symptoms (nocturnal, daytime, nighttime) which showed a statistically significant improvement compared to placebo in one study (study 2303) but not in the other study (study 2302) and individual symptoms (only shortness of breath showed statistical significance in study 2302 while the only symptom that did not show statistical significance in study 2303 was cough). Greater overall effectiveness of formoterol MDDPI at a dose of 10 mcg bid was shown in study 2303 than in study 2302. Study 2303 was also the study in which a statistically significant difference was not demonstrated for albuterol compared to placebo.

In dose ranging study 601, in which doses of 5-30 mcg bid of formoterol was delivered by MDDPI to adults 20-73 years of age, a statistically significantly greater improvement in FEV-1 after treatment for one week was demonstrated for all doses of formoterol as well as for formoterol when delivered at a dose of 12 mcg bid by Aerolizer compared to placebo. However, effectiveness was only demonstrated at a dose of 5 mcg bid for 10 hours after administration of formoterol from the MDDPI, whereas with higher doses of formoterol, efficacy was demonstrated throughout the dosing interval of 12 hours.

COMMENT: *Overall, the effectiveness of formoterol at a dose of 10 mcg bid when delivered by Certihaler (MDDPI) has been demonstrated in adults.*

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Except for tremor, adverse events in patients who used the Certihaler were not dose dependent. The overall incidence of adverse events was low after administration of Foradil Certihaler, adverse events were mostly mild-moderate, the incidence was similar to the incidence seen after placebo administration and no serious adverse events were linked to the administration of Foradil Certihaler. In addition, there were no clinically significant changes in vital signs, in laboratory tests, or on ECGs after the administration of Foradil Certihaler that would preclude the approval of this drug product. There do not appear to be any significant risks associated with the use of Foradil Certihaler beyond those that are already recognized and that would be expected with administration of an inhaled beta adrenergic agonist drug.

On the other hand, it should be noted that for a number of different parameters across study groups, there was a higher incidence of adverse effects and other changes in safety outcomes in patients who received Foradil Certihaler than in patients who received the marketed Foradil Aerolizer. For example, in the group that received formoterol MDDPI, there were 3.2% discontinuations due to adverse events compared to 0.9% in the formoterol Aerolizer group. The percentage of patients in the formoterol MDDPI group who experienced an adverse event was 54% compared to 27% in the formoterol Aerolizer group. Specific adverse events such as pyrexia, nasopharyngitis and tremor were more frequent in the formoterol MDDPI group than in the formoterol Aerolizer group, both in adult and pediatric studies and most occurred at a dose of 10 mcg bid. There were more serious adverse events in the group that received formoterol by MDDPI than in the formoterol Aerolizer group, including exacerbation of asthma, although none were considered due to the study drug. The incidence of severe adverse events was greater in the formoterol MDDPI group than in the formoterol Aerolizer group. The incidence of abnormal laboratory tests of possible clinical significance was also greater in the formoterol MDDPI group than in the formoterol Aerolizer

group. The difference between adverse events in patients who received formoterol by MDDPI and patients who received placebo was not as great, the difference between the incidence of adverse events after use of the Certihaler and the Aerolizer reflecting an unusually low incidence of adverse events in the Aerolizer group.

E. Description of Patient Exposure (v34)

Overall patient exposure (v34, p11,t1.4-1) to all treatments

Categorical exposure	Formoterol MDDPI	Formoterol Aerolizer	Albuterol MDI	Placebo	All
All treated patients	558	215	167	512	1262
Multiple dose controlled studies	558	215	167	512	1262
Short duration studies	144	94	-----	96	246
Study 601	67	46	-----	42	67
Study 602	77	48	-----	54	179
Medium duration studies	414	121	167	416	1118
Study 605	121	121	-----	123	365
Study 2302	86	-----	88	91	265
Study 2303	80	-----	79	80	239
Study 604	127	-----	-----	122	239
Pediatric studies	204	48	-----	176	326
Study 602	77	48	-----	54	179
Study 604	127	-----	-----	122	249

Exposure to formoterol delivered by MDDPI based on dose (v34, p12, t1.4-2)

Categorical exposure	10 mcg daily dose	20 mcg daily dose	30 mcg daily dose	60 mcg daily dose
All treated patients	96	506	98	94
Multiple dose controlled studies	96	506	98	94
Short duration studies	96	92	98	94
Study 601	45	43	46	41
Study 602	51	49	52	53
Medium duration studies	-----	414	-----	-----
Study 605	-----	121	-----	-----
Study 2302	-----	86	-----	-----
Study 2303	-----	80	-----	-----
Study 604	-----	127	-----	-----
Pediatric studies	51	176	52	53
Study 602	51	49	52	53
Study 604	-----	127	-----	-----

Duration of exposure to all treatments (v34, p13, t2.1-1)

Duration of exposure	Formoterol MDDPI (n=558)	Formoterol Aerolizer (n=215)	Albuterol (n=167)	Placebo (n=512)
1-7 days	7 (1.3%)	6 (2.8%)	3 (1.8%)	18 (3.5%)
8-28 days	142 (25.4%)	91 (42.3%)	4 (2.4%)	95 (18.6%)
> 4-12 weeks	154 (27.6%)	70 (32.6%)	41 (24.6%)	144 (28.1%)
> 12-24 weeks	255 (45.7%)	48 (22.3%)	119 (71.3%)	255 (49.8%)
> 24-48 weeks	None	None	None	None
< 48 weeks	None	None	None	None

Duration of exposure in pediatric studies (v34, p17, t2.1-1)

Duration of exposure	Formoterol MDDPI (n=204)	Formoterol Aerolizer (n=48)	Albuterol (n=none)	Placebo (n=176)
1-7 days	2 (1%)	1 (2%)	-----	6 (3%)
8-28 days	75 (36%)	47 (98%)	-----	52 (30%)
>4-12 weeks	40 (20%)	-----	-----	34 (19%)
>12-24weeks	87 (43%)	-----	-----	84 (48%)
>24-48 weeks	-----	-----	-----	-----
> 48 weeks	-----	-----	-----	-----

Duration of exposure with different doses of formoterol MDDPI (v34, p18, t2.1-2)

Duration of exposure	10 mcg daily dose (n=96)	20 mcg daily dose (n=506)	30 mcg daily dose (n=98)	60 mcg daily dose (n=94)
1-7 days	9 (9%)	11 (2%)	4 (4%)	4 (4%)
8-28 days	87 (91%)	95 (19%)	94 (96%)	90 (96%)
>4-12 weeks	-----	145 (29%)	-----	-----
>12-24 weeks	-----	255 (50%)	-----	-----
>24-48 weeks	-----	-----	-----	-----
> 48 weeks	-----	-----	-----	-----

Duration of exposure with different doses of formoterol MDDPI in pediatric studies (v34, p22, t2.1-2)

Duration of exposure	10 mcg daily dose (n=51)	20 mcg daily dose (n=176)	30 mcg daily dose (n=52)	60 mcg daily dose (n=53)
1-7 days	2 (4%)	2 (1%)	1 (2%)	1 (2%)
8-28 days	49 (96%)	51 (29%)	51 (98%)	52 (98%)
> 4-12 weeks	-----	36 (21%)	-----	-----
> 12-24 weeks	-----	87 (49%)	-----	-----
> 24-48 weeks	-----	-----	-----	-----
> 48 weeks	-----	-----	-----	-----

Exposure to all treatments based on age (v34, p23, t2.1-3)

Age range	Formoterol MDDPI (n=558)	Formoterol Aerolizer (n=215)	Albuterol MDI (n=167)	Placebo (n=512)
5-12 years	204	48	1	176
13-18 years	17	7	19	29
19-64 years	307	142	138	281
65-74 years	28	18	7	23
> 74 years	2	-----	2	3

Exposure based on age, gender, race, and dose of formoterol MDDPI (v34, p33, t2.1-4, p63-64, 71-72)

	10 mcg daily dose (n = 96)	20 mcg daily dose (n = 506)	30 mcg daily dose (n = 98)	60 mcg daily dose (n = 94)
Age categories				
5-12 years	51	176	52	53
13-18 years	-----	17	-----	-----
19-64 years	38	284	41	36
65-74 years	7	27	5	5
> 74 years	-----	2	-----	-----
Gender all studies	N = 96	N = 506	N = 98	N = 94
Male	59 (62%)	253 (50%)	59 (60%)	58 (62%)
Female	37 (38%)	253 (50%)	39 (40%)	36 (38%)
Race all studies	N = 96	N = 506	N = 98	N = 94
Caucasian	88 (92%)	393 (77%)	89 (91%)	83 (88 %)
Black	None	55 (11%)	None	None
Oriental	None	4 (1%)	1 (1%)	1 (1%)
Other	8 (8%)	54 (11%)	8 (8%)	10 (11%)
Gender pediatric studies	N = 51	N = 176	N = 52	N = 53
Male	30 (59%)	117 (67%)	28 (54%)	35 (66%)
Female	21 (41%)	59 (33%)	24 (46%)	18 (34%)
Race pediatric studies	N = 51	N = 176	N = 52	N = 53
Caucasian	43 (84%)	119 (67%)	44 (85%)	43 (81%)
Black	None	33 (19%)	None	None
Oriental	None	1 (1%)	None	None
Other	8 (16%)	23 (13%)	8 (15%)	10 (19%)

Exposure to all treatments based on gender (v34, p53, p61)

Gender	Formoterol MDDPI	Formoterol Aerolizer	Albuterol MDI	Placebo
All studies	N = 558	N = 215	N = 167	N = 512
Male	290 (52%)	99 (46%)	67 (40%)	237 (46%)
Female	268 (48%)	116 (54%)	100 (60%)	275 (54%)
Pediatric studies	N = 204	N = 48	N = 0	N = 176
Male	139 (68%)	28 (58%)	-----	104 (59%)
Female	65 (32%)	20 (42%)	-----	72 (41%)

Exposure to all treatments based on race (v34, p54, p62)

Race	Formoterol MDDPI	Formoterol Aerolizer	Albuterol MDI	Placebo
All studies	N = 558	N = 215	N = 167	N = 512
Caucasian	441 (79%)	175 (81%)	145 (87%)	404 (79%)
Black	55 (10%)	2 (1%)	13 (8%)	45 (9%)
Oriental	4 (1%)	1 (1%)	1 (1%)	7 (1%)
Other	58 (10%)	37 (17%)	8 (4%)	56 (11%)
Pediatric studies	N = 204	N = 48	N = 0	N= 176
Caucasian	143 (70%)	36 (75%)	-----	129 (73%)
Black	33 (16%)	None	-----	21 (12%)
Oriental	1 (1%)	None	-----	3 (2%)
Other	27 (13%)	12 (25%)	-----	23 (13%)

C. Methods and Specific Findings of Safety Review

The safety parameters for each individual study were analyzed first and then compared with the ISS in terms of incidence of adverse events, vital signs, ECG findings and laboratory tests. Individual studies that were performed specifically to assess the safety of Foradil Certihaler were studies 603, 701, and 2301.

COMMENT: *There were no data supplied by the sponsor that indicated that there was any safety concern associated with the administration of Foradil Certihaler that would prevent approval.*

Study 603, which was submitted in the 120 day safety update, was an open label 12 month safety study in 411 patients with persistent asthma who received 10 mcg bid formoterol delivered by MDDPI for 12 months. During the first 12 weeks of the study patients received a double-blind rescue medication; either formoterol MDDPI or albuterol MDI which was then continued in an open fashion for a period of 12 months. No significant difference in the incidence of adverse events or other safety parameters was demonstrated between patients who received formoterol alone on a regular basis or received formoterol on a regular basis in conjunction with either formoterol or albuterol rescue medication. There were 27 serious adverse events in this study, which are described below.

Fatalities: No fatalities were reported in any of the studies submitted under this NDA except from study 603 (v48, p3 of appendix 2). The cases provided by the sponsor in regard to fatal events in this study are the following:

1) sudden exacerbation of asthma – respiratory arrest within 30 minutes after the onset of the event in 19 year old female who received double-blind formoterol for rescue medication; the

patient had taken the study medication for about 5 months; there was no previous history of hospitalizations for asthma; (v48, p11 of appendix 2)

2) acute asthma attack – 17 year old female; no history of a previous life-threatening asthma attack; event occurred about 3 months after starting study medication; poor compliance; history of palpitations; FEV-1 5 days before death was 1.91; patient was receiving PRN albuterol for rescue (v48, p11)
3) cerebral hemorrhage – 51 year old female; history of thrombocytopenia; history of allergic reaction to NSAIDs; found in bed barely breathing
4) stroke – 70 year old male, 9 months after starting treatment with the study medication

The following serious non-fatal adverse events were also reported from study 603.

1) eventration and surgery in a 70 year old female
2) surgery for urinary incontinence in a 71 year old female
3) asthma exacerbation in a 40 year old female; requiring ER treatment and hospitalization; last dose of formoterol was on morning of admission; event started about one month after starting study medication; patient received formoterol for rescue medication (v48, p14)
4) asthma exacerbation in a 42 year old male; hospitalized about 10 months after starting treatment with albuterol for rescue medication; d/c inhaled corticosteroids because did not think he needed them; continued on study medication after event (v48, p14)
5) asthma exacerbation, respiratory failure and high glucose in a 25 year old female; patient received formoterol for rescue medication; hospitalized after d/c inhaled corticosteroids for financial reason; no prior history of hospitalization for asthma; about 9 months after starting study medication; also had pneumonia which was considered cause for her admission to ICU (v48, p15)
6) surgery for gallstones in a 71 year old female
7) removal of nasal polyp in a 47 year old female
8) sudden onset of near-fatal asthma in a 62 year old female; patient received formoterol for rescue medication; no previous hospitalization for asthma; event occurred about 5 months after starting study medication; intubation required (v48, p16)
9) epistaxis in a 65 year old male
10) asthma exacerbation in a 26 year old male requiring hospitalization about 2 months after starting study medication; one previous episode requiring hospitalization; received formoterol for rescue medication (v48, p17)
11) gastroenteritis in a 26 year old male
12) acute asthma in a 16 year old male; received formoterol for PRN rescue medication; two previous hospitalizations for asthma; event occurred about 3 months after starting study medication (v48, p18)
13) asthma exacerbation in a 14 year old male; received albuterol for rescue medication; non-compliant, multiple hospitalizations and ICU admissions for asthma; event occurred about 4 months after starting study medication (v48, p19)
14) adenocarcinoma of the uterus in a 41 year old female
15) asthma exacerbation in a 41 year old female; patient received formoterol for rescue medication; no previous hospitalization for asthma; event occurred about 2 months after starting study medication; switched from formoterol PRN to albuterol PRN before hospitalization (v48, p20)
16) pneumonia in a 44 year old male
17) gastroenteritis in a 40 year old female
18) acute asthma in a 43 year old female; received PRN albuterol for rescue; previous hospitalization for asthma; event occurred about 3 months after starting study drug (v48, p20)
19) acute MI in a 65 year old male
20) coronary artery disease in a 42 year old female

21) asthma exacerbation in a 34 year old female; received formoterol for rescue medication; history of multiple ER visits and hospitalization for asthma; event occurred about 11 months after starting study medication(v48, p22)
22) cardiac insufficiency in a 68 year old female
23) shoulder surgery in a 22 year old male
24) appendectomy in a 15 year old female
asthma exacerbation in a 15 year old female; albuterol was PRN rescue medication; one previous hospitalization for pneumonia and asthma; event occurred about 5 months after
25) starting study medication; triggered by dust exposure (v48, p23)
26) concussion from accident in a 22 year old male
27) acute severe asthma exacerbation with respiratory failure in a 28 year old male; received albuterol for PRN rescue medication; event occurred about 11 months after starting the study medication; not previously hospitalized for asthma (48, p24)

The table below is a comparison of asthma-related serious adverse events in patients who were receiving formoterol MDDPI as rescue medication and patients who were receiving albuterol MDI as rescue medication in study 603.

Rescue medication	N	Age (years)	Time from initiation of treatment	M/F	Hospital-ization	Respiratory arrest
Formoterol MDDPI	7	16-62	1-11 months	2/5	7	1
Albuterol MDI	5	14-43	3-11 months	3/2	4	1

Study 701 was a randomized, double-blind, double-dummy, active treatment controlled, 2 way crossover, repetitive dose study in 16 patients with mild persistent asthma 21-49 years of age who received 36 mcg of formoterol delivered by Aerolizer tid compared to 600 mcg of albuterol MDI tid for a period of 3 days. Patients were evaluated in regard to the effect of this high dose on serum glucose and potassium, vital signs, ECGs and Holter monitoring (see complete description of study 701 below). There were no significant differences in adverse events in the two treatment groups and all adverse events were mild or moderate in intensity. Adverse events after administration of formoterol consisted of drowsiness, headache, nausea, internal unrest, back pain, muscle tremor and asthma. There was a decrease in plasma potassium in 15/16 patients after treatment with formoterol and 8/16 patients after treatment with albuterol. There were 93 plasma potassium values > 3.6 mmol/l after administration of formoterol compared with 33 such values after administration of albuterol. The lowest potassium value after treatment with formoterol was 3.05 mmol/l compared with 3.26 during treatment with albuterol. The mean change in plasma potassium was lower during administration of formoterol than during administration of albuterol. Individual decreases in plasma potassium were very small, just outside the lower limit of the normal reference range, often preceded by low levels prior to the first dose administration and occurred after administration of both formoterol and albuterol in some patients. Mean plasma potassium levels did not change significantly over the three days of treatment with either formoterol or albuterol although mean plasma potassium values were slightly lower at most time points,

1. 2 and 3 hours after formoterol administration than after albuterol administration with either sequence of administration.

Both formoterol and albuterol produced a mean increase overall in plasma glucose levels (v52, p30, f7.3-4; v52, p39. t11.1-2). Initially, over the first 4 hours after the first dose of formoterol on day 1, there was a mean decrease in plasma glucose, followed by a mean elevation from 4-6 hours, a decrease from 6-10 hours and a mean increase from 10-12 hours. After 12 hours, the mean plasma glucose level generally was lower than baseline throughout the rest of the 62 hour evaluation period. The number of plasma glucose values above the upper limit of the normal reference range during treatment with formoterol was 273 and during treatment with albuterol 204. Most patients had an increase in plasma glucose on both formoterol and albuterol. These increases were modest and many of these patients had an elevation in plasma glucose above the upper limit of the normal reference range prior to administration of the first dose of drug. There was no pattern in regard to dose or day of administration, e.g. dose 1 on day 1 vs. dose 2 on day 3 (v53, pgs 456-518). There was no clinically significant change in mean plasma glucose after either administration of formoterol or albuterol over the three days of treatment although increases in mean plasma glucose were greater after administration of formoterol when formoterol was administered before albuterol in sequence (v53, pgs 537-481).

COMMENT: *Plasma potassium and plasma glucose are sensitive markers of beta adrenergic effect. It is not surprising that large doses of formoterol would produce a decrease in plasma potassium or changes in plasma glucose. It should be noted, however, that a greater effect on plasma potassium and plasma glucose was seen during formoterol administration than was seen during albuterol administration. This study was performed with administration of formoterol from the approved Aerolizer device and may or may not relate to the effect when formoterol is delivered by Certihaler.*

In terms of vital signs (v52, p30), elevation in pulse rate only occurred during formoterol administration. All blood pressure measurements were normal except for patient 504, whose systolic blood pressure rose to 168 mm Hg 2 hours after administration of the third dose of formoterol on day 1.

There were no clinically significant changes in ECGs noted after administration of either formoterol or albuterol (v52, p32). The QTc interval corrected with Bazett's correction was considered normal if it was < 450 msec in females and < 430 msec in males. A prolonged QTc interval was considered to be > 470 msec in females and > 450 msec in males with values between these being considered borderline. One male patient had a QTc interval of 452 msec prior to the second dose of formoterol on day 1 of treatment and one hour after the third dose on day 2, with a baseline value of 409 msec (v54, p258). One female patient had QTc intervals of 452-464 during treatment with formoterol at a number of time points

after drug administration (v54, p800)(patient 506) and another female patient had two values of 452 msec during treatment with formoterol. There were no prolonged or borderline QTc intervals reported in patients while receiving albuterol, although one patient had a measurement of 450 msec 2 hours after the second dose on day 3 (v54, p799). Both the AUC QTc intervals and mean QTc intervals were significantly greater in patients when they received formoterol than when they received albuterol (v52, p40, t11.1-3). In particular, mean QTc intervals were significantly longer in patients while receiving formoterol during days 2 and 3 (baseline 390 msec, day two 401-417 msec, day three 397-410 msec)(v52, p34, f7.3.7)(v54, pgs816-825). No significant changes were seen on Holter monitoring during treatment with either formoterol or albuterol. Patients that experienced PVCs during treatment with albuterol, experienced PVCs during treatment with formoterol, as well, several patients having 500-800 isolated PVCs (v54, p865-866). These findings were not considered clinically significant by the investigator.

Study 2301 was a randomized, double-blind, placebo-controlled, multiple dose, two-period crossover study to assess the effects of bid administrations of 24 mcg formoterol or placebo on glucose control in type 2 diabetic patients. This was a single center study performed in San Antonio, TX. There were 17 patients enrolled, 16 of whom completed the study. Patients were 30-75 years of age with type 2 diabetes of at least 6 months duration with an average fasting plasma glucose of 7-10 mmol (120-180 mg/dl) and HbA1c $\leq$ 10%, not treated with insulin for at least 3 months. Patients received formoterol 24 mcg (2 inhalations of 12 mcg) bid at 6-9 AM and 6-9 PM, delivered by Aerolizer (capsules for oral inhalation) over 21 days of randomized treatment preceded by a 21 day screening period with a 21 day washout period between treatments. Glucose control was evaluated as well as vital signs, ECGs, laboratory tests, and adverse events. The study objective was to assess the effects of formoterol on prandial plasma glucose excursion (AUC plasma glucose concentration) following a standardized AM meal, serum fructosamine concentrations and plasma glucose concentration two hours after ingestion of a standardized AM meal. After formoterol administration, ten adverse events were reported including single reports of nausea, diarrhea, abdominal bloating, upset stomach, pruritis, wrist pain, nervousness and back pain. There was a mean increase in systolic blood pressure after formoterol Aerolizer administration on day 1 (126-131 mm Hg) and after 3 weeks of treatment (124-138 mm Hg). The mean increase seen after placebo was 124-130 mm Hg on day 1 and 115-128 mm Hg after 3 weeks of treatment. There were no clinically significant changes in ECGs after treatment with formoterol Aerolizer. One patient had an increase from screening in the QTc interval from 400 to 434 msec after formoterol Aerolizer treatment for 3 weeks. Another patient had an increase from baseline in QTc interval from 437 to 465 msec after treatment with formoterol Aerolizer for 3 weeks. Similar or greater increases in QTc interval were seen after administration of placebo. After ingestion of breakfast on day 21, higher levels of glucose 1-4 hours after treatment were seen

after administration of formoterol than after administration of placebo. This produced a greater AUC (748 mg.h/dL vs. 683 mg.h/dL), concentration at 2 hours (208 mg/dL vs 182 mg/dL) and Emax (229 mg/dL vs. 209 mg/dL) after formoterol administration than after placebo administration. The 21 day average prandial glucose levels were 50% higher after administration of formoterol than after administration of placebo. The change in plasma fructosamine from day 1 to day 21 was not statistically different after formoterol and placebo administration. Fasting plasma glucose levels were similar after treatment with formoterol and placebo (p=0.90). After 21 days of treatment, the mean prandial glucose concentration increased from 147 mg/dL prior to treatment to 152 mg/dL 4 hours after treatment with formoterol with a peak level of 215 mg/dL 90 minutes after treatment. By contrast, afte placebo administration there was a decrease from 144 mg/dL to 132 mg/dL 4 hours after administration with a peak of 198 mg/dL one hour after administration. There were a few patients who had a significant increase in plasma glucose after administration of Foradil Aerolizer that included the following (v56, p280): 1) 176 mg/dL prior to the first dose – 265 mg/dL 90 minutes after drug administration on day 21; 2) 140 mg/dL prior to the first dose – 248 mg/dL 2 hours after drug administration on day 1 and day 21; 3) 137 mg/dL prior to the first dose – 197 and 192 mg/dl after drug administration on day 1 and day 21, respectively; 4) 161 mg/dL prior to the first dose – 286 mg/dL 90 minutes after drug administration on day 21; 5) 159 mg/dL prior to the first dose – 273 mg/dL 90 minutes after drug administration on day 1; and 6) 139 mg/dL prior to the first dose – 276 mg/dL 1 hour after drug administration on day 21

D. Adequacy of Safety Testing

The evaluation of safety by the sponsor was adequate for this NDA. Adverse events, vital signs, ECGs and laboratory tests were performed in the patient population that will receive the drug. There was adequate exposure both in terms of total number of adult and pediatric patients who received the drug, as well as the number of patients who received the drug for up to one year's duration, to make a determination of the safety of Foradil Certihaler. Further evaluation would be helpful in regard to the safety of this drug product in certain subsets of patients, e.g. elderly patients.

E. Summary of Critical Safety Findings and Limitations of Data

Premature discontinuations

There were 15 (3.2%) premature discontinuations because of adverse events in all studies after administration of formoterol by MDDPI (v41, p2725)(v48, p5476). These included: 1) asthma exacerbation (study 601)- 30 mcg per day, 57 year old female, not related to study drug; 2) asthma exacerbation (study 601)- 60 mcg per day, 32 year old female, not related to study drug; 3) rash and swelling around mouth (study 604)- 20 mcg per day, 11 year old female, possibly related to study

drug; 4) asthma exacerbation (study 604)- 20 mcg per day, 8 year old female, not related to study drug; 5) rash (study 2302)-20 mcg per day, 30 year old male, not related to study drug; 6) asthma exacerbation (study 2302)- 20 mcg per day, 21 year old female, not related to study drug; 7) asthma exacerbation (study 2302)- 20 mcg per day, 19 year old female, not related to study drug; 8) small cell lung cancer (study 2302)- 20 mcg per day, 42 year old male, not related to study drug; 9) asthma exacerbation (study 2302)- 20 mcg per day, 16 year old male, not related to study drug; 10) vomiting (study 2302)- 20 mcg per day, 29 year old male, not related to study drug; 11) bronchitis (study 2303)- 20 mcg per day, 56 year old female, not related to study drug; 12) respiratory distress (study 2303)-20 mcg per day, 44 year old female, not related to study drug; 13) asthma exacerbation (study 2303)- 20 mcg per day, 21 year old female, not related to study drug; 14) WPW syndrome (study 2303) – 20 mcg per day, 13 year old male, not related to study drug; and 15) asthma exacerbation (study 2303) – 20 mcg per day, 48 year old female, not related to study drug. In contrast, premature discontinuations were seen in two patients who received formoterol Aerolizer (0.9%), in 6 patients who received albuterol MDI (4.8%) and in 14 patients who received placebo (2.9%).

Premature discontinuations in pediatric studies due to adverse events(v34, p47) included: formoterol MDDPI: 2 (1%), formoterol Aerolizer: none, and. placebo: 2 (1.1%). Albuterol was not used as an active treatment control in pediatric studies. Premature discontinuations due to adverse events based on daily dose of formoterol MDDPI (v34, p48) were: formoterol 10 mcg per day 1 (1%); formoterol 20 mcg per day 11 (2.2%), formoterol 30 mcg per day none and formoterol 60 mcg per day 1 (1.1%). The only two premature discontinuations due to adverse events in pediatric studies were at a daily dose of 20 mcg per day.

adverse events (v36, p894)

Comparison of adverse events between treatment groups with inclusion of adverse events of importance because of the class of drug, e.g. cardiovascular effects and adverse events that occurred with an incidence of 2% or more than placebo and more than other active treatment controls (data from all studies) can be seen in the table below.

Parameter	Formoterol MDDPI (N=558)	Formoterol Aerolizer (N=215)	Albuterol MDI (N=167)	Placebo (N=512)
Number of pts with AEs	301 (54%)	59 (27%)	96 (58%)	233 (46%)
Tachycardia	6 (1%)	2 (1%)	None	1 (0.2%)
Palpitations	2 (0.4%)	1 (0.5%)	None	None
Vomiting	16 (3%)	1 (1%)	1 (1%)	7 (1%)
Pyrexia	20 (4%)	4 (2%)	3 (2%)	11 (2%)
Nasopharyngitis	41 (7%)	8 (4%)	10 (6%)	26 (5%)
Tremor	38 (7%)	7 (3%)	1 (1%)	4 (1%)

Adverse events in pediatric studies using the same criteria as in the table above (v36, p977)

Parameter	Formoterol MDDPI (n=204)	Formoterol Aerolizer (n=48)	Albuterol MDI (n=0)	Placebo (n=176)
Number of patients with adverse events	118 (58%)	4 (8%)	-----	76 (43%)
Tachycardia	4 (2%)	None	-----	1 (1%)
Palpitations	1 (1%)	None	-----	None
Vomiting	12 (6%)	None	-----	4 (2%)
Pyrexia	14 (7%)	None	-----	7 (4%)
URI	23 (11%)	None	-----	14 (8%)
Headache	14 (7%)	None	-----	8 (5%)
Tremor	12 (6%)	None	-----	1 (1%)

Adverse events based on daily dose in all studies using the same criteria as in the table above but for the 10 mcg bid dose of formoterol (20 mcg/day)(v36, p989)

Parameter	Formoterol 10 mcg per day (n=96)	Formoterol 20 mcg per day (n=506)	Formoterol 30 mcg per day (n=98)	Formoterol 60 mcg per day (n=94)
number of patients with adverse events	15 (16%)	246 (49%)	20 (20%)	29 (31%)
Tachycardia *	None	3 (1%)	1 (1%)	2 (2%)
Palpitations	None	1 (0.2%)	1 (1%)	None
Vomiting	None	16 (3%)	None	None
Pyrexia	None	20 (4%)	None	None
URIs	2 (2%)	34 (7%)	1 (1%)	None
Nasopharyngitis	2 (2%)	36 (7%)	2 (2%)	1 (1%)
Headache	1 (1%)	34 (7%)	2 (2%)	2 (2%)
Tremor **	2 (2%)	14 (3%)	6 (6%)	19 (20%)
Asthma aggravated	None	46 (9%)	1 (1%)	1 (1%)
Cough	1 (1%)	21 (4%)	1 (1%)	1 (1%)
Pharyngitis	1 (1%)	18 (4%)	1 (1%)	None
Nasal congestion	None	10 (2%)	None	None
Allergic rhinitis	None	10 (2%)	None	None

* There was one patient who received 20 mcg per day of formoterol who developed ventricular bigeminy and one patient who received the same dose who developed WPW. No patients who received the other doses had these or any other cardiovascular adverse event.

** added to table because it was the only adverse event considered related to the administration of beta adrenergic agonist drugs that showed a linear dose-dependent pattern

adverse events based on daily dose in pediatric studies using the same criteria as in the table above based on the 10 mcg bid (20 mcg per day) dose (v36, p 1059) can be seen in the table below.

Parameter	Formoterol 10 mcg per day (n=51)	Formoterol 20 mcg per day (n=176)	Formoterol 30 mcg per day (n=52)	Formoterol 60 mcg per day (n=53)
Number of patients with adverse events	11 (22%)	90 (51%)	11 (21%)	12 (23%)
Tachycardia	None	1 (1%)	1 (2%)	2 (4%)
Palpitations	None	None	1 (2%)	None
Vomiting	None	12 (7%)	None	None
Pyrexia	None	14 (8%)	None	None
URIs	2 (4%)	20 (11%)	1 (2%)	None
Nasopharyngitis	None	11 (6%)	None	1 (2%)
Gastroenteritis	None	4 (2%)	None	None
Pharyngitis	None	4 (2%)	None	None
Headache	None	11 (6%)	1 (2%)	2 (4%)
Tremor	1 (2%)	2 (1%)	4 (8%)	6 (11%)
Asthma aggravated	None	18 (10%)	None	None
Cough	1(2%)	8 (5%)	None	None
Nasal congestion	None	6 (3%)	None	None
Allergic rhinitis	None	4 (2%)	None	None

Serious adverse events based on treatment, total daily dose and type of study (v41, p2692, p2693)

Type of study	Formoterol MDDPI *	Formoterol Aerolizer	Albuterol MDI	Placebo
Controlled short term	2 (1.4%) n =144	None N = 94	None None	None n= 96
Controlled medium term	7 (1.7%) n = 414	1 (0.8%) n = 121	5 (3%) n = 167	4 (1%) n = 416
Pediatric studies	2 (1%) n = 204	None N = 48	None None	2 (0.6%) n = 326
All studies	9 (1.6%) ** N = 558	1 (0.5%) N = 215	5 (3%) N = 167	4 (0.8%) N = 512
Formoterol 10 mcg	None N = 96	-----	-----	-----
Formoterol 20 mcg	7 (1.4%) n = 506	-----	-----	-----
Formoterol 30 mcg	None N = 98	-----	-----	-----
Formoterol 60 mcg	2 (2.1%) n = 94	-----	-----	-----

* Serious adverse events in the formoterol MDDPI group were appendicitis (20 mcg per day), femoral neck fracture (20 mcg per day), basal cell carcinoma (20 mcg per day), small cell lung cancer (20 mcg per day), asthma exacerbated (3) (two 20 mcg per day, one 60 mcg per day), bronchospasm (60 mcg per day), respiratory distress (20 mcg per day) (v48, p5464). More

specifically, these were: 1) asthma exacerbation (study 601)- 60 mcg per day; 32 year old female; not related to study drug; 2) bronchospasm (study 602) – 60 mcg per day, 12 year old male, not related to study drug; 3) asthma exacerbation (study 604) – 20 mcg per day, 8 year old female, not related to study drug; 4) asthma exacerbation (study 605) – 20 mcg per day, 39 year old female, not related to study drug; 5) femoral neck fracture (study 605) – 20 mcg per day, 62 year old female, not related to study drug; 6) appendicitis (study 605) – 20 mcg per day, 32 year old male, not related to study drug; 7) small cell lung cancer (study 2302) – 20 mcg per day, 42 year old male, not related to study drug; 8) respiratory distress (study 2303) – 20 mcg per day, 44 year old female, not related to study drug; and 9) basal cell carcinoma (study 2303) – 20 mcg per day, 54 year old female, not related to study drug.

** Two of the serious adverse events in controlled studies were in controlled pediatric studies

Laboratory tests:

Number (%) of patients who had a laboratory test that was normal at baseline and increased or decreased outside the upper or lower limits of the normal reference range after treatment selected by the reviewer as tests of particular interest(all studies, i.e. studies 605, 2302. 2303, 604)(ITTS population)(v46, p4694) can be seen in the table below.

Laboratory test after treatment compared with normal baseline	Formoterol MDDPI * N = 414	Formoterol Aerolizer N = 121	Albuterol MDI N = 167	Placebo N = 416
Hemoglobin low	13 (3.1%)	2 (1.7%)	1 (0.6%)	6 (1.4%)
Hematocrit low	11 (2.7%)	1 (0.8%)	1 (0.6%)	7 (1.7%)
WBC low	9 (2.2%)	2 (1.7%)	2 (1.2%)	6 (1.4%)
Platelet count low	0	0	0	1 (0.2)
Neutrophils low	34 (8.2%)	3 (2.5%)	4 (2.4%)	25 (6%)
Eosinophils high	36 (8.7%)	7 (5.8%)	7 (4.2%)	24 (5.8%)
Fasting glucose high	18 (4.3%)	2 (1.7%)	8 (4.8%)	12 (2.9%)
Serum potassium low	6 (1.4%)	0	2 (1.2%)	0
Serum Creatinine high	16 (3.9%)	1 (0.8%)	1 (0.6%)	7 (1.7%)
BUN high	6 (1.4%)	6 (5%)	5 (3%)	10 (2.4%)
Total Bilirubin high	3 (0.7%)	0	0	1 (0.2%)
Gamma GT	2 (0.5%)	5 (4.1%)	0	0
SGOT high	14 (3.4%)	1 (0.8%)	7 (4.2%)	13 (3.1%)
SGPT high	13 (3.1%)	4 (3.3%)	5 (3%)	9 (2.2%)

* all changes noted above occurred after administration of the 20 mcg per day dose

ECGs: evaluation of data from studies, 601, 602, 604, 605, 2302, and 2303.

Based on data from all studies, there were 39 patients (9.4% of 414 patients) who had a normal ECG at baseline and an abnormal ECG after they had received formoterol by MDDPI. In comparison, there were 17 (14% of 121 patients), 12 (7.2% of 167 patients) and 42 (10.1% of 416 patients) who had a normal ECG at baseline and an abnormal ECG after receiving formoterol by Aerolizer, albuterol and placebo, respectively. In pediatric studies, there were 6 (4.7% of 127 patients) and 7 (5.7% of 122 patients) who had a normal ECG at baseline and an abnormal ECG after receiving formoterol delivered by MDDPI and placebo, respectively.

There were two patients who had a 40-50% acute maximum increase in PR interval (0.7% of 293 patients) after administration of formoterol MDDPI and none who had this amount of maximum increase after administration of albuterol or placebo. There were 7 patients who had a maximum decrease of 20-30% in PR interval after administration of formoterol MDDPI compared with 1.2% (2/167) and 1.4% (4/293) in the albuterol and placebo groups, respectively. Mean changes in the treatment groups were not significantly different. In terms of chronic effect, there was not a significantly greater number of patients who had a 20% or greater maximum increase or decrease in PR interval in any treatment group and mean changes were not significantly different. There were the same number and percent of patients in the formoterol MDDPI and placebo groups who had at least one value < 120 msec and 2.9% of patients in the formoterol MDDPI group and 1.9% of patients in the placebo group who had at least one value > 200 msec. There was no significant difference in either maximum acute or chronic increase or decrease or percentage of patients with a maximum % increase or decrease of 30% or greater in QRS interval in any treatment group.

Change in QTc interval after administration of study drug (all studies) (ITTS population) (v47, p5152) can be seen in the table below.

Time point	Formoterol MDDPI n = 437	Formoterol Aerolizer N = 94	Albuterol MDI N = 167	Placebo N = 389
Maximum % acute mean increase	5.3	5.0	5.0	5.0
Maximum % acute mean decrease	4.9	5.6	4.1	4.8
Maximum % chronic mean increase	5.2	4.7	4.3	4.6
Maximum % chronic mean decrease	3.2	4.8	4.4	4.5

There was a comparable percent of patients in each treatment group who had a 10% or greater increase or decrease in QTc interval (Bazett's correction) in terms of acute and chronic effect in all the studies and specifically in the pediatric studies. There were 8 patients (1.4% of 558 patients), 3 patients (1.4% of 215 patients), 1 (0.6% of 167 patients) and 4 (0.8% of 512 patients) who had at least one value > 460 msec in the formoterol MDDPI, formoterol Aerolizer, albuterol and placebo groups, respectively. One of the patients who received formoterol MDDPI at a dose

of 20 mcg per day had an increase in QTc interval of > 60 msec, an increase that was not seen in the other treatment groups.

vital signs (v48, p5300)

Mean maximum % increase or decrease in vital signs based on studies 601, 602, 604, 2302, and 2303

Category	MDDPI	Aerolizer	Albuterol	Placebo
N	437	94	167	389
↑ systolic BP	16%	11%	16%	15%
↓ systolic BP	11%	8%	12%	11%
↑ diastolic BP	20%	14%	18%	18%
↓ diastolic BP	17%	12%	16%	16%
↑ pulse rate	25%	17%	26%	23%
↓ pulse rate	15%	11%	15%	14%

Acute maximum percent change in systolic blood pressure based on studies 601, 602, 604, 2302, and 2303

Maximum % increase	MDDPI (n = 437)	Aerolizer (n = 94)	Albuterol (n = 167)	Placebo (n = 389)
> 50%	0.2%	0	0	0
40-50%	0.5%	0	1%	1%
30-40%	5%	1%	4%	5%
20-30%	20%	7%	23%	15%
10-20%	39%	27%	42%	38%
> 0-10%	33%	42%	27%	33%
No change	3%	23%	2%	8%
Maximum % decrease				
> 50%	0	0	0	0
40-50%	0	0	0	0
30-40%	0.2%	0	0	0.3%
20-30%	8%	1%	7%	5%
10-20%	38%	18%	44%	39%
> 0-10%	47%	46%	45%	43%
No change	7%	35%	3%	13%

Acute maximum percent change in diastolic blood pressure based on studies 601, 602. 604. 2302 and 2303

Maximum % increase	MDDPI N = 437	Aerolizer N = 94	Albuterol N = 167	Placebo N = 389
> 50%	2%	0	1%	1%
40-50%	3%	0	1%	1%
30-40%	12%	2%	10%	10%
20-30%	20%	11%	19%	17%
10-20%	36%	26%	40%	34%
> 0-10%	23%	38%	25%	25%
No change	5%	23%	5%	12%
maximum % decrease				
> 50%	1%	0	1%	0
40-50%	1%	1%	0	0.3%
30-40%	5%	0	2%	5%
20-30%	20%	6%	18%	20%
10-20%	47%	25%	60%	44%
>0-10%	22%	29%	17%	23%
No change	5%	39%	2%	8%

Acute maximum percent change in pulse rate based on studies 601, 602, 604, 2302 and 2303

Maximum % increase	MDDPI N = 437	Aerolizer N = 94	Albuterol N = 167	Placebo N = 389
> 50%	7%	3%	5%	3%
40-50%	7%	2%	7%	8%
30-40%	15%	6%	20%	13%
20-30%	23%	16%	26%	22%
10-20%	31%	18%	30%	29%
>0-10%	15%	35%	10%	17%
No change	2%	19%	1%	8%
Maximum % decrease				
> 50%	0.2%	0	0	0
40-50%	0	0	0	0
30-40%	4%	1%	2%	3%
20-30%	18%	11%	14%	15%
10-20%	42%	26%	51%	40%
> 0-19%	30%	39%	24%	32%
No change	6%	23%	9%	10%

COMMENT: *This database supports the safety of administration of formoterol from the Certihaler device at the proposed dose of 10 mcg bid in adults and children 5-12 years of age.*

VIII. Dosing, Regimen, and Administration Issues

Since efficacy was demonstrated with a dose of 10 mcg bid of formoterol delivered by MDDPI in *children 5-12 years of age* to a degree comparable in efficacy to higher doses delivered from the MDDPI and comparable in efficacy to 12 mg bid delivered from the Aerolizer (a dose that is approved for administration to children 5 years of age and older) and since efficacy was not demonstrated throughout the dosing interval with a dose of 5 mcg bid, *the selection of a dose of 10 mcg bid for administration to children is appropriate (see discussion in Dosing section under Summary of Clinical Findings in this review).* There is no indication that any adverse event, with the exception of tremor, or change in vital signs, laboratory tests or ECGs occurs to a significantly greater degree after administration of a dose of 10 mcg bid of Foradil Certihaler than after the administration of placebo in children.

Based on the effectiveness of 10 mcg bid of formoterol delivered from MDDPI in *adults* throughout the dosing interval with somewhat less effectiveness of the 5 mcg bid dose and no significantly greater effectiveness at higher doses delivered by MDDPI and based on an absence of safety concerns when this dose is administered, *the dose selected for administration to adults, 10 mcg bid delivered by MDDPI is appropriate (see discussion in Dosing section under Summary of Clinical Findings in this review).* There is no indication that any adverse event, with the exception of tremor, or change in vital signs, laboratory tests or ECGs occurs to a significantly greater degree after administration of a dose of 10 mcg bid of Foradil Certihaler than after administration of placebo in adults.

The dosing interval of 12 hours is appropriate based on the data in adults and children that shows a decrease in effectiveness at the end of the 12 hour dosing interval. Foradil Certihaler is an inhaled drug product and therefore no studies were performed where the dose of formoterol was administered in a temporal relationship to ingestion of food. There should be no need for dose modification since effectiveness is dependent on the regular administration of this drug product, there is no indication that a 10 mcg dose will provide efficacy for longer than 12 hours and the labeling clearly states that the recommended dose should not be exceeded.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The subgroup analysis of the two adult studies (studies 2302, and 2303) and the 12 week study in patients 5-12 years of age showed that there was a larger treatment effect in males than in females after administration of formoterol MDDPI. There is no reason to believe that Foradil Certihaler is not effective in female patients, although adverse events were generally less in females than in males suggesting greater bioavailability in male patients than in female patients.

Adverse events based on gender all studies (v42, p3322)

Adverse events	Male (n=290)	Female (n=268)
Total adverse events all studies	149 (51.4%)	152 (56.7%)
Adverse events 20 mcg per day dose	116 (45.8%)	130 (51.4%)
Pediatric studies	N = 139	N = 65
Vomiting	7%	3%
Nasopharyngitis	7%	3%
Headache	95	2%
Asthma aggravate	10%	6%
Cough	6%	2%

There was no adverse event that occurred with a 3% or greater incidence considering all studies in either male or female patients after administration of formoterol from the MDDPI. In the pediatric studies, as noted in the table above, there were some specific adverse events that occurred significantly more frequently in males or females after use of formoterol from the MDDPI.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

1. Safety:

a. Adverse events:

1) age-related

Specific adverse events categorized by age where adverse event occurred with a 2% or greater frequently in the pediatric population than in the adult population after use of formoterol MDDPI (v41, p2780) can be seen in the table below.

Adverse event	5-12 years n = 204	13-18 years n = 17	19-64 years n = 307	> 64 years n = 30
URI	23 (11%)	3 (18%)	10 (3%)	1 (4%)
Asthma aggravated	18 (9%)	4 (24%)	25 (8%)	0
Pharyngitis	11 (5%)	3 (18%)	6 (2%)	0
Allergic rhinitis	4 (2%)	2 (12%)	4 (1%)	0

Vomiting occurred in 7% of patients 5-12 years of age and 1.4% of patients 19-64 years of age after 20 mcg per day of formoterol MDDPI (v42, p3112). Pyrexia occurred in 8 % of patients 5-12 years of age, 125 of patients 13-18 years of age and 1.45 of patients 19-64 years of age after 20 mcg per day of formoterol MDDPI. URIs occurred in 11% of patients 5-12 years of age, 18%

of patients 13-18 years of age and 3.5% of patients 19-64 years of age after 20 mcg per day of formoterol MDDPI. Headache and tremor occurred with a greater frequency in patients 19-64 years of age after 20 mcg per day of formoterol MDDPI. Aggravation of asthma and phayngitis occurred more frequently in patients 5-12 years of age (10% and 5% respectively) and patients 13-18 years of age (24% and 18% respectively) than in patients 19-64 years of age (8% and 2% respectively) after 20 mcg per day of formoterol MDDPI. There were no other adverse events that occurred with significantly greater frequency in children and adolescents who received 20 mcg per day of formoterol by MDDPI.

2) race-related (v44, p3781):

Adverse events occurring in 5% or more of the Black, Caucasian or Other patient populations who received formoterol MDDPI and 5% or more of the Caucasian population who received formoteol Aerolizer or placebo can be seen in the table below.

Adverse events	Black N = 55	Caucasian N =441	Oriental N = 4	Other N = 58
Formoterol MDDPI ••••••••••				
Total number of patients with AEs	30 (55%)	234 (53%)	3 (75%)	34 (59%)
Pyrexia	4 (7%)	12 (3%)	3 (25%)	3 (5%)
Nasopharyngitis	2 (4%)	36 (8%)	2 (50%)	1 (2%)
URI	1 2%)	32 (7%)	None	4 (7%)
Tremor	1 (2%)	36 (8%)	None	1 (2%)
Headache	5 (9%)	31 (7%)	None	3 (5%)
Asthma aggravate	11 20%)	27 (6%)	None	10 (17%)
Allergic rhinitis	4 (7%)	6 (1%)	None	1 (2%)
Nasal congestion	4 (7%)	5 (1%)	None	1 (2%)
Formoterol Aerolizer ••••••••	N = 2	N = 175	N = 1	N =37
Total number of patients with AEs	2	39 (22%)	none	18 (49%)
Asthma aggravate	1	12 (7%)	None	6 (16%)
Placebo ••••••••••	N = 45	N = 404	N =7	N =56
Total number of patients with AEs	21 (47%)	181 (45%)	4 (57%)	27 (48%)
URI	4 (9%)	26 (6%)	0	2 (4%)
Nasopharyngitis	2 (4%)	21 (5%)	2 (29%)	1 (2%)
Headache	3 (7%)	23 (6%)	0	8 (14%)
Asthma aggravate	7 (16%)	44 (11%)	1 (14%)	10 (18%)

b. laboratory tests

1) pediatric patients:

Number (%) of pediatric patients who had a normal laboratory test at baseline whose laboratory test (selected by the reviewer as tests of particular interest) after treatment was either higher or lower than the upper/lower limit of the normal reference range (ITTS population)(v46, p4697)(all studies, i.e. study 604) can be seen in the table below.

Laboratory test after treatment compared with normal baseline	Formoterol MDDPI * N = 127	Formoterol Aerolizer N = 0	Albuterol MDI N = 0	Placebo N = 122
Hemoglobin low	3 (2.4%)	-----	-----	0
Hematocrit low	7 (5.5%)	-----	-----	1 (0.8%)
WBC low	5 (3.9%)	-----	-----	3 (2.5%)
Platelet count low	0	-----	-----	0
Neutrophils low	28 (22%)	-----	-----	23 (18.9%)
Eosinphils high	15 (11.8%)	-----	-----	13 (10.7%)
Fasting glucose	1 (0.8%)	-----	-----	4 (3.3%)
Potassium low	2 (1.6%)	-----	-----	0
Serum creatinine high	12 (9.4%)	-----	-----	5 (4.1%)
BUN high	0	-----	-----	0
Total bilirubin high	1 (0.8%)	-----	-----	0
Alk phosph high	2 (1.6%)	-----	-----	4 (3.3%)
Gamma-GT high	0	-----	-----	0
SGOT high	3 (2.4%)	-----	-----	3 (2.5%)
SGPT high	3 (2.4%)	-----	-----	2 (1.6%)

* all changes noted above occurred after administration of the 20 mcg per day dose

C. Evaluation of Pediatric Program

The sponsor has adequately demonstrated the effectiveness and safety of Foradil Certihaler in patients 5-12 years of age. The sponsor has submitted a request for a waiver for study of children less than 5 years of age which is appropriate.

D. Comments on Data Available or Needed in Other Populations

There is no data available to evaluate the efficacy and safety of Foradil Certihaler in patients with renal or hepatic insufficiency. There has been no evaluation of Foradil Certihaler in pregnant patients. Further data on the efficacy and safety of Foradil Certihaler in adolescent and elderly patients would provide a better

understanding of the benefits and risks in this patient population. Absence of such data at this time does not preclude approvability of this drug product.

X. Conclusions and Recommendations

A. Conclusions

Foradil Certihaler was shown to be efficacious for the maintenance treatment of asthma and the prevention of bronchospasm in adults and children 5 years of age and older with reversible obstructive airway disease, based on studies 2302 and 2303 in adults and study 604 in children.

The incidence of side effects, as well as changes in vital signs, ECGs and laboratory tests that were observed when formoterol was delivered by the Certihaler were similar to those seen after administration of placebo, with the exception of tremor, which is a recognized side effect associated with administration of an inhaled beta agonist. There are no serious risks associated with the use of Foradil Certihaler. There is, therefore, an acceptable benefit:risk profile for this drug product has been established.

B. Recommendations

Recommendation is for approval from a clinical standpoint.

The following comments will be conveyed in the action letter:

- You should consider studies to establish a more extensive database for administration of Foradil Certihaler to adolescent and elderly patients.

b(4)

b(5)

b(4)

b(5)

• The Division has recently become aware of data from a large, GlaxoSmith Kline-sponsored clinical study suggesting that the long-acting beta-2 agonist salmeterol xinafoate may be associated with increased risk of life-threatening asthma exacerbations and asthma-related death. The preliminary results from this study, the Salmeterol Multicenter Asthma Research Trial (SMART), have resulted in significant labeling changes for salmeterol-containing products. It is possible that this finding may be due to a class-effect for all long-acting beta2 agonists. Propose language to address this issue in the product label for Foradil Certihaler.

NOTE: *Further discussion of the proposed labeling changes and the rationale for recommending these changes can be found in the Appendix below.*

4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

F. Individual More Detailed Study Reviews:

1. Study 2302 entitled "A 12 week randomized, multicenter, double-blind, double-dummy, placebo and active treatment controlled, parallel group study evaluating the safety and efficacy of formoterol fumarate (10 mcg bid) delivered by the multi-dose dry powder inhaler (MDDPI) versus placebo versus albuterol pMDI qid in patients with persistent asthma":

a. Study Characteristics: This study was performed at 22 centers in the United States.

1) number of patients: 265 patients randomized to treatment; 86 received formoterol; 88 received albuterol and 91 received placebo; 235 patients completed the study; 113 (43%) male, 152 (57%) female; 217 (82%) Caucasian, 31 (12%) Black, 3 (1%) Oriental, and 14 (5%) other (v33, p40).
2) age range: 13-81 years; 44 (17%) 13-17 years; 207 (78%) 18-64 years; 14 (5%) > 64 years
3) patient population: persistent asthma; regular or PRN treatment with inhaled beta agonist; FEV-1 40% or greater of predicted; patients could be on intranasal or orally inhaled CS as long as the patient had been on a stable dose for at least one month prior to entering the study; duration of asthma = 0.4-64.1 years (v33, p45).
4) study design: randomized, multi-center (22 centers), double-blind, double-dummy, placebo and active treatment controlled, parallel group study
5) drug administration: formoterol 1 inhalation (10 mcg) bid; albuterol MDI 2 inhalations (180 mcg) qid; open label albuterol during both periods of study on PRN rescue basis
6) periods of study: 2 week single-blind placebo run-in period followed by a double-blind 12 week period of randomized treatment
7) parameters evaluated: the primary efficacy variable was the 12 hour AUC for FEV-1 after 3 months of treatment calculated relative to baseline (the pre-dose FEV-1 value measured at visit 2 prior to the first dose of study drug); the baseline value was subtracted from each of the serial FEV-1 values taken over the 12 hour evaluation period; secondary efficacy variables included a patient reported miniAQLQ, serial FEV-1 and FVC, number of exacerbation, daily AM/PM PEF measured by a mini-Wright peak flow meter before administration of

the study medication (v19, p575), symptom scores, use of rescue medication; safety parameters included adverse events, laboratory tests, vital signs, ECGs and physical examination. Laboratory tests were done at visit 1 (screening), visit 2 (day 1) and visit 5 (end of study). Fasting blood samples were obtained prior to drug administration on these days. In addition, on visits 2 and 5, a second fasting blood sample was obtained 90 minutes after drug administration for measurement of glucose and potassium (v19, p631). Vital signs were measured at visit 1 (screening). They were also measured at baseline and 30 minutes, 60 minutes, and 2 hours after drug administration and every 2 hours thereafter through 12 hours after the morning dose of study medication at visits 2, 3 and 5. At visit 4, they were measured prior to drug administration and 30 minutes after drug administration. ECGs were done at screening as well as prior to drug administration and 90 minutes after drug administration at visits 2 (day 1) and 5 (end of study)

8) study objectives: to show that formoterol is more effective than placebo and to compare the efficacy and safety of formoterol with albuterol.
9) statistical methods: Intent-to-treat patients were defined as randomized patients who took at least one dose of double-blind treatment; intent-to-treat for efficacy was defined as any randomized patient who took the study drug and had at least one 12 hour spirometry evaluation during the double-blind treatment period; per protocol (PP) patients were defined as those intent-to-treat for efficacy patients who completed 12 weeks of double-blind treatment, had the 12 week spirometry evaluation with a calculable AUC and did not have any major deviations from the study protocol.

The primary efficacy variable was the 12 hour AUC for FEV-1 at the 3 month spirometry evaluation. AUC for FEV-1 was calculated relative to baseline, i.e. the pre-dose FEV-1 value measured at visit 2 (the first day of treatment) prior to the first dose of study drug was subtracted from each of the serial FEV-1 values taken over the 12 hour period. If patients prematurely discontinued the 12 hour spirometry evaluation used rescue medication during this period, the last FEV-1 value before premature termination or before the use of rescue medication was carried forward through the 12 hour period. If the 3 month spirometry day evaluation was missing or the AUC was

not calculable for this spirometry, the last available spirometry evaluation day prior to month 3 for which an AUC was calculable was used to impute the 3 month AUC. This calculation could be the end of study 12 hour spirometry for early terminations or the 1 month or 1 day spirometry performed after the first dose of study drug.

The ITTE population was considered the primary analysis population and the PP population was considered the secondary analysis population. A dose of 10 mcg bid of MDDPI formoterol was considered superior to placebo if the mean difference (from the ITTE population) of 3 month (imputed if necessary) formoterol AUC minus 3 month (imputed if necessary) placebo AUC was positive and statistically significant at the 0.05 level using a two-sided test. The primary and formally tested null-hypothesis was that there was no difference between patients treated with formoterol and patients treated with placebo.

Since the criterion for superiority was based on one efficacy variable for one analysis population for one pre-determined spirometry evaluation, no adjustment for multiple comparisons was necessary for the primary efficacy variable. Informal null-hypotheses regarding the primary efficacy variable were tested without adjustment for multiple comparisons. An analysis of covariance (ANCOVA) model used 3 month 12 hour AUC for FEV-1 = treatment + center + baseline + error. The baseline value was defined as the patient baseline minus the overall basement average where patient baseline was the pre-dose FEV-1 value measured at visit 2 (the first day of treatment) prior to the first inhalation of study drug and an overall baseline average was determined for each respective analysis of population/time-point ignoring the treatment group. Estimates of treatment effect and treatment difference were presented with associated 95% confidence intervals. In regard to 12 hour AUC for FEV-1, 5 end-points were analyzed: 1) 3 month (imputed if necessary) value for the ITTE population; 2) 3 month value for the PP population; 3) 3 month value for the ITTE population; 4) 1 month value for the ITTE population; and 5) 1 day value for the ITTE population (v18, p30).

b. Study Results:

1) EFFICACY:

a) patient disposition and discontinuations (v18, pgs35-37)(v33, p60):

Category	formoterol	Albuterol	placebo
Randomized *	86	88	91
Completed	74	78	83
Total discontinuations	12 (14%)	10 (11.4%)	8 (8.8%)
AE discontinuations	4 (4.7%)	3 (3.4%)	none

* all randomized patients in each treatment group were included in the intent-to-treat efficacy and the intent-to-treat safety analysis

b) demographics (v18, p38):

Variable	Formoterol	Albuterol	placebo
AGE [redacted]			
Mean	37.3	37.3	36.6
Median	36	36	37
Range	13-79	13-81	13-79
13-17 years	12 (14%)	12 (13.6%)	20 (22%)
18-64 years	69 (80.2%)	71 (80.7%)	67 (73.6%)
65 years or more	5 (5.8%)	5 (5.7%)	4 (4.4%)
GENDER [redacted]			
Male	37 (43%)	37 (42%)	39 (42.9%)
Female	49 (57%)	51 (58%)	51 (57.1%)
RACE [redacted]			
Caucasian	68 (79.1%)	77 (87.5%)	71 (79.1%)
African-American	11 (12.8%)	6 (6.8%)	14 (15.4%)
Oriental	1 (1.2%)	1 (1.1%)	1 (1.1%)
Other	6 (7%)	4 (4.5%)	4 (4.4%)
Mean duration asthma (years)	23	22	22
Mean FEV-1 at baseline	2.31 L	2.37 L	2.35 L
% predicted FEV-1 baseline	67%	69%	68%
% FEV-1 increase after albuterol	24%	27%	26%

c) concomitant medications at baseline and use during the study (v18. P41):

Medications for allergic conditions as well as asthma were taken by 90.1% of the patients who received placebo, 79.1% of the patients who received formoterol and 83% of the patients who received albuterol. At baseline, 71.4% of placebo patients, 65.1% of formoterol patients and 63.6% of albuterol patients were using inhaled corticosteroids. At baseline, there were no clinically significant differences between treatment groups in regard to concomitant medication use, except there were more patients in the formoterol group (16.3%) and the albuterol group (11.4%) who were taking fexofenadine than in the placebo group (6.6%). It is unlikely that this difference at baseline influenced the study results in any way. During the study there were more formoterol patients (4) and albuterol patients (5), than placebo patients (1) who took diphenhydramine which was a prohibited medication. This difference did not have any impact on the study results.

c) primary efficacy variable:

12 hour AUC for FEV-1 after 3 months of treatment and comparison to baseline (visit 2 prior to drug administration on the first day of dosing)(v18, p42) based on ITT and PP populations (v18, p 43, t9-1)(v18, p184, t7.4-2)(see table below)

12 hour AUC for FEV-1 after 3 months of treatment compared to baseline using the ITTE population

Treatment	Patient population	N	Mean FEV-1 AUC	Mean change from baseline AUC for FEV1	P value*
Formoterol	Intent-to-treat for efficacy #	86	5.21 L/hr	2.90 L/hr	< 0.0001 **
Formoterol	Per protocol	75	5.11 L/hr	2.80 L/hr	< 0.0001
Albuterol	Intent-to-treat for efficacy	88	3.78 L/hr	1.41 L/hr	0.0005
Albuterol	Per protocol	77	3.72 L/hr	1.35 L/hr	0.0046
Placebo	Intent-to-treat for efficacy	91	1.47 L/hr	- 0.88 L/hr	-
Placebo	Per protocol	82	1.70 L/hr	- 0.23 L/hr	-

* treatment comparison to placebo
** pre-specified primary analysis
# The ITTE population included all randomized patients who took the study drug and had at least one 12 hour spirometry evaluation during the double-blind treatment period.