NOVARTIS

Drug Regulatory Affairs

Foradil® Aerolizer®
(formoterol fumarate inhalation powder) 12 mcg

Pulmonary-Allergy Drugs Advisory Committee on the safety of
long-acting beta-agonist bronchodilators

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ADR	Adverse drug reaction
AE	Adverse event
AERS	Adverse events reporting system
Arg	Arginine
AUC	Area under the curve
b.i.d.	Twice daily
bpm	Beats per minutes
COPD	Chronic Obstructive Pulmonary Disease
CV	Cardiovascular
D/C	Discontinued
ECG	Electrocardiogram
EIB	Exercise-induced bronchospasm
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
Gly	Glycine
GPRD	General practice research database
ICS	Inhaled corticosteroid
HR	Hazard ratio
IMMP	Intensive medicines monitoring programme
ITT	Intent to treat
IVC	Inspiratory vital capacity
IVE	Idioventricular run episode
LABA	Long-acting beta$_2$-agonist
MDI	Metered dose inhaler
NA	Not applicable
MedDRA	Medical Dictionary for Regulatory Activities
NR	Not reported
PD	Pharmacodynamics
PEF	Peak expiratory flow
PEFR	Peak expiratory flow rate
PI	Package insert
PK	Pharmacokinetics
prn	As needed
q.i.d.	Four times a day
SABA	Short-acting beta$_2$-agonist
SGRQ	Saint George's Respiratory Questionnaire
SAE	Serious adverse event
SVPE	Supraventricular premature beats
TDD	Total daily dose
t.i.d.	Three times a day
VT	Ventricular tachycardia

| VTE | Ventricular tachycardia episode |
| VPB | Ventricular premature beats |

1   Executive summary

Asthma and COPD are respiratory illnesses that adversely affect a significant proportion of the population leading to considerable morbidity and mortality. Prior to the development of inhaled beta$_2$-agonist bronchodilators, there was a limited number of treatment options that were all associated with significant systemic side effects. Inhalant technologies allowed specific targeting of beta$_2$-agonists to the lung, resulting in improvements in bronchodilator efficacy. With the advent of inhaled long-acting beta$_2$-agonists (LABAs) and corticosteroids, symptoms and exacerbations were reduced, resulting in improvements in quality of life with an acceptable side effect profile. Recommendations from US and international professional organizations have underscored the importance of these agents in the treatment of asthma and COPD.

Recently, concerns about the safety of a long-acting beta$_2$-agonist bronchodilator were raised when the results of a large clinical trial became known. The Food and Drug Administration (FDA) requested an Advisory Committee meeting to publicly discuss safety data involving this class of drugs. This briefing book provides a review and analysis of the following:

- Novartis clinical trial database of more than 13,000 patients from both asthma and COPD studies, in terms of efficacy or safety (respiratory exacerbations, cardiovascular endpoints or death), including recently completed studies specifically conducted to examine safety endpoints.

- A summary of the safety data available from the FDA adverse event reporting system (AERS) with more than 10 million patient-years of exposure to formoterol, and other post-marketing safety surveillance data from outside the US.

- A literature review of formoterol safety from 25,000 patients involved in non-Novartis formoterol trials.

- The pharmacology of formoterol including molecular structure, agonist effects, potency and intrinsic efficacy, which distinguishes this molecule from others in its class.

Extensive review from all of these sources supports the conclusion that formoterol does not exhibit a safety profile of concern and is comparable in terms of the relevant safety measures to albuterol. Although epidemiologic data from post-marketing surveillance is limited, analysis of the available information appears to indicate that formoterol is associated with a rate of adverse events and deaths that is lower than salmeterol.

Novartis Pharmaceuticals Corporation remains committed to the safety of patients and to monitoring the safety of our products. We believe that the current package insert provides complete guidance as to the appropriate use of formoterol in asthma and COPD.

2   Introduction

Novartis Pharmaceuticals is making this submission in response to the notice of the FDA that its Pulmonary-Allergy Drugs Advisory Committee will discuss safety issues of long-acting beta-agonist bronchodilators on July 13, 2005.

Foradil® Aerolizer® (formoterol fumarate inhalation powder) 12 mcg is approved in the US for the twice-daily (b.i.d.) maintenance treatment of asthma in adults and children 5 years of age and older, and of COPD, including chronic bronchitis and emphysema. It is also approved for the treatment of exercise-induced bronchospasm (EIB) on an occasional, as-needed basis in adults and children 5 years of age and older. Foradil Aerolizer consists of dry powder capsules for oral inhalation intended for use with the Aerolizer Inhaler.

In addition, Foradil Aerolizer is approved in many other countries for these indications, at a dose up to 24 mcg b.i.d. In some countries, it has also been approved in a metered dose inhaler and a multi-dose dry powder inhaler 10 mcg (Certihaler®).

Marketed in the US since 2001, there has been no detectable safety signal from Foradil in either clinical trial data or post-marketing surveillance data.

This safety assessment focuses on significant respiratory adverse events, as well as deaths. Serious cardiovascular adverse events have also been evaluated in the pooled database of the Novartis clinical trials.

Information in this briefing document includes the following:

- Analysis of safety data from integrated databases of Novartis clinical trials of ≥4 weeks duration, testing formoterol fumarate (Foradil) in two dry powder formulations: Foradil Aerolizer 12 mcg (approved in the United States for asthma and EIB in February 2001 and for COPD in September 2001) and Foradil Certihaler 10 mcg, which is currently under review by FDA.

- The pooled analysis is complemented by a summary of results of two safety trials (D2307 and D2308) requested by FDA as phase IV commitment studies.

- Analysis of safety data from FDA Adverse Event Reporting System (AERS) database (which includes formoterol data compared to salmeterol and albuterol) and Intensive Medicines Monitoring Programme (IMMP) data from New Zealand.

- Analysis of safety data from the literature of non-Novartis formoterol trials.

- Overview of pre-clinical, clinical pharmacology, and pharmacogenetic studies, relevant to the assessment of the safety of formoterol.

- Overview of the benefit/risk relationship for formoterol.

3   Review of safety data from Novartis clinical trials

3.1   Summary

This section covers Novartis-sponsored formoterol trials in two formulations/inhalers: the Foradil Aerolizer single-dose dry powder inhaler, which is available to patients in the US, and the Foradil Certihaler multi-dose dry powder inhaler, the NDA of which is undergoing review.

For the evaluation of deaths, the full safety data for all controlled trials and for all uncontrolled trials were used. For significant respiratory and cardiovascular events, integrated safety data from all controlled-trials and all placebo-controlled trials of at least 4 weeks

duration were analyzed. Results refer to the placebo-controlled trials, unless specified otherwise.

The asthma database includes 5,907 patients receiving formoterol in controlled trials (median exposure: 89 days per patient) and 2,783 in uncontrolled trials (median exposure: 75 days per patient). The subsets of controlled trials and placebo-controlled trials lasting at least 4 weeks include 5,048 and 3,768 formoterol treated patients respectively (median exposure: 94 days per patient for each subset). The COPD dataset includes 1,071 patients receiving formoterol in all controlled trials (median exposure: 85 days per patient). There are no uncontrolled trials in this indication and all controlled trials have a placebo control group. The subset of controlled trials (and placebo-controlled trials) lasting at least 4 weeks include 908 formoterol treated patients (median exposure: 86 days per patient).

There was only one **asthma-related death** in the 5,907 patients treated with formoterol in controlled clinical trials (0.06 / 100 treatment years). In the uncontrolled trials, which included large studies in elderly and severe asthmatics, 5 asthma-related deaths were documented in 2783 patients (0.40 / 100 treatment years).

Asthma-related adverse events considered to be serious by the investigators (SAEs) and asthma-related adverse events (AEs) which were bad enough to induce the patient to leave the study prematurely are **significant asthma exacerbations.** Asthma-related SAEs occur more frequently in the formoterol group and albuterol group when compared with the placebo group. However, asthma-related adverse events (AEs) which were bad enough to induce the patient to leave the studies were worse in the placebo group as compared to the formoterol group and albuterol group. Therefore when both measures are analyzed in combination no safety signal is apparent. Similar rates were observed for formoterol, albuterol and placebo. Furthermore, compared to formoterol-treated patients, placebo-treated patients demonstrate a shorter time to first significant exacerbation and greater use of courses of rescue oral steroids and/or theophylline. This may occur because placebo patients either leave the study earlier because of an AE before they potentially experience a more severe event, or if staying in the study, resort more commonly to rescue courses of oral steroids/theophylline, compared to patients on formoterol or albuterol. Therefore, despite a higher rate of asthma-related SAEs in the formoterol group, this is off-set by a higher premature drop-out rate from the study, suggesting no difference between treatment groups.

Novartis was asked to conduct a phase **IV commitment asthma study D2307** to examine asthma-related AEs. Study D2307 was a double-blind trial conducted in 2,085 asthmatics, who were randomized to one of four treatment groups: low dose formoterol (12 mcg b.i.d., the US labeled dose), flexible dose formoterol (12 mcg b.i.d. + up to two additional 12 mcg doses per day, open label), high dose formoterol (24 mcg b.i.d., twice the maximum US labeled dose) or placebo. The primary variable, asthma related SAEs, occurred in less than 1% of patients in each treatment group (9 events in total). Of interest is the distribution of the 9 asthma-related SAEs among the treatment groups. The highest number of such events (5, 0.9%) occurred in the low dose formoterol group; the flexible formoterol dose group had the lowest number of events (1, 0.2%), the same as in the placebo group; the highest formoterol dose group (24 mcg b.i.d.) had a number of events (2, 0.4%) in between the two other dose groups. This kind of distribution, combined with the low number of events, suggests a random effect.

The **COPD** clinical trial database is relatively small, and deaths are rare events. However, the fact that there were no COPD-related or respiratory-related deaths in Foradil COPD clinical trials is reassuring. As for asthma, no safety signal emerges with regard to significant COPD exacerbations (COPD-related SAEs or discontinuations due to COPD-related AEs). In fact, there were less than half the number of significant COPD exacerbations in patients receiving formoterol compared to patients receiving placebo. This pattern was observed for both types of events contributing to significant COPD exacerbations. Thus, the apparently diverging pattern observed in asthma trials was not replicated in COPD trials. The fact that COPD patients have had their chronic illness for a longer period of time may explain why they are less inclined to leave the trial immediately when no benefit is received from the study treatment.

Upon approval of Foradil Aerolizer in September 2001 for COPD, the FDA requested a commitment to conduct a phase IV placebo-controlled trial in COPD (Study D2308) focusing on Holter ECG monitoring. The results showed no clinically meaningful differences between groups. The results of this study are provided in this section.

A safety signal was not identified for **serious cardiovascular adverse events** in the integrated asthma and COPD databases.

3.2 Integrated database of Novartis clinical trials: asthma-related adverse events

Integrated safety data for multiple-dose clinical trials using the Aerolizer and/or Certihaler formulations of formoterol with at least a four week treatment duration were assessed for significant asthma-related events, including deaths, serious adverse events (SAEs) and discontinuations due to asthma-related adverse events (AEs).

Events were selected using a list of pre-defined terms (See Appendix 1). All events were included, whether or not they were considered by the investigator to be related to the use of study drug.

3.2.1 The integrated database

Two integrated datasets were used for the assessment of significant asthma exacerbations, one which pooled all multiple-dose controlled trials of at least four weeks duration, and a subset of this dataset, which looked at placebo-controlled trials only. The dataset from placebo-controlled trials (Table 3-2) is considered more relevant for drawing meaningful conclusions because a comparison can be made to a matched group of patients who did not receive a LABA. The tables in this document refer to the dataset for placebo-controlled trials. Reference to the multiple dose controlled trial dataset (Table 3-3) is made as supporting evidence.

Several uncontrolled studies were also performed. A large proportion of the patients included in these studies belongs to higher risk populations, such as severe asthmatics and elderly patients. Reference to deaths from the uncontrolled database will only be made for completeness.

When considering the deaths reported during clinical trials, the integrated data from all trials have been considered for controlled and uncontrolled subsets separately including those of shorter duration such as single dose studies.

The numbers of patients exposed to each treatment, as well as the patient-years of treatment exposure in the multiple-dose placebo-controlled trials and in the multiple-dose controlled trials are presented in Table 3-1 and Table 3-2, respectively.

Table 3-1 **Number of patients treated and extent of exposure in multiple-dose placebo-controlled asthma trials of at least 4 weeks duration – Aerolizer and Certihaler combined**

Subsets of trials included (all multiple-dose placebo-controlled)	Formoterol			Placebo	Albuterol*
	All doses [1]	20/24 mcg TDD[2]	48 mcg TDD[3]		
All patients, N	3,768	1,948	1,156	1,863	630
Exposure in treatment years	1,171	593	396	568	160
Patients using ICS, n (%)	2,488 (66)	1,389 (71)	685 (59)	1,319 (71)	427 (68)
Exposure in treatment years	789	428	248	407	115
Patients not using ICS, n (%)	1,280 (34)	559 (29)	471 (41)	544 (29)	203 (32)
Exposure in treatment years	383	165	148	161	45

ICS = inhaled corticosteroids; TDD = total daily dose

[1]   All doses include 12 mcg TDD (included in trials DPPD2 and MTA03 only) and 24-48 mcg TDD (included in D2307 only)

[2]   Includes Aerolizer 12 mcg b.i.d. and Certihaler 10 mcg b.i.d.

[3]   Twice the maximum US labeled dose; only included in Aerolizer trials

prn albuterol allowed for rescue in all treatment groups

* dosed regularly q.i.d.

Table 3-2 **Number of patients treated and extent of exposure in multiple-dose controlled asthma trials of at least 4 weeks duration – Aerolizer and Certihaler combined**

Subsets of trials included (all multiple-dose controlled)	Formoterol			Placebo	Albuterol*
	All doses [1]	20/24 mcg TDD[2]	48 mcg TDD[3]		
All patients, N	5,048	2,957	1,353	1,863	990
Exposure in treatment years	1583	942	441	568	238
Patients using ICS, n (%)	3,484 (69)	2,179 (74)	850 (63)	1,319 (71)	636 (64)
Exposure in treatment years	1103	695	286	407	162
Patients not using ICS, n (%)	1,564 (31)	778 (26)	503 (37)	544 (29)	354 (36)
Exposure in treatment years	480	247	155	161	76

ICS = inhaled corticosteroids; TDD = total daily dose

[1]   All doses include 12 mcg TDD (included in trials DPPD2 and MTA03 only) and 24-48 mcg TDD (included in D2307 only)

[2]   Includes Aerolizer 12 mcg b.i.d. and Certihaler 10 mcg b.i.d.

[3]   Twice the maximum US labeled dose; only included in Aerolizer trials

prn albuterol allowed for rescue in all treatment groups

* dosed regularly q.i.d.

3.2.2   Asthma-related deaths and all deaths in asthma trials

3.2.2.1   Results

Table 3-3 presents the deaths reported during the study for all asthma studies controlled and uncontrolled, in Aerolizer and Certihaler irrespective of duration of planned exposure. All deaths are included, whether or not they were considered by the investigator to be related to study drug. In the controlled trials, there was a lower rate of overall deaths in the formoterol groups compared to albuterol or placebo.

There was only one asthma-related death in almost 6,000 patients treated with formoterol (5,907 patients, 1,610 patient treatment years). No asthma-related deaths were reported in the 1,238 patients of the albuterol control group (242 treatment years) and in the 2,446 patients of the placebo group (572 treatment years).

In the uncontrolled trials there were 5 asthma-related deaths in 2,783 patients who cumulatively received formoterol for 1,240 treatment years (rate: 0.40 events / 100 treatment years).

Table 3-3   **Deaths in all asthma trials– Aerolizer and Certihaler combined**

Subsets of trials included		Formoterol All doses	Albuterol	Placebo
Controlled [1]	N Total exposure (years)	**5,907** **1,610**	**1,238** 242	**2,446** 572
all deaths	n % n/100 years	1 (0.02) 0.06	1 (0.08) 0.41	1 (0.04) 0.17
asthma related deaths	n % n/100 years	1 (0.02) 0.06	0	0
cardiovascular related deaths	n % n/100 years	0	0	1 (0.04) 0.17
Uncontrolled	N Total exposure (years)	**2,783** **1,240**	**NA**	**NA**
all deaths	n % n/100 years	14 (0.50) 1.13	NA	NA
Asthma-related deaths	n % n/100 years	5 (0.18) 0.40	NA	NA
Cardiovascular-related deaths	n % n/100 years	6 (0.22) 0.48	NA	NA

TDD = total daily dose   NA = not applicable   Total exposure is measured in patient years
[1]   Controlled trials where at least one patient died were all placebo controlled

Of the three patients who died from non-asthma related, non-cardiovascular events in the uncontrolled trials, one died from a metastatic neoplasm, one from bronchopneumonia and the other was reported as sudden death.

3.2.2.2   Discussion

There was only one asthma-related death in nearly 6,000 patients receiving formoterol in the multiple dose controlled trials (rate: 0.06 deaths/100 patient years, 95% CI: $0 - 3$ deaths). No asthma-related death was documented in the placebo and albuterol groups of these studies. The average duration of exposure in these trials was 89 days per patient in the formoterol group, 85 days per patient in both the albuterol and placebo groups.

In the uncontrolled trials, the rate of asthma-related deaths was 0.40 / 100 treatment years. These trials involved particularly elderly patients and those with more severe disease. Of the total of 14 deaths, 4 patients were in a study of elderly asthmatics and 6 patients were in a study which allowed the inclusion of severe asthmatics. This could explain the overall higher rate of deaths in the uncontrolled trials compared to the controlled studies.

3.2.3 Significant asthma exacerbations: asthma-related SAEs and discontinuations due to asthma-related AEs

3.2.3.1 Results

Significant asthma exacerbations are defined in this report as asthma-related events reported as serious (SAEs) by the investigator according to pre-defined criteria and asthma-related adverse events (AEs) which were meaningful enough to prompt the patient to discontinue from the study early (whether labeled serious or not by the investigator).

Table 3.4 summarizes for multiple dose placebo controlled trials those patients reporting a significant asthma exacerbation, ensuring that patients who discontinued prematurely because of an asthma-related serious adverse event were not counted twice.

The table indicates that the rate of significant asthma exacerbations for formoterol at both 12 mcg and 24 mcg was similar to that for placebo.

When the data were analyzed according to concomitant ICS use, similar rates were seen for formoterol and placebo for those patients not using ICS compared with those being treated according to the guidelines with ICS.

Similar rates were found for all multiple dose controlled trials including those without a placebo control group.

Table 3-4   Patients with significant asthma exacerbations (asthma-related SAEs or premature discontinuations because of an asthma-related AE) in multiple-dose placebo-controlled trials of at least 4 weeks duration

Subsets of trials included (all multiple-dose placebo - controlled)		Formoterol			Placebo	Albuterol*
		All doses [1]	20/24 mcg TDD[2]	48 mcg TDD[3]		
All patients	N	3768	1948	1156	1863	630
	n (%)	95 (2.5)	39 (2.0)	40 (3.5)	60 (3.2)	14 (2.2)
	n/100 years	8.7	7.1	10.9	10.9	9.4
Patients using ICS	N	2488	1389	685	1319	427
	n (%)	63 (2.5)	29 (2.1)	25 (3.6)	43 (3.3)	13 (3.0)
	n/100 years	8.1	6.8	10.5	10.8	12.2
Patients not using ICS	N	1280	559	471	544	203
	n (%)	32 (2.5)	10 (1.8)	15 (3.2)	17 (3.1)	1 (0.5)
	n/100 years	9.9	7.9	11.5	11.2	2.2

ICS=inhaled corticosteroids, TDD = total daily dose

[1]   All doses include 12 mcg TDD (included in DPPD2 and MTA03 only) and 24-48 mcg TDD (included in D2307 only)

[2]   Includes Aerolizer 12 mcg b.i.d. and Certihaler 10 mcg b.i.d.

[3]   Twice the maximum US labeled dose; only included in Aerolizer trials

prn albuterol allowed for rescue in all treatment groups

* dosed regularly q.i.d.

The two components of the definition of significant asthma exacerbations were also considered separately.

Patients reporting **asthma-related SAEs** whether or not discontinuing from the trial prematurely, are presented in Table 3-5. The number of asthma-related serious adverse events (SAEs) per 100 patient treatment years was higher for the formoterol than for the placebo group (3.9 compared to 0.9 events/100 treatment years). The difference was more marked with the higher formoterol dose level (5.6 events/100 treatment years) than at the lower one (3.5 events/100 treatment years). Also, this difference was more marked in the sub-group of patients not using concomitant ICS than those being treated according to current guidelines, with ICS. The rate for albuterol was similar to that for formoterol (3.1 events/100 treatment years). Similar results were seen for all multiple dose controlled trials.

Table 3-5   Patients experiencing asthma-related SAEs in multiple-dose placebo-controlled trials of at least 4 weeks duration

Subsets of trials included (all multiple-dose placebo-controlled)		Formoterol			Placebo	Albuterol*
		All doses [1]	20/24 mcg TDD[2]	48 mcg TDD[3]		
All patients	N	3768	1948	1156	1863	630
	n (%)	43 (1.1)	18 (0.9)	22 (1.9)	5 (0.3)	4 (0.6)
	n/100 years	3.9	3.5	5.6	0.9	3.1
Patients using ICS	N	2488	1389	685	1319	427
	n (%)	26 (1.0)	13 (0.9)	12 (1.8)	4 (0.3)	4 (0.9)
	n/100 years	3.3	3.0	4.8	1.0	4.3
Patients not using ICS	N	1280	559	471	544	203
	n (%)	17 (1.3)	5 (0.9)	10 (2.1)	1 (0.2)	0
	n/100 years	5.2	4.8	6.8	0.6	0

ICS=inhaled corticosteroids, TDD = total daily dose

[1]   All doses include 12 mcg TDD (included in DPPD2 and MTA03 only) and 24-48 mcg TDD (included in D2307 only)

[2]   Includes Aerolizer 12 mcg b.i.d. and Certihaler 10 mcg b.i.d.

[3]   Twice the maximum US labeled dose; only included in Aerolizer trials

prn albuterol allowed for rescue in all treatment groups

* dosed regularly q.i.d.

Patients discontinuing the trial prematurely due to asthma-related AE presented in Table 3-6 below, showed the opposite trend. More patients receiving placebo discontinued prematurely due to asthma-related events than patients receiving formoterol (10.7 vs. 7.1 discontinuations/100 treatment years). The difference was more marked for the patients on the lower formoterol level, who represent the majority of formoterol patients in the database (10.7 vs. 5.6 discontinuations/100 treatment years). In this case there was no apparent difference between the sub-groups of patients according to concomitant ICS use. The corresponding rate for albuterol was 8.1 discontinuations/100 treatment years. Similar results were seen for all multiple dose controlled trials.

Table 3-6   **Patients discontinuing the study prematurely because of an asthma-related AE in multiple-dose placebo-controlled trials of at least 4 weeks duration**

Subsets of trials included (all multiple-dose placebo-controlled)		Formoterol			Placebo	Albuterol*
		All doses [1]	20/24 mcg TDD[2]	48 mcg TDD[3]		
All patients	N	3768	1948	1156	1863	630
	n (%)	80 (2.1)	33 (1.7)	33 (2.9)	59 (3.2)	13 (2.1)
	n/100 years	7.1	5.6	8.8	10.7	8.1
Patients using ICS	N	2488	1389	685	1319	427
	n (%)	55 (2.2)	25 (1.8)	21 (3.1)	42 (3.2)	12 (2.8)
	n/100 years	7.1	5.8	8.9	10.6	10.4
Patients not using ICS	N	1280	559	471	544	203
	n (%)	25 (2.0)	8 (1.4)	12 (2.5)	17 (3.1)	1 (0.5)
	n/100 years	7.0	4.8	8.8	11.2	2.2

ICS=inhaled corticosteroids, TDD = total daily dose

[1]   All doses include 12 mcg TDD (included in DPPD2 and MTA03 only) and 24-48 mcg TDD (included in D2307 only)

[2]   Includes Aerolizer 12 mcg b.i.d. and Certihaler 10 mcg b.i.d.

[3]   Twice the maximum US labeled dose; only included in Aerolizer trials

prn albuterol allowed for rescue in all treatment groups

* dosed regularly q.i.d.

At times, patients leaving a study because of an exacerbation attribute their condition to a failure of the study treatment. Therefore, the cause of discontinuation for an asthma-related event may also be captured in the Case Record Form as "unsatisfactory therapeutic effect". Discontinuations for unsatisfactory therapeutic effect are presented in Table 3-7 below. The table confirms the pattern shown above, with placebo patients about twice as likely to discontinue than formoterol patients (2.3% vs. 0.9% discontinuations). Once again, albuterol was similar to formoterol (1.0% discontinuation).

Table 3-7   Patients discontinuing the study prematurely because of unsatisfactory therapeutic effect in multiple-dose placebo-controlled trials of at least 4 weeks duration

Subsets of trials included (all multiple-dose placebo-controlled)	Formoterol			Placebo	Albuterol
	All doses [1] N=3768	20/24 mcg TDD N=1948	48 mcg TDD[2] N=1156	N=1863	N=630
Number (%)	35 (0.9)	23 (1.2)	10 (0.9)	43 (2.3)	6 (1.0)

TDD = total daily dose
[1]   All doses include 12 mcg TDD (included in DPPD2 and MTA03 only) and 24-48 mcg TDD (included in D2307 only)
[2]   Only included in Aerolizer trials

Investigation of **the time to significant asthma exacerbation** is presented in Table 3-8 for those patients who experienced such an event. Formoterol demonstrated consistently longer time to an event than placebo, although, as a small number of events were reported in the placebo group. Data for formoterol and placebo from multiple-dose placebo-controlled trials is shown because of their comparable planned treatment duration.

Table 3-8   **Time to first event of significant asthma exacerbation (asthma-related SAE or premature discontinuation because of an asthma-related AE) in multiple-dose placebo-controlled trials* of at least 4 weeks duration**

Subsets of trials included (all multiple-dose placebo-controlled)	Time (days) to first asthma-related SAE		Time (days) to premature discontinuation due to an asthma-related AE		Time (days) to first asthma-related SAE OR premature discontinuation due to an asthma-related AE	
	Formoterol All doses[1]	Placebo[2]	Formoterol All doses[1]	Placebo	Formoterol All doses[1]	Placebo
n/N	43/3751	5/1845	80/3751	59/1845	95/3751	60/1845
Median	62	55	42	30	48	32
25th – 75th centile	30 - 110	55 - 69	21 - 80	7 - 60	22 - 83	7 - 64

*   excluding cross-over trials
[1]   All doses include 12 mcg TDD (included in DPPD2 and MTA03 only) and 24-48 mcg TDD (included in D2307 only)
[2]   Small number of events in placebo group: therefore care needed in the interpretation

The protocols of the majority of trials in this group allowed for **courses of oral corticosteroids or theophylline** to treat exacerbations while the patient remained in the study. Usually two such courses were allowed before a patient had to be discontinued from the trial. Table 3-9 presents the number and percentage of patients who received at least one course of treatment of this kind for an exacerbation, showing a trend toward more placebo patients resorting to courses of oral steroids/theophylline compared to formoterol patients (12.3% vs. 9.3%).

Table 3-9   Number (%) of patients who received oral steroids or theophylline for exacerbation of asthma in multiple-dose placebo-controlled trials* of at least 4 weeks duration

Subsets of trials included (all multiple-dose placebo-controlled parallel group only)	Formoterol All doses[1] N=3,751	Placebo N=1,845
Number (%) of patients	349 (9.3)	227 (12.3)

*   excluding cross-over trials
[1]   All doses include 12 mcg TDD (included in DPPD2 and MTA03 only) and 24-48 mcg TDD (included in D2307 only)

3.2.3.2   Discussion

Asthma-related events defined as serious by the investigators and asthma-related events which are bad enough to induce the patient to leave the study prematurely are manifestations of significant asthma exacerbations.

For significant asthma exacerbations, no safety signal emerges from the integrated formoterol clinical trial safety database, which showed very similar rates for formoterol, albuterol and placebo.

While asthma-related SAEs occur more frequently in the formoterol group (and the albuterol group), asthma-related premature discontinuations occur more frequently in the placebo group. Patients who suspect that they are receiving placebo may discontinue earlier. Furthermore placebo patients appear to have a shorter time to first significant exacerbation and a greater use of courses of rescue oral steroids and/or theophylline than formoterol patients.

Although asthma exacerbations may be sudden events reaching their peak within minutes, in most cases, exacerbations "build-up" over many hours or days. In this context, a patient receiving placebo is more likely to decide to discontinue from the study as soon as the worsening of symptoms starts to occur (i.e. before the event becomes serious).

A different behavioral pattern for placebo patients experiencing an increase in symptoms might be to continue in the trial by using protocol-permitted rescue treatments, such as oral corticosteroids or theophylline more so than patients on active study medication. This will also reduce the possibility of asthma-related SAEs in the placebo group. Indeed in the clinical

trial database more placebo- than formoterol-treated patients resorted to courses of oral steroids and/or theophylline during the study.

In conclusion, the divergent trend for asthma-related SAEs and discontinuations due to asthma-related AEs probably occurs because placebo patients leave the study earlier and without waiting for the event to reach its peak or, if staying in the study, resort more commonly to rescue courses of oral steroids/theophylline, compared to patients on formoterol or albuterol.

Therefore, when these data are considered together, it is unlikely that the increased rates of asthma related SAEs in the formoterol and albuterol groups reflects a safety signal and more likely that it is an artifact of patients remaining in the studies longer in the active treatment arms of the trial.

3.3   Integrated database of Novartis clinical trials: COPD-related events

3.3.1   The integrated database

Three multiple-dose controlled trials with at least a four week treatment duration are included in the integrated data. All three trials were placebo-controlled and utilized the Aerolizer formulation. A total of 908 patients were treated with formoterol (502 received 24 mcg total daily dose and 406 received 48 mcg total daily dose) and 527 patients were treated with placebo. Exposure in patient treatment-years was as follows: 460 for formoterol (with 234 for the lower dose and 226 on the higher dose) and 237 for placebo. Active comparators were theophylline (N=209) and ipratropium bromide (N=194). No trial included albuterol as active comparator. The assessment is limited to a comparison between formoterol and placebo.

3.3.2   COPD-related deaths and all deaths in COPD trials

3.3.2.1   Results

Table 3-10 presents the deaths reported during the study for all COPD studies, irrespective of planned duration of exposure, all conducted with the Aerolizer formulation. All deaths are included, whether or not they were considered by the investigator to be related to study drug.

No COPD-related death occurred in patients receiving formoterol or placebo.

Table 3-10   Patients who died in all COPD trials – Aerolizer

Subsets of trials included		Formoterol All doses	Placebo
Controlled [1]	**N** **Total exposure**	**1071** **470**	**527** **237**
all deaths	N n (%) n/100 years	4 (0.37) 0.85	0
COPD-related deaths	N n (%) n/100 years	0	0
cardiovascular related deaths	N n (%) n/100 years	2 (0.19) 0.43	0

TDD = total daily dose

[1]   Controlled trials where at least one patient died were all placebo controlled; no uncontrolled COPD trials

The two patients who died from non-COPD related, non-cardiovascular events in the controlled trials were as a result of suicide and brain edema.

3.3.2.2   Discussion

COPD patients are often elderly and typically have a long history of cigarette smoking, both risk factors for cardiovascular and respiratory deaths. The COPD clinical trial database is small, so no definitive conclusion can be drawn on rare events such as deaths. However, the fact that no COPD-related or any other respiratory-related death occurred is reassuring. No safety signal is raised from these data.

3.3.3 Significant COPD exacerbations: COPD-related SAEs and discontinuations due to COPD- related AEs

3.3.3.1 Results

Multiple-dose controlled trials with at least a four week treatment duration were assessed in terms of COPD-related SAEs and discontinuations due to COPD-related AEs. Events were selected using a list of pre-defined terms (see Appendix 1). All events were included, whether or not they were considered by the investigator to be related to study drug.

As with asthma exacerbations, a significant exacerbation of COPD was considered to be a COPD-related SAE or a COPD-related adverse event leading to premature discontinuation from the trial. Patients who discontinued because of an SAE were only counted once in the summary presented in Table 3-.11.

The number of significant COPD exacerbations per 100 treatment years was 7.0 for formoterol, less than half of the rate for placebo at 15.6. There is no apparent dose-response relationship for formoterol.

Table 3-11 **Patients with significant COPD exacerbations (COPD-related SAEs or premature discontinuations because of a COPD-related AE) in multiple dose controlled trials of at least 4 weeks duration**

Subsets of trials included (all multiple dose)		Formoterol			Placebo
		All doses	24 mcg TDD	48 mcg TDD	
Controlled – all patients	N	908	502	406	527
	n (%)	29 (3.2)	15 (3.0)	14 (3.4)	30 (5.7)
	n/100 years	7.0	6.8	7.1	15.6

TDD = total daily dose

The two components of the definition of a significant COPD exacerbation were considered individually.

As shown in Table 3-12, the number of COPD-related serious adverse events per 100 patient treatment years was considerably lower for formoterol than for placebo (4.3 vs. 10.5 respectively).

Table 3-12   Patients reporting COPD-related SAEs in multiple-dose controlled trials of at least 4 weeks duration

Subsets of trials included (all multiple dose)		Formoterol			Placebo
		All doses	24 mcg TDD	48 mcg TDD	
Aerolizer only					
Controlled – all patients	N	908	502	406	527
	n (%)	18 (2.0)	12 (2.4)	6 (1.5)	20 (3.8)
	n/100 years	4.3	5.6	3.1	10.5

TDD = total daily dose

The number of premature discontinuations due to a COPD-related adverse event, showed a very similar trend, with an event rate in the formoterol group less than half that in the placebo group (4.1 versus 8.9 discontinuations /100 treatment years). Table 3-13 below summarizes these results.

Table 3-13   Patients discontinuing the study prematurely because of a COPD-related adverse event in multiple-dose controlled trials of at least 4 weeks duration.

Subsets of trials included (all multiple dose)		Formoterol			Placebo
		All doses	24 mcg TDD	48 mcg TDD	
Controlled – all patients	N	908	502	406	527
	n (%)	17 (1.9)	6 (1.2)	11 (2.7)	17 (3.2)
	n/100 years	4.1	3.0	5.3	8.9

TDD = total daily dose

Premature discontinuations due to unsatisfactory therapeutic response are presented in Table 3-14. Similar percentages of patients were seen across all treatments with a slightly higher percentage in the placebo group.

Table 3-14   **Patients discontinuing the study prematurely because of unsatisfactory therapeutic effect in multiple dose controlled trials of at least 4 weeks duration**

Subsets of trials included (all multiple dose)		Formoterol			Placebo
		All doses N=908	24 mcg TDD N=502	48 mcg TDD N=406	N=527
Controlled – all patients	n (%)	10 (1.1)	6 (1.2)	4 (1.0)	10 (1.9)

TDD = total daily dose

3.3.3.2   Discussion

COPD-related events labeled as serious by the investigators and COPD-related events which are bad enough to induce the patient to leave the study prematurely are manifestations of significant COPD exacerbations.

As for asthma, no safety signal emerges from the integrated COPD clinical trial database. In fact, there were less than half the significant COPD exacerbations in patients receiving formoterol compared to patients receiving placebo.

This pattern was observed for both types of events contributing to significant COPD exacerbations. Thus the divergent pattern observed in asthma trials was not replicated in COPD trials. A possible explanation is that COPD patients are typically less active than asthma patients. Therefore a pro-active management of their treatment, which may lead to the decision to leave the trial early and/or induce prompt intake of courses of rescue medication, is less likely in COPD patients. Furthermore, the impact of worsening of symptoms may not be perceived by the house- or chair-bound COPD patient to induce them to seek medical attention until the exacerbation is more advanced.

3.4   Integrated database of Novartis clinical trials: cardiovascular events

3.4.1   The integrated database

Cardiovascular serious adverse events (including cerebrovascular accidents) were evaluated in multiple-dose controlled studies of at least four weeks treatment duration utilizing the Aerolizer and Certihaler formulations of formoterol. Events were selected using a list of pre-defined terms (Appendix 1). All events are included, whether or not they were considered by the investigator to be related to study drug. Please see Table 3-2 and Section 3.3.1 for a description of the number of patients in controlled studies for asthma and for COPD,

respectively. Cardiovascular deaths were evaluated from all trials constituting all asthma and COPD trials.

3.4.2   Cardiovascular deaths

Cardiovascular deaths occurring in asthma trials are reported in Table 3-3. In the controlled trial database there were no deaths in the formoterol groups and there was one death in the placebo groups. In the uncontrolled trials, where all patients received formoterol, 6 (0.22%) deaths associated with cardiovascular events occurred. Elderly patients made up a substantial proportion of the uncontrolled trial dataset and 4 of the 6 deaths occurred in patients over 65 years of age.

Cardiovascular deaths occurring in COPD trials are reported in Table 3-10. Two (0.19%) deaths occurred in the formoterol group in this database.

3.4.3   Cardiovascular SAEs

3.4.3.1   Results

In asthma trials, the number of **serious cardiovascular adverse events** per 100 patient treatment years was low and similar for formoterol and placebo (0.4 and 0.5 events/100 treatment years respectively), and slightly higher for albuterol (1.7 events/100 treatment years respectively).

There was a somewhat higher rate of SAEs for COPD patients than for asthma patients, which is to be expected for this comparatively older patient population with more significant concomitant illnesses. The higher formoterol dose had the lowest event rate (0.9 events/100 treatment years). The lower formoterol dose and the placebo dose had very similar rates (3.0 and 3.4 events/100 treatment years, respectively).

Table 3-15   Patients reporting cardiovascular SAEs in multiple-dose controlled trials of at least 4 weeks duration

Subsets of trials included (all multiple dose controlled)		Formoterol			Placebo	Albuterol
		All doses [1]	20/24 mcg TDD	48 mcg TDD[2]		
ASTHMA TRIALS – Aerolizer plus Certihaler combined						
All patients	N	5048	2957	1353	1863	990
	n (%)	5 (0.1)	4 (0.1)	1 (0.1)	3 (0.2)	4 (0.4)
	n/100 years	0.4	0.4	0.5	0.5	1.7
COPD TRIALS – Aerolizer only						
All patients	N	908	502	406	527	NA
	n (%)	9 (1.0)	7 (1.4)	2 (0.5)	6 (1.1)	
	n/100 years	2.0	3.0	0.9	3.4	

TDD = total daily dose   NA =   not applicable

[1]   All doses include 12 mcg TDD (included in DPPD2 and MTA03 only) and 24-48 mcg TDD (included in D2307 only)

[2]   Only included in Aerolizer trials

All COPD controlled trials included placebo

3.4.4   Discussion

Serious cardiovascular events occurred at a similar rate in the formoterol and placebo groups in both asthma and COPD. No safety signal emerges.

3.5   Individual safety studies requested by FDA as phase IV commitments

As part of the approval of Foradil Aerolizer 12 mcg in asthma and COPD, FDA requested two additional studies in the approved populations focusing on safety issues. The first study (Study D2307) was to be conducted in asthmatic patients at the approved dose and at a higher doses, to assess the incidence of asthma-related SAEs. The second study (Study D2308) was to be conducted in COPD patients to evaluate cardiovascular safety via 24-hour continuous ECG monitoring (Holter) at the approved dose. These trials have been completed and design and results are summarized in this section. Both studies are included in the integrated datasets presented in sections 3.2 to 3.4. above.

3.5.1   Study D2307: evaluation of asthma-related events in patients with asthma

3.5.1.1   Results

Study D2307 was a randomized, multicenter, placebo-controlled, parallel group Phase IV commitment study conducted in 2,085 adolescent and adult patients with persistent stable

asthma. There were three double-blind treatment groups: formoterol Aerolizer 12 mcg b.i.d. (24 mcg TDD), formoterol Aerolizer 24 mcg b.i.d. (48 mcg TDD), and placebo b.i.d.; and one open-label treatment group receiving formoterol Aerolizer 12 mcg b.i.d. with up to two additional doses per day of formoterol Aerolizer 12 mcg as needed for worsening of symptoms (24-48 mcg TDD). The duration of treatment was 16 weeks.

The focus of this study was on asthma-related event and the primary end-point was the percentage of patients with serious asthma-related adverse events (SAEs). An important secondary end-point was asthma-related adverse events requiring courses of oral steroids. Asthma-related adverse events were predefined as those events with the following preferred terms: chest discomfort, asthma, cough, wheezing, dyspnea, dyspnea exacerbated, status asthmaticus, respiratory distress, bronchospasm, acute respiratory failure, and hypoxia.

The following table summarizes the number and percent of patients with asthma-related events by treatment. All events are included, whether or not they were considered by the investigator to be related to the use of study drug. Also reported in the table are a breakdown of patients into those who were and were not on regular anti-inflammatory medication during the study, and the number and percent of patients who started regular anti-inflammatory medication during the trial.

Table 3-16   Number (%) of patients with asthma-related events in study D2307

	Formoterol 12 mcg b.i.d. N=527	Formoterol 24 mcg b.i.d. N=527	Formoterol 12 mcg b.i.d. + formoterol prn N=517	Placebo N=514
Patients with asthma-related SAEs	5 (0.9)	2 (0.4)	1 (0.2)	1 (0.2)
Patients taking regular concomitant anti-inflammatory therapy	331 (62.8)	345 (65.5)	331 (64.0)	340 (66.1)
with asthma-related SAEs	3 (0.9)	0	1 (0.3)	1 (0.3)
Patients not taking regular concomitant anti-inflammatory therapy	196 (37.2)	182 (34.5)	186 (36.0)	174 (33.9)
with asthma-related SAEs	2 (1.0)	2 (1.1)	0	0
Patients who started regular anti-inflammatory treatment after randomization	9 (1.7)	7 (1.3)	13 (2.5)	16 (3.1)
Exacerbations requiring oral or parenteral corticosteroids	31 (5.9)	33 (6.3)	23 (4.4)	45 (8.8)
Exacerbations requiring oral or parenteral corticosteroids in patients taking anti-inflammatory medication	22/331 (6.9)	23/345 (6.7)	16/331 (4.8)	36/340 (10.6)
Patients with asthma-related AEs (serious or non-serious) leading to premature discontinuation	7 (1.3)	12 (2.3)	7 (1.4)	12 (2.3)

prn = on demand use: up to two 12 mcg doses of formoterol were allowed in this group on top of the regular b.i.d. 12 mcg regimen.

Serious asthma-related adverse events (the primary end-point) were reported by a total of 9 patients in the study, with 5 cases (0.9%) in the formoterol 12 mcg b.i.d. group, 2 cases (0.4%) in the formoterol 24 mcg b.i.d. group, 1 case (0.2%) in the in the formoterol 12 mcg b.i.d. + prn group and 1 case (0.2%) in the placebo group. There was no significant difference between groups (Fisher's exact test). The circumstances in which 3 of the 9 asthma-related SAEs occurred are worth mentioning, as they reduce the likelihood of a causal association with study drug. All three were in the formoterol 12 mcg b.i.d. group: the first case occurred in a patient who had discontinued the study drug for 5 days before the onset of the exacerbation (because of the events following a motor vehicle accident), the second in a

patient for whom the investigator stated that the respiratory distress was related to a myocardial infarction, not asthma; the third case was attributed by the investigator to gastro-esophageal reflux.

Premature discontinuations due to asthma-related AEs (serious or non-serious) occurred in a small and similar percentage in all treatment groups.

A pattern showing a greater frequency in the placebo group was observed for secondary end-points related to clinically meaningful exacerbations, namely

- patients who required courses of oral corticosteroids; this difference was more pronounced in the patients who also were on regular anti-inflammatory medication.

- patients who required the start of regular anti-inflammatory medication during the study.

3.5.1.2 Discussion

The primary end-point of this study, asthma-related SAEs occurred rarely, in less than 1% of patients in each treatment group (9 events in total). Of interest is the distribution of the 9 asthma-related SAEs among the treatment groups. The highest number of such events (5, 0.9%) occurred in the low dose formoterol group (12 mcg b.i.d.); the intermediate (flexible) formoterol dose group (12 mcg b.i.d. + up to two additional 12 mcg doses per day) had the lowest number of events (1, 0.2%), the same as in the placebo group; the highest formoterol dose group (24 mcg b.i.d.) had a number of SAEs (2, 0.4%) that was in between the two other dose groups.

This distribution, combined with the low number of events, points in the direction of a random effect. This conclusion is strengthened by the circumstances of three of the five cases in the low formoterol dose group and by the trend toward a higher frequency in the placebo group for patients who started regular inhaled steroids and/or required courses of oral steroids during the study. On the other hand, it should be noted that the group receiving intermediate dose formoterol (12 mcg b.i.d. + up to 2 extra doses prn) was not blinded.

3.5.2 Study D2308: Holter monitoring in COPD patients

3.5.2.1 Results

Study D2308 was a randomized, double-blind, multicenter, placebo-controlled, parallel group Phase IV commitment study conducted in 204 adult patients with COPD (chronic obstructive pulmonary disease). Patients were randomized to receive 8 weeks treatment with either formoterol Aerolizer 12 mcg b.i.d. or placebo.

The primary objective of the study was to compare the safety of regular twice-daily use of 12 mcg formoterol dry powder inhalation capsules delivered by the Aerolizer Inhaler with placebo, as evaluated by 24-hour Holter monitoring. Holter monitoring was performed at screening to provide a baseline, after 14 days of treatment (Visit 3) and then again after 8 weeks of treatment (Visit 4). Holter monitoring data by treatment were evaluated for proarrhythmic events, ventricular findings (premature beats and run events), and supraventricular findings (premature beats and run events).

Proarrhythmic events were identified according to predefined criteria established by an independent consultant on ECG interpretation. These criteria define proarrhythmia based on the change from the baseline visit in the number of ventricular premature beats per hour (VPB/hr) and/or the frequency of ventricular tachycardia (VT) events (non-sustained or sustained) as described in Table 3-17, any post-baseline run of ventricular ectopic beats associated with symptoms (e.g. hypotension or syncope), regardless of the rate, and any post-baseline episode of ventricular flutter and/or ventricular fibrillation.

Table 3-17   VPB and VT criteria for proarrhythmia events

	Baseline	Criteria Post-baseline
Mean VPB/hr	0 - 1	≥10 Mean VPB/hour
	1 - 100	increase of ≥ 10 times baseline
	Over 100	increase of ≥ 3 times baseline
Non-sustained VT events*	0	≥ 5 events or > 15 beats in events/24 hrs
	≥1	increase of ≥ 10 times baseline events or beats
Sustained VT events*	0	≥1

* Ventricular tachycardia (VT) is defined as a run of 3 or more ventricular premature beats (VPB's) with a rate ≥100 beats per minute. Sustained VT is defined as VT lasting ≥ 30 seconds or ≥ 60 beats. Non-sustained VT is a run of 3 or more VPB's with a rate ≥ 100 beats per minute which does not fulfill the criteria for sustained VT.

The following table provides information on patients in each treatment group meeting the predefined criteria for proarrhythmia.

Table 3-18   Patients with proarrhythmic events

	Mean VPB/hr			Non-sustained VT events (total number of beats)		
Patient	**Baseline**	**Visit 3**	**Visit 4**	**Baseline**	**Visit 3**	**Visit 4**
Formoterol						
1	39.40	73.08	1158.25*	0	3	40*
2	239.79	219.94	246.93	0	41*	18*
3	0.21	250.58*	173.93*	0	0	0
4	0	0	26.19*	0	0	0
Placebo						
1	1.34	26.00*	–	0	0	0
2	5.39	36.74	80.74*	6	0	0
3†	147.71	123.07	1170.13*	0	0	11

* relevant increase which meets the criteria for proarrhythmia
† Visit 4 data for this patient was based on an invalid Holter recording as it took place one day after the dose of study medication

Four formoterol patients and three placebo patients met the criteria based on changes in mean VPB per hour and/or nonsustained ventricular tachycardia. No patient in either group had sustained post-baseline ventricular tachycardia episodes or met the other criteria for a proarrhythmic event such as a run of ventricular premature beats associated with relevant symptoms (e.g. hypotension or syncope), or an episode of ventricular flutter or ventricular fibrillation.

Data for patients with ventricular premature beats (VPBs) are summarized in Table 3-19. There was a wide variation in values between patients within each treatment group, due to the skewed nature of the data, particularly for the placebo group where a few patients with very high values at Visit 1 influenced the mean values for the total number and mean and maximum rates of VPBs. Despite the high variability, the median and 25% and 75% quartile values do not indicate consistent or meaningful differences between treatment groups.

Table 3-19   Holter variables: Ventricular premature beats (ITT population)

Variable	Formoterol 12 mcg b.i.d. N=97				Placebo N=107			
Statistic	V1	V3	V4	Last	V1	V3	V4	Last
Total VPBs								
n	96	89	80	92	107	103	90	106
Mean	543	490	785	732	1040	904	539	650
SD	1253.0	1271.5	2864.8	2685.4	4112.4	4250.9	2017.2	2090.6
25% quartile	3	1	1	1	3	3	3	4
Median	11	8	10	9	61	34	46	40
75% quartile	287	198	150	213	300	291	204	228
Mean VPBs / hour								
n	96	89	80	92	107	103	90	106
Mean	25	23	37	35	46	40	25	30
SD	57.0	57.5	139.8	131.0	181.9	185.5	100.2	101.3
25% quartile	0	0	0	0	0	0	0	0
Median	0	0	0	0	3	2	2	2
75% quartile	14	8	8	10	13	15	9	10
Maximum VPBs / hour								
n	96	89	80	92	107	103	90	106
Mean	61	64	78	76	121	89	75	88
SD	126.7	147.9	210.4	199.7	484.0	319.4	246.7	256.5
25% quartile	1	1	1	1	2	2	2	2
Median	5	3	4	3	10	6	9	8
75% quartile	61	26	30	35	41	39	28	30

Only valid Holter data were included in the summary.
VPBs = Ventricular premature beats

A maximum of 12% of patients in either treatment group experienced a ventricular tachycardia episode (a run of 3 or more VPBs with a rate $\geq$ 100 bpm) at any visit and a maximum of 5% of patients in either treatment group experienced a idioventricular run episode (run of 3 or more VPBs with a rate < 100 bpm) at any visit. As a result, the rate of VTEs and IVEs was very low in both treatment groups as shown in the following table.

Table 3-20   Holter variables: Ventricular run events (ITT population)

Variable	Formoterol 12 mcg b.i.d. N=97				Placebo N=107			
Statistic	**V1**	**V3**	**V4**	**Last**	**V1**	**V3**	**V4**	**Last**
Total VTEs								
n	96	89	80	92	107	103	90	106
Mean	0.2	0.3	0.4	0.4	1.2	2.2	1.2	1.0
SD	1.09	1.37	1.81	1.70	8.28	20.64	10.01	9.23
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Mean VTEs / hour								
n	96	89	80	92	107	103	90	106
Mean	0.01	0.01	0.02	0.02	0.05	0.10	0.06	0.05
SD	0.048	0.065	0.088	0.082	0.354	0.885	0.520	0.479
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Maximum VTEs / hour								
n	96	89	80	92	107	103	90	106
Mean	0.1	0.1	0.2	0.2	0.7	0.7	0.3	0.3
SD	0.35	0.53	0.62	0.58	4.64	6.21	1.92	1.77
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total IVEs								
n	96	89	80	92	107	103	90	106
Mean	0.0	0.0	0.1	0.0	0.1	0.1	0.1	0.1
SD	0.23	0.18	0.22	0.21	0.69	0.89	0.35	0.33
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Mean IVEs / hour								
n	96	89	80	92	107	103	90	106
Mean	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00
SD	0.010	0.008	0.010	0.010	0.029	0.038	0.017	0.017
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Only valid Holter data were included in the summary.
VTE = Ventricular tachycardia episode (run of 3 or more VPBs with a rate ≥ 100 bpm)
IVE = Idioventricular run episode (run of 3 or more VPBs with a rate < 100 bpm)

Holter data for supraventricular premature beats (SVBPs) and supraventricular run events (a run of 3 or more SVBPs) did not show meaningful differences between treatment groups.

3.5.2.2   Discussion

The number of patients who met the pre-defined criteria for proarrhythmia was small and similar for both treatments (4 of 97 formoterol and 3 of 107 placebo patients). There were no clinically meaningful differences between groups for ventricular and supraventricular premature beats and run events. No safety signal was seen in this study.

3.6   Conclusions

No safety signal emerges from the analysis of the integrated safety database of Foradil asthma and COPD clinical trials.

4   Review of safety data from spontaneous reports and post-marketing surveillance data on marketed Foradil

4.1   Introduction

Salmeterol and formoterol are both long-acting beta$_2$-agonists. They both provide bronchodilating and bronchoprotective effects in patients with asthma and in patients with at least moderate, stable, symptomatic COPD [van der Woude 2002].

Albuterol is a short-acting beta$_2$-agonist. Short acting beta agonists, which produce rapid relief from bronchoconstriction, have been used routinely in asthma treatment since the 1960s.

The objectives of this review were:

- To evaluate the adverse event (AE) reports resulting in death recorded in the FDA Adverse Events Reporting System (AERS) database and reported among formoterol, salmeterol and albuterol users.

- To evaluate the reports containing respiratory AEs recorded in the FDA Adverse Events Reporting System (AERS) database and reported among formoterol, salmeterol and albuterol users.

- To summarize the literature on asthma related death rates and on Chronic Obstructive Pulmonary Disease (COPD) therapeutics.

4.2   Methods

In recent years, the Food and Drug administration (FDA) has received over 250,000 reports of adverse events annually. The total number in the database exceeds 2.5 million, which encompasses all drug products marketed in the US with an approved NDA/ANDA.

An analysis of the FDA Spontaneous Reporting System and Adverse Event Reporting System (SRS/AERS) combined data up to the 4th quarter, 2004, was performed to describe the reporting of death and specific respiratory symptoms among formoterol, salmeterol and albuterol users.

We selected each of the following single drugs from the database: formoterol, salmeterol, albuterol.

Cases were defined by using preferred terms from MedDRA (version 7.1) and one report outcome, as follows:

Death case: Accidental death, Agonal death struggle, Brain death, Cardiac death, Death, Death neonatal, Intra-uterine death, Maternal death affecting foetus, Near sudden infant death syndrome, Sudden cardiac death, Sudden death, Sudden infant death syndrome, completed suicide or

and/or

the outcome of the report was death.

Respiratory symptoms are defined using preferred terms from MedDRA outlined in Appendix 2.

To evaluate the reporting of deaths and respiratory symptoms to the FDA among users of the drugs of interest, the following summary measures were computed:

- Reporting proportion is defined as the proportion of all reports in the FDA AERS database containing the drug of interest that also meet the case definition (number of reports with the case definition and drug X / Total number of adverse events reports and drug X). All reports up to 12/31/2004 were included in this analysis.

- Reporting rate, defined as the yearly number of cases as defined above per 100,000 users estimated from the kilograms of substance sold according to the IMS database MIDAS Quarterly /59 Countries, and the ATC/DDD system defined daily doses (DDD) for the drugs. Reporting rates were computed for the period up to 12/31/2004.

The search for cases was performed using WebVDME 5.1 by Lincoln Technologies Inc.

The results were stratified by origin of the report (US versus Foreign) and by reporter causality assessment (suspect versus non suspect). Unless otherwise specified, Worldwide refers to all reports, including those from the US.

4.3 Summary of results from AERS review

4.3.1 Death

The reporting proportion for death can be seen in Table 4-1:

Table 4-1   Number and reporting proportion of death AE reports, by drug, all reports

	Number of AE reports with death*	Total n° of AE reports for the drug	Reporting proportion (per 100 AE reports) †
Formoterol	139	1,252	11.1%
Salmeterol	1,182	16,064	7.4%
Albuterol	3,989	47,447	8.4%

*Including those with a preferred term meaning death or with a fatal outcome (see case definition in section 4.3) either suspected or non suspected.

† Number of AE reports with death/Total number of AE reports for the drug

The distribution of the cases by drug and origin of the report is in Table 4-2:

Table 4-2   **Distribution of death AE reports according to origin of the report, by drug, all reports.**

	US reports n (%)	Ex-US reports n (%)	Total
Formoterol	45 (32.4%)	94 (67.6%)	139
Salmeterol	705 (59.6%)	477 (40.4%)	1182
Albuterol	2893 (72.5%)	1096 (27.5%)	3989

The distribution of cases by drug and reporter causality assessment is in Table 4-3:

Table 4-3   **Distribution of death AE reports according to their reporter causality assessment, by drug (suspected versus non suspected)**

	Suspected* n (%)	Non Suspected n (%)	Total
Formoterol	40 (28.8%)	99 (71.2%)	139
Salmeterol	615 (52.0%)	567 (48.1%)	1182
Albuterol	1145 (28.7%)	2844 (72.7%)	3989

*Including suspected, primary suspected and secondary suspected

From Table 4-1 above, the proportion of deaths appears to be higher (11.1%) than for salmeterol (7.4%) or albuterol (8.4%). However, it is well known that reporting rates for adverse events and death decrease with patient exposure as a function of time after commercialization. This phenomenon is called the "Weber" effect [Hartnell 2004]. The overall exposure of patients to formoterol is greater than 10,000,000 person-years, while for salmeterol it is greater than 40,000,000 person-years. In order to correct for the Weber effect, the US and worldwide reporting rates for suspected death reports from the FDA AERS (Adverse Event Reporting System) database for the first 3 years on the market following the US launches for formoterol and salmeterol are compared (Figure 4-1). Both for worldwide as well as for the US data alone, formoterol death rates are substantially lower than salmeterol.

Therefore, the proportions calculated from data accumulated from the time of first commercialization until the end of 2004 in Table 4-1 may be biased against formoterol. Whereas for salmeterol the three years following the US launch (1994) represent less than one third of the time window considered (ending Dec 2004), for formoterol the three years following US launch (2001) represent more than two thirds of the time window considered (ending Dec 2004). Therefore, the proportion in Table 4-1 for salmeterol (7.4%) is diluted compared with that for formoterol (11.1%). It should be noticed the spontaneous event reporting rate in the US is higher than in the rest of the world.

Figure 4-1 **US and worldwide cumulative reporting rates of death for the first 3 years following US launch, suspected cases**
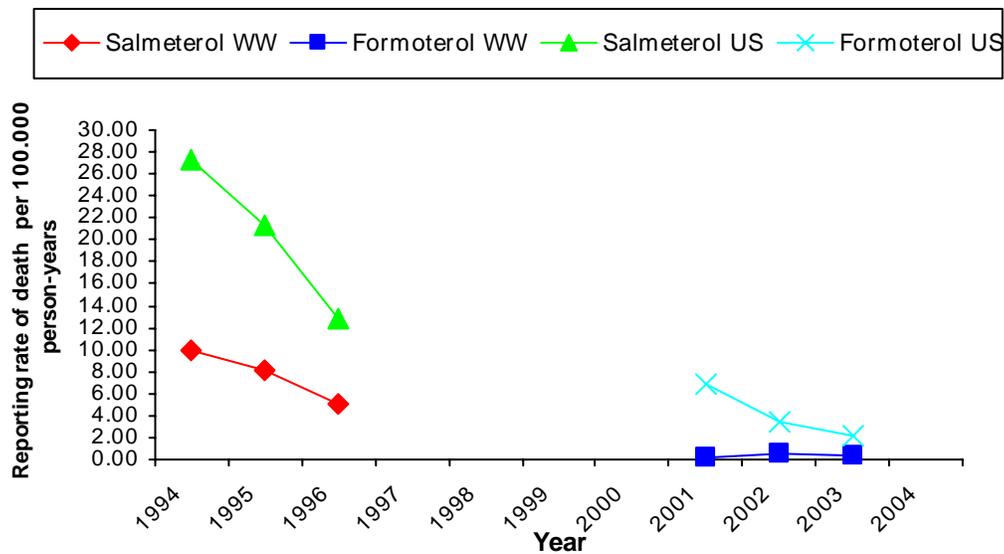
4.3.1.1   Respiratory Symptoms

Asthma and COPD were defined separately as respiratory symptoms using specific AE terms from FDA AERS listed in Appendix 2. Below are tables indicating reporting rates from the AERS database while these drugs were on the US market.

Table 4-4   Number and reporting proportion of asthma and chronic obstructive pulmonary disease (COPD) AE reports, by drug, all reports

	Number of AE reports*		Total nº of AE reports for the drug	Reporting proportion (*100 AE reports) †	
	Asthma	COPD		Asthma	COPD
Formoterol	276	211	1,252	22.0%	16.9%
Salmeterol	3,582	2,518	16,064	22.3%	15.7%
Albuterol	9,395	6,327	47,447	19.8%	13.3%

*Including those with a preferred term meaning asthma, COPD or any of them (see case definition)

† Number of AE reports with respiratory symptoms/Total number of AE reports for the drug

Table 4-4 shows that the respiratory reporting proportions for asthma and COPD are similar among these three drugs.

Table 4-5   Distribution of respiratory symptoms AE reports according their causality assessment for the drug (suspected versus non-suspected)

	Asthma			COPD		
	Suspected*	Non suspected	Total	Suspected*	Non suspected	Total
Formoterol	79 (28.6%)	200 (71.4%)	276	59 (28.0%)	154 (72.0%)	211
Salmeterol	1,784 (49.8%)	1,825 (50.2%)	3,582	1,163 (46.2%)	1,373 (53.8%)	2,518
Albuterol	2,872 (30.6%)	6,849 (69.4%)	9,395	1,577 (24.9%)	4,931 (75.1%)	6,327

*Including primary suspected and secondary suspected

Table 4-5 indicates that the proportion of asthma and COPD AE reports suspected to be associated with drug for formoterol is similar to albuterol and lower than salmeterol.

Figure 4-2   **3-year Asthma-related terms cumulative Reporting Rates per 100,000 person-years. Suspected cases by calendar year**

Figure 4-2 displays the cumulative asthma AE reporting rate per 100,000 person-years for the first 3 years that salmeterol and formoterol were on the US market. Formoterol demonstrates a substantially lower rate of asthma-related AE reports.

Figure 4-3   **3-year COPD related terms cumulative Reporting Rates per 100,000 person-years. Suspected cases by calendar year**
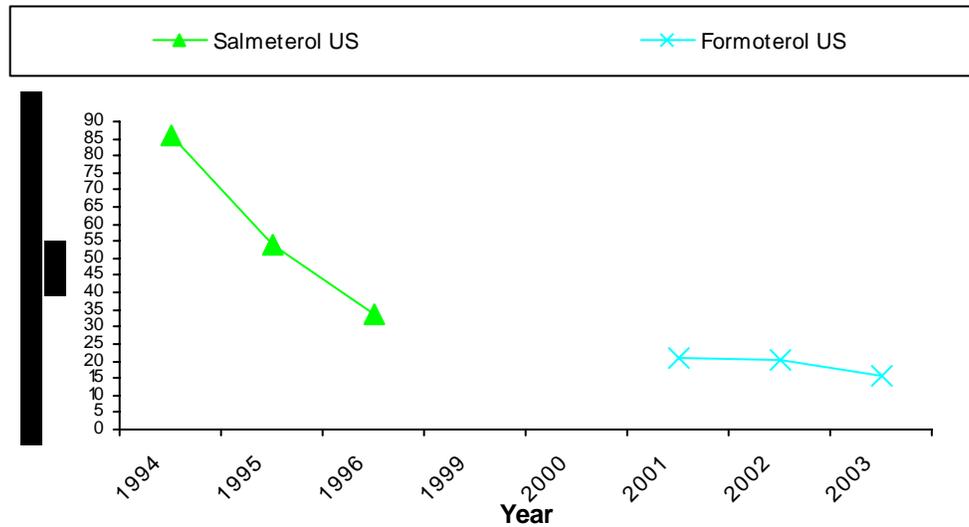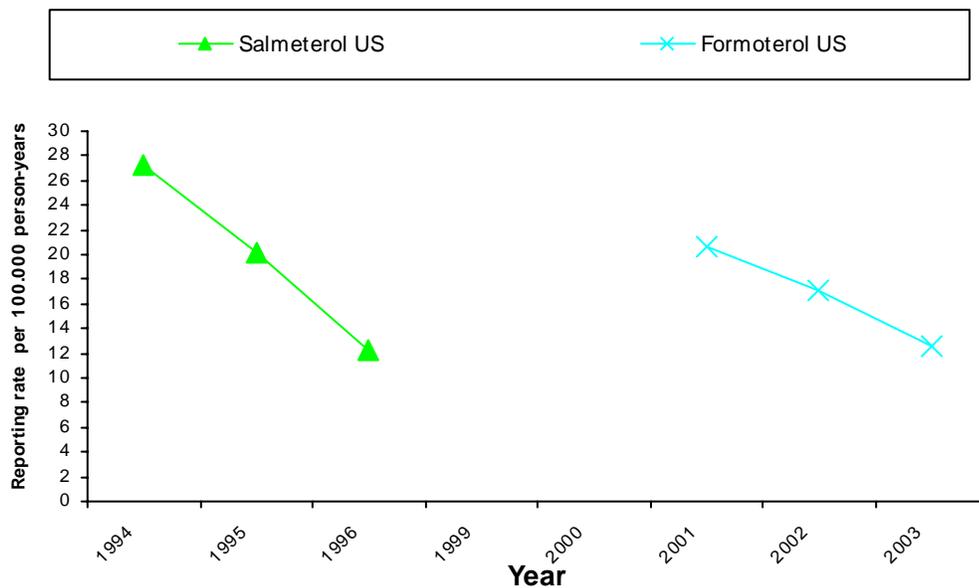

Figure 4-3 displays the cumulative COPD AE reporting rate per 100,000 person-years for the first 3 years that salmeterol and formoterol were on the US market. Formoterol demonstrates a lower rate of COPD-related AE reports over the relevant 3 year time periods.

4.4   Characteristics and limitations

Spontaneous reporting of ADRs remains one of the most important methods for monitoring the safety of drugs. Because of potential limitations, however, analysis of adverse event databases are useful for perceiving trends and hypothesis generation; any finding may be further confirmed in properly conducted epidemiological studies and randomized clinical trials.

The main limitations are:

- The under-reporting of ADRs has been estimated to range between approximately 50% and more than 99% [Strom 2004], depending on the drug and AE in question. For example, reporting may be more frequent with severe events and less frequent the better understood the effects. All analyses therefore must be interpreted in light of this underreporting.

- Other biases that can affect the estimation and interpretation of the reporting proportion are:

    o   The channeling of a drug to lower or higher risk patients may alter the occurrence of adverse events [Leufkens 2000].

    o   Adverse event identification and reporting rates may be higher if there have been warnings about a drug (notoriety bias) or early after marketing authorization [de Graaf 2003].

    o   Length of time on the market and familiarity with the drug have been shown to affect reporting rates (as discussed above, i.e. the Weber effect).

4.5   Intensive Medicines Monitoring Programme

The IMMP was established in New Zealand in 1977 with the object of monitoring adverse events of selected medicines during the early post-marketing period. The regulatory authority (Medsafe) of the New Zealand Ministry of Health decides which medicines should be monitored based on recommendations of the Medicines Assessment Advisory Committee and/or the Medicines Adverse Reactions Committee. Once a medicine has been selected for monitoring every prescription dispensed is recorded and sent to the IMMP where detailed information is registered in a computerized database. Prescription information is provided by all community and hospital pharmacies of New Zealand which are the only outlets permitted to dispense prescription medicines.

Information collected includes National Health Identification number, gender and date of birth of the patient, doctor identification, date of dispensing, medicine name and formulation, dose, and quantity dispensed. Adverse events are reported to the IMMP through regular follow-up questionnaires to prescribers who also have the option of reporting spontaneously. Events are recorded only if they are new events or a pre-existing condition worsens. Only events occurring at the time the patient is taking the medicine or within a plausible period after stopping the medication are recorded. Adverse events are subject to causality assessment by a physician using the guidelines promoted by the WHO Collaborating Centre for International Drug Monitoring.

4.5.1   Foradil IMMP

Foradil was approved for marketing in New Zealand in March 1992 and monitored by the Intensive Medicines Monitoring Programme from inception until 30 November 2000. Initial usage was low and the cohort only reached 500 in the third quarter of 1996. A report with results from 1,605 patients who commenced treatment with Foradil between 01 March 1992 and 30 November 2000 was produced. The average age of the cohort is 50 years. Data on baseline asthma severity is available for 446 patients (27.8%). The information on this group of patients indicates that, in the year prior to commencing Foradil, 27% required at least one acute asthma hospital admission, 7% were admitted to an Intensive Care Unit and 55% had at least one emergency visit for acute asthma. The majority of these patients (74%) had been treated with short courses of oral steroids in the prior 12 months and 18% had received continuous oral steroids in the prior 6 months. This group reflects the same demographic distribution as the total cohort.

Cessation of treatment has been reported in 347 patients with 22 (6.2%) due to inadequate therapeutic effect and 28 (7.9%) due to an adverse reaction. 63 patients have died with all deaths assessed as 'Unlikely' to be causally related to Foradil.

4.6   Summary of the epidemiological literature: Asthma

Asthma is a common respiratory disease among both adults and children. National treatment guidelines for asthma have been published in several countries including Britain, the US and Australia. They recommend the use of inhaled corticosteroids (ICS) as 'preventer' maintenance therapy for all but mildest grades of asthma severity. In addition, bronchodilator therapy is an essential component of treatment, traditionally used for relief of symptoms as needed. The most widely used bronchodilators in asthma are inhaled $beta_2$-agonists which can be divided into two groups: those with a short duration of action (2-6 hours) which are used in a reactive 'relief' mode and those with a longer duration of action ($\geq$12 hours). The latter are used as prospective 'symptom controllers'.

4.6.1   Trends in mortality rates for asthma

When we examine the trends in mortality rates for asthma in the general population there seems to be a decrease in the last decades. These figures consider general population as the denominator and are not specific to patients diagnosed with asthma.

A study examined trends in mortality for asthma in the general population of Switzerland between the periods 1969-1973 and 1989-1993. Asthma mortality declined from 4.3 per 100,000 to 2.8 per 100,000, in men, and from 2.0 per 100,000 to 1.5 per 100,000, in women [La Vecchia 1996].

Another study was conducted in the general population of Israel. In the age group 5 to 34 years, asthma mortality between 1971 and 1980 decreased from 0.43 to 0.18 per 100,000 population per year. However, from 1981 to 1990 asthma mortality increased to 0.40 per 100,000 population [Livne 1996]. A new review of national trends of death from asthma in Israel between the years 1980 and 1997 in young patients (age 5 to 34 years) yielded a mean mortality rate of 0.226 per 100,000 population [Picard 2002].

In a study carried on in Italy, asthma mortality decreased between 1974 and 1978, increased ten-fold from 1979 to 1985, rising from 0.30 to 4.2 per 100,000 population, and remained stable from 1986 to 1989 [Mormile 1996].

In a Japanese study, with data from the National Vital Statistics [Ito 2002], the mortality rates for males with asthma decreased from 23.2 to 6.8 per 100,000 inhabitants in the period 1950 to 1980 and from 16.1 to 4.2 per 100.000 inhabitants in females for the same period. Since 1980, crude and age-adjusted mortality rates have reached 1.0 per 100,000 inhabitants in males and 0.5 per 100,000 inhabitants in females in 1993.

Similarly in the US, asthma mortality increased during the 1980's, but has decreased during the 1990's. This is thought to be the result of better treatment and decreased prevalence [Sly 2004].

4.6.2 Death from asthma in asthmatics: Population based studies and risk factors

The rate of death from asthma has been estimated to be between less than 1 and 4 per 100,000 per year among the general population worldwide and up to 10 per 10,000 per year among people with asthma in Canada taking medications [Sears 1997, Suissa 1994].

Another report using data from the General Practice Research Database (GPRD), evaluated the relationship of each major class of respiratory drug and asthma death [Lanes 2002]. The source population included 96,258 patients 10-79 years with a physician diagnosis of asthma. The overall asthma mortality rate in this population during the study period 1994 to 1998 was 12.5 deaths per 100.000 person years; this increased with age and was similar for males and females. Adjusted relative risk estimates showed that inhaled steroids constituted the only class of respiratory drug in that study which was consistently related to a decrease risk of asthma death. The observed relation between short acting beta$_2$-agonists and increased risk of asthma death achieved statistical significance when there were more than 7 prescriptions in the previous year.

ICS are the most commonly used asthma medications in children and adults. ICS are anti-inflammatory agents and are first-line therapy in the treatment of asthma. The beneficial effects of ICS in reducing asthma morbidity and mortality [Suissa 2000] have been described. A population-based cohort of 30,569 patients with asthma aged 5 to 44 years identified from the Saskatchewan Health databases during the period 1975 through 1997 was used. Patients were followed until 54 years of age. All 66 asthma deaths identified from the cohort were matched to 2681 controls on markers of asthma severity. The rate of death from asthma was found to decrease by 21% with each additional canister of inhaled corticosteroids used in the prior year (95% CI, 3% to 35%). Alternatively, the decrease was 54% (95% CI, 21% to 74%) for each additional canister used in the prior 6 months.

A recent study using Saskatchewan Health databases including a total of 29,957 persons aged 5 to 54 years who had at least five asthma-related visits to physicians between 1991 and 2000 examined the rate of hospitalization considering the treatments administrated to patients [Senthilselvan 2005].

In this study the incidence rate of hospitalization in patients treated with LABA was 6.64 per 1,000 person-years; the rate of hospitalization in those not treated with LABA is 15.12 per

1,000 person-years. The rate of hospitalization in those not treated with combination therapy (ICS plus LABA) is 15.06 per 1,000 person-years whereas the rate among those treated with combination therapy was 0.00 per 1,000 person-years.

In summary, there seems to be a relationship between the use of ICS, as recommended by guidelines, and reduction of death rate in asthma patients. Inadequate use of other therapies increases the rate of hospitalization and death.

4.7 Summary of the epidemiological literature: Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality in the industrialized world. Several studies have shown that mortality is increased in patients with asthma and COPD, with increasing excess mortality related to low forced expiratory volume in one second (FEV_1).

COPD is characterized by the progressive development of airflow limitation that is not fully reversible. The term COPD encompasses chronic obstructive bronchitis, with obstruction of small airways, and emphysema, with enlargement of air spaces and destruction of lung parenchyma, loss of lung elasticity, and closure of small airways. Chronic bronchitis, by contrast, is defined by the presence of a productive cough of more than three months' duration for more than two successive years. The cough is due to hypersecretion of mucus and is not necessarily accompanied by airflow limitation. However, there is some epidemiologic evidence that mucus hypersecretion is accompanied by airflow obstruction, perhaps as a result of obstruction of peripheral airways. Most patients with COPD have all three pathologic conditions (chronic obstructive bronchitis, emphysema, and mucus plugging), but the relative extent of emphysema and obstructive bronchitis within individual patients can vary

Approximately 14 million people in the United States have COPD. In the third U.S. National Health and Nutrition Examination Survey, airflow obstruction was found in approximately 14 percent of white male smokers, as compared with approximately 3 percent of white male nonsmokers; the figures for white female smokers and for black smokers were slightly lower than those for white male smokers [CDC 1995]. COPD is now the fourth leading cause of death in the United States, and it is the only common cause of death that is increasing in incidence.

The recognition that chronic airway inflammation has a critical role in producing the symptoms of asthma led to the earlier and more widespread use of anti-inflammatory treatments, particularly inhaled corticosteroids, which have become the mainstay of asthma management. It is now apparent that there is a chronic inflammatory process in COPD, but it differs markedly from that seen in asthma, with different inflammatory cells, mediators, inflammatory effects, and responses to treatment. Smoking cessation is the only measure that will slow the progression of COPD [Anthonisen 1994].

Bronchodilators are the mainstay of current drug therapy for COPD. Bronchodilators cause a small (<10 percent) increase in FEV_1 in patients with COPD, but these drugs may improve symptoms by reducing hyperinflation and thus dyspnea, and they may improve exercise tolerance, despite the fact that there is less dramatic improvement in spirometric measurements [O'Donnell 1998] than in asthma. Several studies have demonstrated the

usefulness of the long-acting inhaled beta$_2$-agonists salmeterol and formoterol in COPD [O'Donnell 1998, Boyd 1997, Mahler 1999]. An additional benefit of long-acting beta$_2$-agonists in COPD may be a reduction in infective exacerbations, since these drugs reduce the adhesion of bacteria such as *Haemophilus influenzae* to airway epithelial cells [Dowling 1998].

Indeed, inhaled corticosteroids are now widely prescribed for COPD. However, the inflammation in COPD is not suppressed by inhaled or oral corticosteroids, even at high doses. Recent studies found no evidence that long-term treatment with high doses of inhaled corticosteroids reduced the progression of COPD, even when treatment was started before the disease became symptomatic [Pauwels 1999, Vestbo 1999, Burge 2000].

4.8 Conclusion

Although there are limitations to the conclusions that can be drawn from these data, both the US and worldwide reporting rates for asthma-related death for formoterol are lower than for salmeterol, in the first three years following US launch. There are inherent limitations to the interpretation of reporting rate analyses, in addition to uncertainties as to which bronchodilator is prescribed for which disease and severity. For example, in asthma, LABAs are second line therapy, marking a potentially more severe patient population, which may lead to higher reporting rates.

4.9 References

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5 Review of the literature of non-Novartis formoterol trials

In order to assess the association of formoterol with respiratory events including deaths in non-Novartis trials, a literature search was performed for reports published over the past 10 years of trials involving 1,000 patients or more in asthma and COPD, as well as any trials focusing on cardiovascular outcomes with this drug. The databases used included: Derwent, Medline, Embase and eNova. A total of four asthma publications, one COPD publication and 2 cardiovascular endpoint publications were identified.

Total number of patients

- Asthma Trials: 24,005 patients, age groups 4 to 91 years

  (9,064 patients on formoterol / 3,911 on a formoterol combination product)

- COPD Trials: 1,022 patients, age groups ≥40 years

  (255 patients on formoterol / 254 on a formoterol combination product)

- Cardiovascular Trials: 40 patients, age groups ≥18 years

  (40 patients on formoterol)

Number of Trials / Publications

- Asthma: 4

  - as well as 3 sub-analyses of one trial as indicated in 5.1.1.2, 5.1.1.3, 5.1.1.4

- COPD: 1

  - 2 publications

- Cardiovascular as an Endpoint: 2

The findings from these trials/publications showed: a total of 24,005 asthmatic patients (total of 12,975 patients on any non-Novartis formulation containing formoterol); a total of 1,022 COPD patients (total of 509 patients on any non-Novartis formulation containing formoterol). The cardiovascular trials included a total of 40 patients (total of 40 patients on any non-Novartis formulation containing formoterol). In total, 13,524 formoterol-treated patients were involved in these trials.

Table 5-1   Pooled non-Novartis published trials: Treatment assignment and patient disposition

	Total # of Trials	Total # of Patient Population / Tx Group	Total Age of Patient Population	Total # of Patients with *Resp AEs (%)	Total # of Patients with **CV AEs (%)	Total # of Patient Deaths (%)	Total # of Patients with SAEs (%)	Total # of Patients who ***D/C'd due to Resp AEs (%)	Total # of Patients who D/C'd due to CV AEs (%)

	Total # of Trials	Total # of Patient Population / Tx Group	Total Age of Patient Population	Total # of Patients with *Resp AEs (%)	Total # of Patients with **CV AEs (%)	Total # of Patient Deaths (%)	Total # of Patients with SAEs (%)	Total # of Patients who ***D/C'd due to Resp AEs (%)	Total # of Patients who D/C'd due to CV AEs (%)
All Groups	7	25,131	4-91 yrs	2,632 (10.5)	226 (0.9)	53 (0.2)	806 (3.2)	441 (1.8)	1 (0.003)
Formoterol (incl. any combination) Group	7	13,536	4-91 yrs	1,286 (9.5)	119 (0.9)	31 (0.2)	429 (3.2)	287 (2.1)	1 (0.007)
[1]Active Comparator Groups	3	9,100	4-91 yrs	1,205 (13.2)	107 (1.2)	11 (0.1)	299 (3.3)	48 (0.5)	0
[2] ICS	1	257	>40 yrs	62 (24.1)	****NR	6 (2.3)	40 (15.6)	46 (17.9)	0
[3]Placebo	2	268	>40 yrs	79 (25.9)	NR	5 (1.9)	38 (14.2)	60 (22.4)	0
OPTIMA Trial (See Publication Overview #4) - Asthma	1	1,970	>12 yrs	NR	NR	NR	NR	NR	NR

*Resp = Respiratory

**CV = Cardiovascular

***D/C = Discontinued

****NR = Not Reported

[1] Comparator Groups: B$_2$ Agonists - Albuterol; Salmeterol, Terbutaline

[2] ICS: Budesonide

[3] Placebo – Only noted as a placebo if no active comparator arm is in the trial

5.1   Summary of individual trials: asthma

Data from this review was obtained from 4 trials.   There were a total of 24,005 patients randomized, with ages ranging from 4 – 91 years, in trials of 4 weeks to one year in duration. In addition, there were 3 sub-analyses of the RELIEF Trial published as abstracts (3.3.1.2-4), resulting in a total of 7 publications.

5.1.1.1 Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial - The RELIEF Trial [Pauwels 2003]

Patient Population

18,124 patients aged 4-91 years of age entered the 6-month trial.

Methodology

This was a an open-label randomized multinational 6 month study to compare the safety and effectiveness of as-needed treatment with formoterol 4.5 mcg Turbuhaler® (Oxis®) or albuterol 200 mcg pressurized metered-dose inhaler (MDI) to examine the safety and effectiveness in the treatment of asthma. Up to 12 inhalations of day for adults and 8 inhalations per day for children were allowed.

Primary safety variables

All asthma-related and non-asthma related AEs and SAEs and discontinuations due to adverse events. Primary efficacy variable: Time to first asthma exacerbation, defined as an asthma deterioration requiring hospitalization, emergency treatment, a course of oral corticosteroid or increased maintenance therapy (intention-to-treat analysis).

Results

There was a lower proportion of asthma-related AEs in the formoterol group (12.3 vs. 13.5%; p=0.018), a numerical difference in asthma-related SAEs favoring formoterol (108 vs. 121; p=0.39) and no difference in overall SAEs (278 vs. 299; p=0.38) or discontinuations due to SAEs (40 versus 37; p=0.73). Time to first asthma exacerbation was more prolonged on formoterol compared to albuterol (HR 0.86 formoterol vs. albuterol; p<0.001). Mean usage of drugs (inhalations/d) was significantly lower for formoterol than albuterol during each treatment period (Periods 1: 1.36 vs. 1.57; 2: 1.29 vs. 1.50; 3: 1.23 vs. 1.46) and respectively, for decreases in days with asthma symptoms (1: 42.35 versus 44.37; 2: 41.49 versus 42.55; 3: 39.49 versus 41.20).

Deaths

In all, there were 24 deaths with no significant difference in groups, 13 (formoterol) and 11 (albuterol), of which five were asthma-related (formoterol 3, albuterol 2) and 11 were CV-related (formoterol 5, albuterol 6).

Table 5-2   **Number of Patients by Treatment Group Experiencing Asthma Exacerbations, CV adverse events, Deaths, SAEs and Discontinuations in the RELIEF Trial**

Treatment Groups	Total # of evaluable patients/group	# of patients with Asthma Exacerbations (%)	# of patients with CV AEs (%)	# of patient deaths (%)	# of patients with SAEs (%)	Patient discontinuations due to asthma-related AEs (%)
Formoterol 4.5 mcg	8924	1097 (12.1)	119 (1.3)	13 (0.1)	278 (3.0)	89 (1.0)
Albuterol 200 mcg	8938	1205 (13.3)	107 (1.2)	11 (0.1)	299 (3.3)	48 (0.5)

Conclusions

Asthma-related AEs decreased with formoterol compared to albuterol but more asthma-related discontinuations occurred in the formoterol group. Time to first exacerbation was longer and less as-needed and maintenance medication was used with formoterol than albuterol. Greater reduction of exacerbations with as-needed formoterol versus albuterol occurred which increased with increasing age and usage of other asthma medication. Formoterol, as-needed, had a similar safety profile to albuterol and its use as a reliever therapy was associated with fewer asthma symptoms and exacerbations.

5.1.1.2   Safety of formoterol Turbuhaler used as reliever in asthma: relationship with age and baseline treatment including regular long-acting beta2-agonists (the RELIEF study) [Pauwels 2002a Abstract]

Patient Population

Total patient population of the RELIEF trial cited above.

Methodology

Open label randomized multinational study to compare as-needed formoterol 4.5 mcg via Turbuhaler versus albuterol 200 mcg via MDI or DPI in the treatment of asthma as described above.

Methodology

To assess the safety of formoterol Turbuhaler (Oxis) as a reliever therapy compared with albuterol prn in a multinational 6-month, open-label trial. For this analysis, subjects were stratified by age and by level of maintenance medications as recommended for the levels of severity based on GINA guidelines.

Adverse Events

There was no increase in adverse events with formoterol compared with albuterol, in any of the studied age groups, or related to any maintenance treatment group. There was a trend for fewer AEs when formoterol was used in patients taking regular maintenance formoterol compared with maintenance salmeterol. The greatest number of AEs were seen with albuterol in patients taking maintenance salmeterol. Numbers relating to adverse events not provided.

SAEs

Not reported

Deaths

Not reported

Conclusion

The formoterol Turbuhaler, as a reliever therapy, was as safe as albuterol in all age groups and all strata of asthma severity, irrespective of maintenance medication requirements.

5.1.1.3 Formoterol Turbuhaler compared with salbutamol as reliever in asthma: an exploratory analysis of the RELIEF study in patients using formoterol as maintenance therapy. [Pauwels 2002b Abstract]

Patient Population

Total patient population of the RELIEF trial cited above.

Methodology

Open label randomized multinational study to compare as-needed formoterol 4.5 mcg via Turbuhaler versus albuterol 200 mcg via MDI or DPI as rescue therapy in the treatment of asthma as described above. Analyzed were the effects on outcome variables in the subgroup of patients who were receiving maintenance therapy with formoterol during the study.

Primary Outcome variable

Time to first asthma exacerbation.

Results

Formoterol reduced the risk of exacerbation by 18% (HR: 0.82; p=0.006) compared to as-needed albuterol and was associated with lower use of reliever therapy. Hazard ratios for outcomes of all types and significance level as listed below.

Table 5-3   Rate of outcome measure for formoterol relative to albuterol expressed as hazard ratio

Variable	Hazard ratio	p-value
All exacerbations*	0.861	<0.001
Severe exacerbations	0.880	0.0013
Hospitalization +	0.841	0.141
Emergency treatment +	0.885	0.027
Oral corticosteroids +	0.870	0.0033
Increased maintenance	0.839	<0.001

*All exacerbations decreased by 14%

+Classed as severe

Adverse Events / SAEs

Not quantified. Reported as not significant.

Deaths

Not reported for the subgroup analyzed.

Conclusion

Formoterol was safe to use as a reliever in patients already taking formoterol as a maintenance medication and improved overall asthma control compared with albuterol.

5.1.1.4   Safety of formoterol turbuhaler when used as a reliever therapy in asthma (the RELIEF study). [Pauwels 2002c Abstract]

Patient Population

Abstract publication of RELIEF study as cited above.

Methodology

Overall analysis of the RELIEF study as cited above.

Results

Safety: Number of AEs and SAEs was not statistically different. Discontinuations due to AEs were somewhat higher in the formoterol group (2.4 versus 1.3%; p<0.001), which was due to non-serious AEs. Discontinuation due to SAE was 0.4% in both groups.

Efficacy: Formoterol resulted in lower incidence of "asthma aggravated" reports (p=0.018 versus. albuterol) and asthma exacerbations (<0.001 versus albuterol).

Conclusions

There was no substantive difference in safety profile for as-needed formoterol compared to as-needed albuterol in patients on other asthma therapies.

5.1.1.5   Adjustable maintenance dosing with budesonide/formoterol in a single inhaler provide effective asthma control at a lower dose than fixed maintenance dosing. [Canonica 2004]

Patient Population

2358 randomized patients from Italian sites, age group >6 years with a >6 month history of asthma, subgroup analysis of the SAMD (Symbicort® Adjustable Maintenance Dosing Programme).

Methodology

To assess the efficacy and safety of budesonide/formoterol in a single inhaler [Symbicort Turbuhaler 160/4.5 mcg or 80/4.5 mcg (depending on baseline inhaled steroid dose; metered dose for formoterol = 6 mcg)] given as an adjustable maintenance or fixed maintenance dosing. This was an open-label, parallel-group, multi center, 12-week study with a 4-week run-in period. Patients were randomized to budesonide/formoterol fixed maintenance dosing (2 inhalations b.i.d.) or adjustable maintenance dosing comprised of 2 inhalations b.i.d., stepping up to 4 inhalations b.i.d. if asthma worsened for a maximum of 14 days.

Primary efficacy variables

1) Frequency of asthma exacerbations defined as a serious asthma-related adverse event, hospitalization/emergency treatment, or course of oral steroids, withdrawal from study due to lack of efficacy.

2) Change in patients' asthma symptom severity.

Primary safety variables

Number of patients with non-asthma and asthma-related adverse events; number with serious adverse events; number who discontinued due to non-asthma or asthma-related adverse events.

Results

Efficacy The proportion who experienced asthma exacerbations in the adjustable and fixed dose regimens (4.8% vs. 4.6%) was similar. Total exacerbation rates was somewhat higher in the higher dose steroid group. There was no significant difference in the proportion of patients. Asthma symptom severity was improved or maintained in 94.9% of patients receiving adjustable and 94.5% of patients treated with fixed maintenance dosing.

Safety Individual AEs occurred in <5% of all patients with respiratory tract infection being the most frequently reported event. A small proportion of patients discontinued therapy due to adverse events (3.1 versus 3.5% in adjustable versus fixed dose regimens). Asthma exacerbations were very low in both groups.

SAEs

There were three reported asthma-related SAEs in the fixed maintenance dosing group at the higher steroid dose (160/4.5 mcg). There were two other reported hospitalizations or admissions to the emergency department due to asthma (1 in the adjustable 160/4.5 and the other in the fixed 80/4.5 treatment group).

Deaths

No deaths occurred.

Conclusions

Both adjustable maintenance dosing and fixed maintenance dosing were associated with similar low frequency of exacerbations (5% both groups), improved lung function, and lower asthma severity scores compared with the run-period.

5.1.1.6 Adjustable and fixed dosing with budesonide via a single inhaler in asthma patients: the ASSURE study. [Ind 2004]

Patient Population

1719 patients 18 years or older with diagnosis of asthma who had been receiving 400 mcg or more of inhaled corticosteroids who were taking LABA with controlled symptoms, or were not controlled while taking reliever medication alone.

Methodology

This was a six month randomized, open-label, 12-week, multi-center trial conducted in the UK to assess adjustable and fixed dosing with budesonide / formoterol via a single inhaler in asthmatics. After a run-in period patients were converted to budesonide/formoterol: two inhalations of 80/4.5 mcg or 160/4.5 mcg b.i.d. (depending on original does of inhaled corticosteroid used on screening) with subsequent re-characterization of their asthma at the end of run-in. Groups were then randomized either to continue a fixed dose regimen, or an adjustable dose regimen whereby they could either step up to or down to one inhalation b.i.d. or if symptoms warranted, step up to 4 inhalations b.i.d. for two weeks or less. Assessment of asthma status (according to NHLBI definitions) was performed at weeks 4, 8 and 12.

Primary efficacy variable

Number of treatment successes and treatment failures.

Primary safety variables

No pre-specified safety analysis. Number, type and severity of adverse events were recorded.

Results

Efficacy At the end of run-in there was a significant improvement in severity status (p<0.001). During the randomized treatment period, the majority of patients in both fixed dose and adjustable dose regimens either maintained or improved asthma status class. 6% in both arms experienced a treatment failure with a similar proportion of patients in each who experienced serious asthma exacerbation (1-2%) or discontinued due to treatment failure (2-3%).

Safety Discontinuations due to AEs occurred in 4% during run-in and 2% (both groups) during randomization, with cause due to worsening of asthma approximately 1% in both run-in and randomization for both arms (17 in each group; Table 5-4)

SAEs

Occurred in 1% in run-in and 3-4% during the randomization period. The incidence and type were similar both groups. (Table 5-4).

Deaths

2 in run-in; none during randomization period.

Table 5-4   **Number of Patients by Treatment Group Experiencing Asthma Exacerbations, CV adverse events, Deaths, SAEs and Discontinuations due to AEs**

Treatment groups	Total # of patients/ group	# of patients with Asthma-Related Exacerbations (%)	# of patients with CV AEs (%)	# of patient deaths (%)	# of patients with SAEs (%)	# of patient discontinuations due to AEs (%)
Fixed dosing Bud/For 80µg/4.5 mcg 160µg/4.5 mcg	771	35 (4.5)	NR	0	28 (3.6)	19 (2.5)
Adjustable dosing Bud/For 80 mcg/4.5 mcg 160 mcg/4.5 mcg	782	33 (4.2)	NR	0	24 (3.1)	15 (1.9)

Conclusions

In both groups, symptom control was maintained or improved in the vast majority of patients. There was no meaningful difference between fixed dose regimen and adjustable dose regimens in terms of efficacy or safety.

5.1.1.7   Low dose inhaled budesonide and formoterol in mild persistent asthma. The OPTIMA trial. [O'Byrne 2001]

Patient Population

1970 patients (Group A = 698 patients and Group B = 1272 patients), > 12 years of age with mild to moderate asthma.

Methodology

This was a six-month randomized, open-label, 12-week, multinational trial conducted in the UK to assess adjustable and fixed dosing with budesonide / formoterol via a single inhaler in asthmatics. Patients were comprised of two groups: group A with no requirement of inhaled corticosteroids and an FEV_1 of 80% or greater after beta-agonist and a second group B who were stable taking 400 mcg/day or less of budesonide or equivalent and had an predicted FEV_1 of 70% or greater after beta-agonist. After a run-in period patients were converted to budesonide/formoterol: two inhalations of 80/4.5 mcg or 160/4.5 mcg b.i.d. (depending on original does of inhaled corticosteroid used on screening) with subsequent re-characterization of their asthma at the end of run-in. Groups were then randomized either to continue a fixed

dose regimen, or an adjustable dose regimen whereby they could either step up to down to one inhalation b.i.d. or if symptoms warranted, step up to 4 inhalations b.i.d. for two or two or less weeks. Assessment of asthma status (according to NHLBI definitions) was performed at weeks 4, 8 and 12.

Primary efficacy variables

1) Time to first severe asthma exacerbation

2) Number of poorly controlled asthma days.

Primary safety variables

Number, type and severity of adverse events were recorded.

Results

Group A: Budesonide reduced risk of first asthma exacerbation by 60% and poorly controlled asthma days by 48%; there was no additional improvement on these variables with addition of formoterol.

Group B: Addition of formoterol to lower or higher dose budesonide resulted in a further 43% reduced risk of asthma exacerbation and a 30% reduction in number of poorly controlled asthma days. There was a 52% reduction in severe asthma exacerbations as well as improvements in FEV_1, morning PEF, percentage of asthma-free days and need for rescue albuterol. Addition of formoterol was more effective than doubling the dose of budesonide.

Deaths

None reported.

Conclusion

In summary, in this one year trial, very mild asthmatics not requiring ICS at baseline benefited from the addition of budesonide, but not formoterol. In contrast, in those needing ICS at baseline, the addition of formoterol significantly improved pre-specified efficacy measures with no meaningful adverse effect on safety.

5.2   Summary of individual trials: COPD

5.2.1.1   Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. [Calverley 2003]

Patient Population

1022 patients aged 40 or greater (mean 64) with severe COPD (FEV_1/FVC 50% or less and FEV_1 50% of less of predicted).

Methodology

Randomized double-blind, placebo-controlled multinational trial of 12 months in treatment duration. After a 2 week run-in period during which all patients were treated with oral prednisone (30 mg) and inhaled formoterol (2 inhalations of 4.5 mcg b.i.d.) and terbutaline rescue as needed, patients were randomized to treatment over 12 months with budesonide 200 mcg b.i.d., formoterol 2 x 4.5 mcg b.i.d., budesonide/formoterol or placebo. All treatment groups also received rescue with terbutaline as needed.

Primary efficacy variables

Time for first exacerbation; change in post-medication FEV_1.

Primary safety variables

Not specified. No primary safety analysis performed. Listed were AEs, SAEs, withdrawals and deaths.

Results

Time to first exacerbation was longer in all active treatment groups compared to placebo (budesonide/formoterol: 254, budesonide: 178, formoterol: 154, placebo: 96 days). The total number of exacerbations and number of exacerbations requiring corticosteroids was lower than placebo in all treatment groups, and lowest with budesonide/formoterol. The mean number of AEs was no difference between groups (5, 5, 6 and 5 AEs per 1000 treatment days, respectively). The number of serious AEs was lowest in the budesonide/formoterol and placebo groups (65, 88, 85, and 66, respectively). The number of serious COPD-related AEs was 40, 40, 55, and 38, respectively. The proportion of withdrawals due to COPD worsening was   lowest   in   the   budesonide/formoterol   group   and   highest   in   placebo. Budesonide/formoterol was significantly better than budesonide alone (11 versus 18%; p=0.038).

Deaths

The number of deaths in the budesonide/formoterol, budesonide, formoterol and placebo groups were 5, 6, 13, 5, respectively, mostly assessed to be due to COPD.

Conclusions

The combination of inhaled corticosteroid and formoterol provided incremental benefits in efficacy outcome measures compared to formoterol, budesonide or placebo.   In this study of severe COPD patients, more deaths occurred in the formoterol arm compared to other groups: the budesonide/formoterol group was similar to placebo.

5.2.1.2 COPD Exacerbations are reduced by budesonide/formoterol in a single inhaler [Calverley 2003a Abstract]

Patient Population

First communication of results of above publication. Severe COPD patients (mean FEV_1 36% predicted), mean age 64 years.

Methodology

Two week run-in followed by randomization to determine if combining ICS and LABA in a single inhaler was more effective than the single components. During the run-in period patients were randomized to 2 inhalations b.i.d. of budesonide/formoterol in a single inhaler 160/4.5 mcg (Symbicort), budesonide 200 mcg, formoterol 4.5 mcg or placebo.

Primary efficacy variable

Time to first exacerbation requiring medical intervention (hospitalization and/or use of oral steroids/antibiotics).

Deaths

Not reported

Results

Focused on the primary outcome variable described in published full manuscript: time to first exacerbation.

Conclusion

Budesonide/formoterol (Symbicort) provided better protection against exacerbations than monocomponents and placebo, suggesting synergy between formoterol and budesonide.

5.2.1.3 Budesonide/formoterol in a single inhaler sustains lung-function improvements in COPD [Calverley 2003b Abstract]

Patient Population

Study 1 = 812 COPD patients; Study 2 = 1022 COPD patients. Mean age 64 years old; mean FEV_1 predicted: 36%.

Methodology

Pooled analysis of two parallel-group, double-blind studies to assess degree of lung function improvement in patients treated with B/F, budesonide, formoterol or placebo.

Primary outcome variables

FEV_1 and PEF.

Results

Mean FEV_1 with budesonide/formoterol remained >14% above placebo and >9% above budesonide (both p<0.001) in both studies.

Deaths

Not reported.

Conclusion

In both studies, budesonide/formoterol (Symbicort) showed sustained improvements in lung function (with no signs of tachyphylaxis over 12 months); there was an incremental benefit of formoterol when added to budesonide.

5.3 Summary of individual trials: cardiovascular endpoints

5.3.1.1 Cardiac effects of formoterol and salmeterol in patients suffering from COPD with pre-existing cardiac arrhythmias and hypoxemia [Cazzola 1998]

Patient Population

12 male/female COPD patients >40 years of age with pre-existing mild to moderate cardiac arrhythmias and hypoxemia.

Methodology

A small randomized, single-blind, balanced crossover, placebo-controlled trial to assess the cardiac effects of two single doses of formoterol (12 mcg and 24 mcg) and one single dose of salmeterol (50 mcg) and placebo. Each patient stayed in the clinical trial unit for 36 hours at a time. Each patient was evaluated at a screening visit that included spirometry, blood gas analysis, plasma potassium measurement and a 12-lead ECG. All patients underwent Holter monitoring 24 hours during each of the four treatments. None of the patients took rescue medication during this time.

Results

Cardiac changes observed included: Supraventricular dysrrhythmias, isolated ventricular premature beats, complex ventricular arrhythmias and an overall observation was the reduction in plasma potassium. There was no significant difference among treatment groups in proportions of patients with supraventricular arrhythmia. A small increase in ventricular paroxysmal beat frequency was observed compared to placebo (1-2 beats/hr), but no significant difference among active treatments. There was a somewhat higher number of subjects in whom multiform VPBs were observed in the 24 mcg formoterol dose.

Deaths

Not reported.

Conclusion

Both salmeterol and formoterol induced increases in heart rate and reductions in serum potassium relative to placebo which tended to be greater in the high dose formoterol group. Cardiac arrythymias were observed in all treatment groups including placebo and clear differences among groups were not observed. Similar cardiac effects were generally seen among all active treatment groups compared to placebo, although the study was too small to draw definitive conclusions.

5.3.1.2   Tolerability to high doses of formoterol and terbutaline *via* Turbuhaler for 3 days in stable asthmatic patients [Totterman 1998]

Patient Population

A total of 27 asthmatics who required regular inhaled corticosteroid and as-needed beta-agonist, aged 18 or older, were involved two studies, reported as Part A and B. Mean age was 56 and 59 years old, respectively.

Methodology

Two part study. Part A: 12 patients received formoterol via Turbuhaler (72 mcg total daily dose), or terbutaline via Turbuhaler (6 mg total daily dose) for three consecutive days and after a wash-out were crossed over to receive the other treatment. Part B: 15 different patients received formoterol via Turbuhaler (120 mcg total daily dose), or terbutaline via Turbuhaler (10 mg total daily dose) for three consecutive days and after a wash-out were crossed over to receive the other treatment..

Primary safety variables

Pulse, blood pressure, serum potassium, electrocardiogram and FEV_1 were registered at regular intervals and Holter monitoring.

Results

Terbutaline 6mg showed significantly greater systemic effects than formoterol 72 mcg on pulse, blood pressure, and QTc (QT interval corrected for heart rate). Terbutaline 10 mg had significantly greater effects than formoterol 120 mcg on serum potassium levels, pulse, cardiac frequency and QTc. No differences in FEV_1 levels were found. Both drugs were reported to be safe and generally well tolerated at both dose levels.

Deaths

None Reported.

Table 5-5   **Summary of CV Outcome Measures – Mean Changes Over 3 Days**

Treatment Groups (total daily dose)	Total # of Pts / Group	Systolic BP Mm Hg	Diastolic BP mm Hg	Cardiac Frequency bpm	Increase in QTc (ms)
Group A Formoterol 72 mcg	13	REF	REF	18.5	18.7 ms
Terbutaline 6mg	13	↑5.0*	↓2.7*	23.4*	28.3*
Group B Formoterol 120 mcg	15	ND	ND	13.3	17
Terbutaline 10 mg	15	ND	ND	23.6*	40*

--- = no value given
ND – no difference
*Statistically different from corresponding formoterol group

Conclusion

High doses of formoterol Turbuhaler over 3 days were generally safe and well tolerated. Daily doses of 6 mg and 10 mg terbutaline Turbuhaler were systemically more potent than 72 mcg and 120 mcg formoterol, respectively. The authors posited that the safety margin for formoterol appeared to be wider than terbutaline at higher dose levels.

5.4 Conclusions

An extensive review of the published literature over the past 10 years was conducted, focusing on safety as assessed by serious asthma- and COPD-related adverse events, all cause death and cardiovascular endpoints. The vast majority of trials indicated no difference between formoterol and comparator arms that included albuterol-, salmeterol-, and placebo-treated groups where albuterol was used as a rescue medication. Formoterol appeared to be better tolerated than terbutaline. There is evidence that formoterol provided added benefit to budesonide with no change in tolerability. The overall results were consistent in asthma and COPD patients.

5.5 References

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6   Review of the efficacy of formoterol

6.1   Introduction

Long-acting beta$_2$-agonists (LABAs) have been a very significant addition to the treatment armamentarium for moderate and severe asthma (GINA, NHLBI) and for COPD (GOLD, ATS COPD). Because of their clinical advantages, they have largely replaced short-acting beta$_2$-agonists for long-term maintenance treatment. Their use in asthma and COPD is recommended by US sponsored NHLBI and International GINA guidelines.

Despite their q.i.d. labeling, short-acting beta$_2$-agonists do not provide bronchodilation for the 6 hour dosing interval in many patients. These patients are forced to choose between either dosing SABAs more frequently than recommended and thus overuse them, or to face a "rollercoaster" of their lung function several times a day. Importantly, SABAs do not provide

protection from the development of airway obstruction through the night and in the early morning hours. At a time when lung function in most patients is lowest due to the diurnal variation in airway tone, these patients may awake with nocturnal asthma symptoms.

The use of inhaled corticosteroids and a LABA is the preferred treatment for patients with moderate and severe persistent asthma. In particular for patients with chronic, more permanent airflow obstruction, LABAs have been a major advance in providing bronchodilation of 12 hour duration. This benefit, shown in numerous studies, is reflected in more consistent improvements of Quality of Life, and reduction of symptoms and asthma exacerbations.

A recent Cochrane Database System Review [Ram 2005] concluded that a LABA as an add-on therapy to inhaled corticosteroids is superior to leukotriene receptor antagonists for reduction of exacerbations requiring systemic steroids, symptoms, and use of rescue beta$_2$-agonists as well as for improving lung function.

6.2 Efficacy in asthma

The formoterol studies in subjects with asthma support the following efficacy conclusions:

- Single-dose studies showed a dose related bronchodilator response between 6, 12 and 24 mcg and there were no significant differences in bronchodilator effects between higher doses from 24 to 96 mcg. Formoterol at its recommended dose of 12 mcg was not different from albuterol MDI 180 mcg/albuterol DPI 400 mcg for peak bronchodilator effect.

- The onset of the bronchodilator effect at doses of 6 mcg, 12 mcg and 24 mcg occurs rapidly. Using body plethysmography, onset of action occurred between 1 and 3 minutes. The peak effect of these doses was reached at approximately 2 hours. Duration of action exceeds 12 hours at doses of 12 and 24 mcg, which has not been consistently observed for 6 mcg.

- Multiple dose therapeutic studies support 12 and 24 mcg as effective bronchodilator doses for the treatment of asthma, whereas formoterol 6 mcg was less effective. Regular treatment with 24 mcg appeared numerically superior to 12 mcg in improving end of dosing interval pulmonary function, nocturnal asthma symptoms and reducing the use of rescue medication. The advantage of the higher 24 mcg dose was less obvious for post bronchodilator FEV$_1$. The therapeutic effect was maintained during chronic and long-term treatment up to one year. In the pivotal studies, formoterol was significantly superior to placebo in all clinical variables measured: daytime asthma symptom scores, nocturnal asthma score, morning and evening rescue medication use and, importantly, frequency of asthma exacerbations.

- Regular treatment with formoterol causes tolerance to some airway responses and, as expected and demonstrated for other beta$_2$-agonists, most systemic responses. Whereas tolerance to the bronchodilator effect, if observed, was small and not clinically relevant, the tolerance to the protective effect measured by a methacholine challenge was somewhat more pronounced. However, all data from clinical trials showed that significant and clinically relevant protection over time was preserved. Moreover, regular treatment with formoterol was not followed by an increase in "rebound" hyperresponsiveness.

- There was no evidence for gender-related differences in various efficacy outcomes. No differences in bronchodilator effects were observed in subgroups by age (12-18, 19-64, ≥ 65), race (Caucasian, African-American) or concomitant use of corticosteroids or theophylline. The number of patients in several subgroups though was too small to reach definitive conclusions.

- The advantage of the 24 mcg dose over the 12 mcg dose seemed to be somewhat more pronounced in patients with more severe disease, although this was more obvious on day one than with subsequent measurements.

- Formoterol at its recommended dose of 12 mcg was not different from albuterol MDI 180 mcg/salbutamol DP 400 mcg for peak bronchodilator effect. While the onset of action was similar between both compounds, formoterol's duration of action was longer. At 6 hours post-dose, the FEV_1 mean change from baseline for albuterol was largely indistinguishable from placebo, supporting the concept that the duration of action of albuterol is shorter than its dosing interval (6 hours). Formoterol 12 and 24 mcg was superior to placebo for pre-dose AM and PM PEF. In contrast, albuterol tended to be worse than placebo in many instances.

- Formoterol 12 and 24 mcg was superior to both regular maintenance and on-demand treatment with albuterol. Formoterol 12 and 24 mcg were more effective in improving morning PEF and nocturnal asthma symptoms scores compared to albuterol.

- Formoterol 12 and 24 mcg provided similar protection against exercise induced bronchoconstriction (EIB) compared to albuterol at 15 minutes, but was significantly superior at 4, 8 and 12 hours.

- Formoterol 12 and 24 mcg were effective in reversing methacholine-induced bronchoconstriction within 2 minutes post-dose. The effect was similar between both formoterol doses and albuterol up to 90 minutes post-dose.

- The protective effect of formoterol 12 mcg and formoterol 24 mcg as assessed by a methacholine challenge was similar.

- A single dose of 24 mcg of formoterol provided protection against the allergen-induced late asthmatic reaction for at least 32 hours. While there was no convincing evidence in support of anti-inflammatory effects, no evidence for pro-inflammatory effects was found either.

A meta-analysis of the pivotal and non-pivotal studies generally supported the conclusions summarized above.

The conclusions supported by the studies of formoterol performed in children 6 – 12 years of age were similar overall. The duration of the bronchodilator effect of formoterol 12 and 24 mcg was 10 - 12 hours as opposed to more than 12 hours in adults. As is adults, formoterol 6 mcg appeared less effective. Conclusions on comparisons with albuterol and the effect on exercise-induced bronchoconstriction were similar to the conclusions summarized above for adults. A more recently conducted study generally supported the conclusions drawn from previous trials, showing significant bronchodilation at 5 minutes. Trends favored both active groups with regards to asthma exacerbations.

6.3   Efficacy in COPD

Formoterol is also approved for the treatment of COPD. Two large pivotal studies in 770 and 824 patients were conducted comparing formoterol 12 mcg b.i.d., formoterol 24 mcg twice, placebo and ipratropium (Study 056) or theophylline (Study 058). Study 056 was a 12 week study and Study 058 was a 12-month study.

Study 056 showed significant efficacy for the primary endpoint, FEV_1AUC, the improvements were 194 mL and 223 mL for 24 and 12 mcg b.i.d., respectively.

- It showed statistically significant and clinically relevant improvements in reversible and irreversible populations.

- Significant improvements were also observed for IVC, FVC AUC and morning premedication PEF, for total diary scores, number of puffs of rescue medication and percentage of bad days. Quality of Life as assessed by the St. Georges Respiratory Questionnaire (SGRQ), showed for the 12 mcg group both statistically significant and clinically relevant improvements as compared with placebo.

- Formoterol was superior to ipratropium for the primary endpoint and many secondary endpoints.

The efficacy conclusions for Study 058 were similar. The estimated improvements in FEV_1AUC were 208 and 200 mL for formoterol 24 and 12 mcg, respectively. Significant improvements over placebo were also seen for post-medication FEV_1, pre-medication IVC, FVCAUC, morning pre-medication PEF and the mean number of puffs of rescue medication. Quality of Life, as measured by the SGRQ, was statistically significantly improved in all areas (total, symptoms, activity and impacts) for formoterol 12 mcg b.i.d. when compared to placebo after 6 months of treatment, and for both impact and total scores for 24 mcg b.i.d.. Clinically relevant improvements in the symptoms score were seen in the formoterol 12 mcg b.i.d. treatment group at both 6 and 12 months and in the impacts score for the formoterol 24 mcg b.i.d. treatment group at 12 months.

- In Study 058, both doses were also significantly superior to theophylline.

6.4   Conclusions

Formoterol and other LABAs have clinically important benefits which have changed the treatment of asthma and COPD. Inhaled beta$_2$-agonists are the most effective bronchodilators in asthma. While formoterol has similar peak effects on FEV_1 and onset of action compared to SABAs, its duration of action avoids the variability of lung function which can occur with the use of shorter acting beta agonists over the course of a day. They also provide bronchodilation when it is needed most, in the early morning hours, when a significant decline in lung function occurs in most patients. In addition, significant improvements in daytime asthma symptom scores, nocturnal asthma score, morning and evening rescue medication use and, importantly, frequency of asthma exacerbations has been demonstrated. Similar and consistent effects on these endpoints have not been demonstrated with SABAs.

In COPD, formoterol provides statistically significant and clinically relevant bronchodilator effects in both "reversible" and "irreversible" populations. The bronchodilator effects were significantly larger than those with ipratropium and theophylline. Statistically significant

improvements were also noted for other lung function parameters including IVC, FVC and PEF. While generally this effect has not been seen with SABAs, significant effects on symptoms, on the use of rescue medication and statistically significant and clinically relevant improvements in quality of life as assessed by the SGRQ have been observed with formoterol.

6.5   References

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7   Review of pre-clinical, clinical pharmacology, and pharmacogenetic studies

7.1   Molecular Structure

Although salmeterol and formoterol both exhibit long (12 hour) durations of action, they differ in molecular structure. Both molecules bind to the active site of the beta$_2$-adenorecptor, and both are lipophilic, which contributes to their long duration of action. Salmeterol has a lipophilic domain which differs in structure from formoterol. This lipophilic domain has been demonstrated to bind to a site termed the exosite, which is separate from the active site of the receptor. The exosite has been identified by directed mutagenesis [Green 1996]. While formoterol is also lipophilic, it does not bind to the salmeterol exosite [Green 1996].

7.2   *In Vitro* Pharmacology

The mechanisms by which formoterol and salmeterol act on their molecular target are further distinguished by their characteristic *in vitro* efficacy dose-response profiles. Formoterol is a full agonist that demonstrates 90% of the maximal efficacy response relative to isoprenaline in transfected cells. Salmeterol is a partial agonist that demonstrates 38% of the maximal efficacy response relative to isoprenaline [Leighton-Davies 2005]. Their relaxant effect profiles on isolated human bronchi differ as well; formoterol does not decrease the potency of isoprenaline while salmeterol decreases the relaxant effect of this model asthma-rescue medication in a significant manner [Naline 2005].

7.3   Primate Model Studies

Consistent with the full versus partial agonist profiles exhibited *in vitro,* in Rhesus monkeys, formoterol is more efficacious than salmeterol in inhibiting bronchoconstriction. In addition, the increase in heart rate induced by salmeterol is greater than that of formoterol [Fozard 2001].

7.4 Pharmacogenetics

Certain genetic variants have been reported to be associated with a loss of responsiveness to beta$_2$-agonists (both short- and long-acting) in asthma patients taking these drugs on a daily basis over a period of several weeks [Israel 2001; Wechsler 2004; Green 2004; Israel 2004]. Specifically, patients homozygous for Arginine (Arg) as opposed to Glycine (Gly) at amino acid position 16 of the beta$_2$-adenoreceptor were reported to exhibit a decrease in morning PEF over time. Such results were observed in primarily retrospective studies where patients were taking albuterol, salmeterol, or salmeterol and inhaled corticosteroids. In general, the pharmacogenetic findings have not been reliably reproduced; however, some studies may have been underpowered to identify a true pharmacogenetic effect. Nevertheless, it has been hypothesized that a loss of responsiveness to salmeterol in a genetically defined sub-population of patients may be an underlying cause of the higher rate of asthma-related SAEs observed in the SMART trial. To determine whether polymorphisms in the beta$_2$-adenoreceptor have an effect on responsiveness to formoterol, the available genetic data from the two largest efficacy trials comprising the clinical program for formoterol Certihaler (F2302 and F2303) were analyzed. The analysis failed to reveal a genetic influence on loss of responsiveness to daily treatment with beta agonists over time. It should be noted that a systematic comparison of the different beta agonists in a trial designed to address this question has not been published to date. It is concluded, therefore, that any association between genetic variation and loss of responsiveness to beta agonists is unclear at the present time.

7.5 *In Vitro* Genetic Experiments

In an effort to better understand the hypothesis that genetic variation in the beta$_2$ receptor causes a loss in responsiveness to beta agonists over time, the efficacy of drug treatments in isolated cells expressing either of the two of most common genetic variants of the beta 2 adrenergic receptor was characterized. In transfected cells formoterol was equally efficacious, while salmeterol was less efficacious in the cells expressing the Arg/Arg phenotype. In primary human airway smooth muscle cells, formoterol was as effective in the Arg/Arg variant as in the Gly/Gly version, while salmeterol's effect was too low to measure an accurate difference between the variants. Further work needs to be done to understand the potential underlying cause for the published observations that patients homozygous for Arginine at codon position 16 of the beta$_2$-adenoreceptor exhibit a loss of responsiveness to certain of the beta agonists over time.

7.6 Systemic Exposure

Systemic side effects of beta$_2$-agonists depend on their concentration in the blood circulation. Both formoterol and salmeterol are present at very low concentrations; therefore, limited data are available. Based on information on salmeterol in the US product information for Serevent[®] Diskus[®] (inhalation powder) [Serevent Diskus package insert (PI)] [Cazzola 2002] and on formoterol delivered by Foradil Aerolizer [Foradil Aerolizer PI] [Lecaillon 1999] or Certihaler Inhaler [Clinical Pharmacology Report Study 2303], peak plasma concentrations per mcg dose are larger for salmeterol compared to formoterol by approximately 2 to 4-fold. However, dose-normalized AUCs, which are representative of the overall systemic exposure at steady state, are more similar for the two compounds [Kempsford 2005] [Lecaillon 1999] [Clinical Pharmacology Report Study 2303].

In order to compare the systemic exposure of two drugs of the same class, it is important to note the relative potency of the two compounds, as well as the therapeutic doses. The therapeutic dose for salmeterol of 50 mcg b.i.d. is about 4-fold greater than for formoterol Aerolizer, at 12 mcg b.i.d.. This difference in dose reflects a corresponding difference in potency, thus the therapeutic effect following 50 mcg salmeterol should be about the same as that following 12 mcg formoterol. When the potency of formoterol and salmeterol for systemic effects was compared in healthy subjects [Guhan 2000], the authors concluded that the 4-fold difference in the recommended doses of formoterol and salmeterol reflects their relative dose potency for systemic effects over four hours post-dose. Salmeterol was noted to have more prolonged systemic effects than formoterol, in the 8-hour period studied.

Formoterol and salmeterol also differ in their mode of elimination. Salmeterol is almost exclusively eliminated by metabolism, [Serevent Diskus PI]; with oxidation via cytochrome P450 3A4 (CYP3A4) as the major route of metabolism [Cazzola 2002]. The following statement appears in the US PI: "Since salmeterol is predominantly cleared by hepatic metabolism, liver function impairment may lead to accumulation of salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored." [Serevent Diskus PI]. Likewise, concomitant administration of drugs which inhibit CYP3A4 may produce increased systemic exposure to salmeterol.

For formoterol, metabolism is the main route of elimination, but the compound is also excreted unchanged in the urine. Direct glucuronidation is the most prominent pathway of biotransformation, O-demethylation followed by conjugation is the second major pathway [Foradil Aerolizer PI]. Since multiple isozymes catalyze the glucuronidation (UGT1A1, 1A3, 1A6, 1A7, 1A8, 1A9, 1A10, 2B7 and 2B15) and O-demethylation (CYP2D6, 2C19, 2C9 and 2A6) of formoterol [PCS(EU) R0101616] [Report DMET(EU) 26/1996], there is a low potential for drug-drug interaction by inhibition of specific isozymes involved in formoterol metabolism. Thus, formoterol pharmacokinetics is expected to be less affected by concomitant medications or hepatic impairment than salmeterol.

7.7 Potency and intrinsic efficacy

Formoterol is a more potent inducer of beta$_2$-adrenergic activity than salmeterol [Kallstrom 1994]. This is consistent with the corresponding relative bronchodilator potencies of LABAs in asthmatics [Palmqvist 1999]. In vitro studies on animal and human bronchial tissue preparations show that formoterol also has higher efficacy than salmeterol at relaxing smooth muscle [Kallstrom 1994] [Naline 1994] [Ellis 1995] [Scott 1999] [Molimard 1998].

Formoterol is a full agonist and thus requires lower receptor occupancy to provide full effect. This may provide better bronchodilator efficacy in patients with poor function when overall bronchial drug deposition is potentially lower and due to less penetration into constricted peripheral airways. It is also expected to provide better efficacy in the presence of bronchoconstrictive stimuli. Increasing doses of formoterol have been observed to provide increasing levels of protection against bronchoconstriction elicited by a methacholine challenge, whereas much less increase and less maximal effect was observed for increasing doses of salmeterol [Palmqvist 1999].

7.8   High-dose systemic effects

As a beta$_2$-agonist, formoterol is expected to exert various extrapulmonary effects on beta$_2$-adenoreceptors located throughout the body. Two studies have been conducted to compare the safety and tolerability of high doses of formoterol and albuterol in subjects with asthma and in subjects with COPD. In order to examine the systemic side effects of the two drugs, supra-therapeutic doses were administered, over a period of three days. The formoterol and albuterol doses for comparison in each study were multiples of existing recommendations for the therapeutic dose, and thus differed in the two patient populations.

Both studies used a 2-period, randomized, double-blind, double-dummy, crossover design. Study G0701 compared a total daily dose of 108 mcg formoterol by Aerolizer (36 mcg t.i.d.) for 3 days with a total daily dose of 1800 mcg albuterol by MDI (600 mcg t.i.d.) for 3 days in 16 patients with mild persistent asthma, [Kruse 2005] [Clinical Pharmacology Study Report G0701]. Study G0702 compared a total daily dose of 96 mcg formoterol by Aerolizer (24 mcg q.i.d.) for 3 days with a total daily dose of 2,400 mcg albuterol by MDI (600 mcg q.i.d.) for 3 days in 16 patients with mild to moderate COPD, [Clinical Pharmacology Study Report G0702].

Although the doses were intended to be therapeutically equivalent, the FEV$_1$AUC over the 3-day period during formoterol treatment was greater than for albuterol treatment, indicating that that the doses of formoterol given were actually greater in pharmacodynamic effect than those of albuterol in both studies. Likewise, some of the systemic effects were slightly greater as well; for QTc, potassium, and pulse rate the differences were statistically significant at some time during both studies. Both high dose formoterol and albuterol treatments were safe and well tolerated in both studies, and there were no serious adverse events or discontinuations due to adverse events. Although administration of such supra-therapeutic doses was not recommended, they were assessed not to pose any safety risk when given over 3-days for either drug.

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8 Benefit-risk assessment

8.1 Summary of benefits

This section summarizes the efficacy of formoterol (Foradil). Formoterol is a highly selective beta$_2$-agonist. In the clinic, administration of beta$_2$-agonists by inhalation, allowing delivery of the dose directly to the site of action in the bronchi, has advantages over oral administration. Inhalation provides efficacy with a lower dose than would be required with systemic administration and a consequent reduction in the incidence of systemic side effects would be expected.

An analysis of the efficacy of Foradil inhalation based on data from more than 40 trials is included in this briefing book. This analysis shows that Foradil is effective in the treatment of patients 5 years of age and older with asthma, including patients with nocturnal asthma symptoms, and for the prevention of exercise-induced bronchospasm. In addition, data is provided showing the efficacy of formoterol in the treatment of adults with COPD.

Asthma

Foradil delivered by inhalation to patients with asthma in doses of 12 mcg and 24 mcg produces clinically effective bronchodilation comparable to albuterol and has a duration of action of at least 12 hours. Maximum bronchodilation is achieved within two hours. Foradil therefore differs from currently-marketed long-acting or short-acting bronchodilators.

Foradil, administered in dosages of 12 mcg b.i.d. and 24 mcg b.i.d. via Aerolizer was shown to be effective for the treatment of asthma in adolescent and adult patients (5 years of age and older), improving pulmonary function as measured by spirometry and peak expiratory flow

rate (PEFR), decreasing the daytime and nighttime symptoms, and reducing rescue medication requirements. Clinical trials evaluating the long-term usage of formoterol over periods of six to fifteen months demonstrated that efficacy is well-maintained. Regular treatment with formoterol is not followed by a rebound increase in bronchial hyper-responsiveness after cessation of therapy. The bronchodilator effect of formoterol does not vary in subgroups of patients defined by gender, age (12-18, 19-64, $\geq$ 65 years), race, or concomitant usage of corticosteroids or theophylline. In most patients 5 years of age and older with asthma, formoterol 12 mcg b.i.d. provides effective treatment. The bronchodilator dose-response of the 24 mcg dose seems to be greater than the 12 mcg dose in some patients with more severe disease.

In clinical trials in adolescents and adults with asthma comparing formoterol capsules for inhalation with the short-acting beta$_2$-agonist albuterol, formoterol demonstrated a similar onset, but significantly longer duration of action, which resulted in better control of nocturnal asthma symptoms and greater improvements in morning PEFR measurements.

Foradil via the Certihaler Inhaler, at doses of 10 mcg b.i.d. was shown to be effective in two dose finding studies and three large pivotal phase 3 studies, leading to clinically relevant increases compared to placebo in 12-hour AUC of FEV$_1$ after 12 weeks of treatment. Secondary efficacy analyses, including serial FEV$_1$ measurements, morning PEF, asthma symptom scores and rescue use, supported the primary analyses. No bronchodilatory tolerance was observed after 3 months of treatment. In addition, in two pivotal phase 3 studies (F2302 and F2303), the bronchodilatory response of Foradil via the Certihaler Inhaler was shown to be superior to that of placebo with respect to primary and secondary variables. In dose ranging studies, doses of Foradil delivered via Aerolizer (12 mcg b.i.d.) were observed to be comparable to those delivered via the Certihaler Inhaler (10 mcg b.i.d.) in adults and children.

Exercise-induced bronchospasm

In clinical trials evaluating efficacy in the prevention of exercise-induced bronchospasm in adult and adolescent patients, it was shown that a single 12 or 24 mcg dose (via Aerolizer) provided significant protection against exercise-induced bronchospasm (EIB). The bronchoprotective effect of formoterol in EIB lasts for up to 12 hours. The bronchoprotective effect of formoterol in EIB is comparable to that of albuterol at 15 minutes after dosing, but significantly superior at 4, 8, and 12 hours.

Pediatrics

In children (ages 5-17 years), formoterol inhalation capsules administered 12 mcg b.i.d. is effective for the treatment of asthma, and is superior to albuterol in the improvement of morning PEFR. The therapeutic efficacy of formoterol in the treatment of asthma in children is maintained over fifteen months of treatment. A single dose of formoterol inhalation capsules 12 mcg provided significant protection against exercise-induced bronchospasm (EIB) in children which lasted for up to 12 hours. The bronchoprotective effect of formoterol against EIB was comparable to that of albuterol at 3 hours after dosing, but significantly superior at 12 hours. Similar results were seen when Foradil was administered via the Certihaler Inhaler.

COPD

COPD alone is the fourth leading cause of death in the United States, with approximately 14 million people currently affected and projected to increase in prevalence. Impairment of respiratory function can lead to disabling symptoms and adversely impact quality of life in generally older patients who are often concomitantly treated with multiple medications due to co-morbidities. Bronchodilation is a mainstay of treatment. In clinical studies Foradil administered via the Aerolizer Inhaler at a dose of 12 mcg or 24 mcg b.i.d. in COPD demonstrated onset of action within 5 minutes and long duration of action (12 hours). There was no substantive tachyphylaxis over a period of 12 months of treatment. Both doses yielded clinically meaningful and statistically significant improvement in lung function in moderate to severe COPD treated for 3 months or 12 months as assessed by FEV_1AUC assessed by serial spirometry, FEV_1 at each time point measured, FVC AUC over 12 hours, IVC, morning PEF, symptom scores and use of rescue medication. Though the degree of improvement varied in groups defined by degree of reversibility, efficacy was established in both reversible as well as poorly reversible patients. Subgroup analysis of elderly subjects ($\geq$ 65 years) showed improvements that that were consistent with those observed in the total study population.

In a study comparing Foradil Aerolizer to an active comparator, Foradil 12 and 24 mcg b.i.d. demonstrated superiority over ipratropium as defined by time to bronchodilation endpoint and bronchodilator efficacy over 12 hours. In addition, equal or superior efficacy was demonstrated in a study compared to theophylline. Durability of effect was demonstrated in a study over one year. Patient discontinuations rates were lower with formoterol compared to theophylline or placebo and no withdrawal effects were noted in formoterol patients who discontinued.

In the 12-month study, quality of life improvements compared to placebo were demonstrated at 3, 6 and 12 months using the St. George's Respiratory Questionnaire (SGRQ) that were statistically significant for the majority of measures that included individual domain and total scores. Additional outcomes of importance tested in this study included improvement in hospitalization rates compared to placebo, a lower rate of premature discontinuations compared to placebo or theophylline, and significantly less additional therapy compared to placebo.

8.2   Summary of risks

An analysis of the safety of formoterol has been provided in this briefing book. The preclinical data, pharmacokinetic and pharmacodynamic (PK/PD) profile, and preclinical toxicology results relevant to the characterization of the safety and tolerability of formoterol are reviewed. In addition, analysis of safety data from clinical trials sponsored by Novartis, published reports of clinical trials conducted by others, and spontaneous safety reports from the U.S. and worldwide where Foradil is marketed was performed.

The major theoretical risk of beta$_2$-agonists in patients with COPD and asthma relates to serious cardiac effects. Respiratory alkalosis and hypoxemia, which can be observed in acute exacerbations of these conditions can directly increase myocardial susceptibility to arrhythmia. Respiratory acidosis can increase pulmonary artery pressures, leading to afterload increases impacting the not uncommonly overloaded right heart circuit which can

also provoke arrhythmias. This later possibility is especially relevant in the COPD population. Since beta$_2$-agonists can also theoretically increase myocardial irritability, detailed study of the potential for these effects was examined in COPD patients treated with 12 mcg b.i.d. of formoterol using Holter monitoring (Study D2308). Results showed no clinically important changes in QTc interval or cardiac rhythm.

In asthmatics, concerns about the potential for beta$_2$-agonists to increase asthma-related serious adverse events, including formoterol, especially when given at high doses, led to the design of protocol D2307. The primary outcome measure was the incidence of serious asthma-related adverse events in a study conducted over 4 months involving over 2000 patients. Treatment groups included Foradil 12 mcg b.i.d. (n=527), Foradil 24 mcg (n=527) and placebo (n=514). An additional open label arm of 517 patients was included to examine the effect of increasing by up to 2 doses of Foradil as needed above the baseline dose of 12 mcg b.i.d. on the primary outcome measure of incidence of asthma-related SAEs. Results showed no significant difference in asthma-related SAEs among the 24 mcg b.i.d., placebo and intermediate dose groups with a somewhat higher incidence (although not statistically significant) in the lower 12 mcg b.i.d. group. The latter was small and was not considered clinically meaningfully different from results seen in the other groups. When comparing the 12 and 24 mcg b.i.d. doses in terms of asthma exacerbations requiring systemic corticosteroid (oral or parenteral), there was no significant difference. In addition, the incidence of asthma-related adverse events (of non-serious nature), was highest in the placebo group and there were no significant differences between 12 and 24 mcg b.i.d. doses in terms of this outcome. Moreover, no meaningful differences were observed among treatment groups for cardiac disorders.

Analysis of the multiple-dose, placebo-controlled database of Foradil studies conducted by Novartis (>6,000 patients) showed that although the rate of asthma-related serious adverse events and premature discontinuations due to asthma-related adverse event was similar when comparing Foradil at all doses (8.7 events per 100 patient-years), Foradil 20/24 mcg total daily dose (TDD; 7.1/100 p-yr), Foradil 48 mcg TDD (10.9/100 p-yr), placebo (as needed albuterol; 10.9/100 p-yr) and regularly dosed albuterol (not prn; 9.4/100 p-yr). In addition, the proportion of patients using rescue corticosteroids or theophylline was higher in the placebo-treated arms and patients in the placebo groups presented with asthma-related serious adverse event and premature discontinuation due to asthma-related adverse events earlier than Foradil-treated groups. Cardiovascular SAEs were similar in groups treated with Foradil at 20 or 24 mcg TDD, 48 mcg TDD and placebo (0.4, 0.4, 0.5 n/100 p-yr, respectively) and was higher in groups treated with regular doses of albuterol (1.7/100 p-yr). The rates for all deaths or categorized as asthma- or cardiac-related deaths did not differ among Foradil-treated (n=5,907), albuterol-treated (n=1,238) or placebo-treated (n=2,446) groups.

Using data from the FDA AERS, a detailed epidemiologic assessment of spontaneous reports of deaths and of respiratory symptoms was conducted on a database representing greater than 10,000,000 person-years of exposure to formoterol. The analysis showed worldwide reporting proportions of deaths and respiratory symptoms that were similar to albuterol and salmeterol. If this analysis is adjusted to focus on the relative rates of reporting of these events in the three years each of these drugs was on the US market, the formoterol rates are approximately 50% of the rate for salmeterol.

Analysis of the combined clinical database of COPD trials conducted by Novartis showed a decrease in COPD-related adverse events on Foradil (individual or all doses combined) that was approximately half the rate of groups treated with placebo. Assessment of spontaneous reports of respiratory symptoms or death in Foradil-treated patients compared to albuterol- or salmeterol-treated patients also confirmed this observation using post-marketing surveillance databases.

8.3 Conclusions

The overall findings of this extensive safety analysis indicate that Foradil has a safety profile which is comparable to that of regularly-dosed albuterol and similar to placebo groups where albuterol was used on an as-needed basis. Where possible, relying on post-marketing surveillance, a comparison to salmeterol has been provided.

Though the results of these analyses, based on studies where salmeterol and Foradil were never directly compared must be interpreted with caution, the safety profile of Foradil appears to be superior to salmeterol. This suggests that the long-acting beta$_2$-agonists may not all be the same in terms of side effect profiles, which may reflect other well-established differences in molecular structure, receptor binding, degree of receptor antagonism and bronchodilator effects, outlined in the pharmacology, pre-clinical and clinical sections.

Moreover, clinical experience has demonstrated no clinically meaningful safety signal on detailed analysis of the safety database based on clinical studies involving nearly 6,000 patients treated with Foradil and spontaneous reports compiled after 5 years on the US market representing over 10,000,000 person-years of exposure.

In view of all of the evidence, the favorable benefit-risk ratio supports the continued use of formoterol in the treatment of patients with asthma and COPD.

9   Appendices

Appendix 1   List of pre-defined terms

Appendix 2   AE terms from FDA AERS