

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-457

MEDICAL REVIEW(S)

DIVISION DIRECTOR'S MEMORANDUM

Date: October 29, 2004

To: NDA 21-457

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Drug products, HFD-570

Product: Albuterol sulfate HFA Inhalation Aerosol

Applicant: Ivax Research, Inc.

This memorandum comments on the review findings of the complete response to our previous approvable action taken on this application on November 28, 2003. Detailed review of the submission can be found in Dr. Shah's review of the CMC section, and in Dr. Starke's summary clinical review. The application was not approved in the previous cycle because of outstanding CMC issues. The CMC issues are now resolved and there are no outstanding issues from other disciplines. Therefore, the action on this application will be an APPROVAL.

My previous memorandum that summarizes the whole development program for this application is appended to this summary.

One of the major CMC issues that precluded approval in the previous cycle was that the applicant did not provide adequate controls for the drug substance particle size distribution. The applicant has now provided adequate controls, and has specification and acceptance criteria on various critical parameters that are reflective of the data. There are two other points from CMC that are worth noting. First, the expiry dating period will be 15 months rather than [REDACTED] which was sought by IVAX. The stability data submitted by IVAX was limited and could only justify the 15 month expiry period. Second, the drug product has [REDACTED] leachables [REDACTED] that IVAX will qualify post-approval. Post-approval qualification of these leachables are reasonable because the same product has been marked in other countries for a number of years, and other products have the same [REDACTED] as that are used in this product.

The product label was extensively reviewed by all disciplines of this Division. The Division and IVAX have agreed on a final labeling text. The labeling is similar to other albuterol products. Unfortunately, IVAX has not yet proposed a proprietary name that is acceptable to the Agency. The previous proprietary names Volare [REDACTED] and the new proprietary name [REDACTED] was not found acceptable by DDMETS of Office of Drug Safety.

This is review of the complete response to an Approvable action taken on November 28, 2003 for a 505(b)(2) NDA application (NDA 21-457, N-000, January 31, 2003) from IVAX Research, Inc., of Miami, Florida. The drug product is a pressurized metered dose inhaler (pMDI) formulation of racemic albuterol sulfate with a hydrofluoroalkane (HFA-134a) propellant. The drug product was developed and will be manufactured by Ivax Pharmaceuticals, Inc., located in Waterford, Ireland, a wholly owned subsidiary of IVAX Corporation. The active comparator drug product used in the clinical trials in support of the application was Proventil HFA Inhalation Aerosol.

As of the previous action, the remaining unresolved issues were drug product quality (CMC), trade name, and labeling issues. From a clinical perspective, the drug product was considered as having satisfied all the clinical requirements for approval in the first cycle. Other than completion of the labeling, there were no remaining clinical issues to be addressed in this cycle. All issues were addressed in this cycle, as discussed below. Therefore, I recommend that this product be Approved on this cycle.

Drug product quality (CMC) issues: Issues pertaining to the quality assurance of the drug product were the main reason that precluded approval in the first cycle. These issues included specifications for the drug substance particle size, stability testing of the drug product, and qualification of leachables from the valve and its components (valve gasket, case, etc.). In this application, all issues were resolved or agreements were made for post-approval submission of several CMC validations, methodologies, qualifications, etc. within specified time periods, as outlined in a fax of October 21, 2004, and agreed to in a teleconference of October 25, 2004. A dose counter is not included in this drug product. This will be addressed by the applicant in future submissions.

Drug substance issues were resolved. Stability data supported 15 months of dating rather than the requested _____, when stored up to 25°C. Criteria for dose content uniformity (DCU) data were agreed upon. APSD acceptance criteria and Cascade Impactor stage groupings _____ were agreed upon. A time commitment for submission of test methodology and acceptance criteria for identification and quantification of foreign particulate matter were agreed upon. The main issue in this cycle, however, was the acceptance criteria for leachables. _____ leachables _____ were considered to be above the qualification limit, which carries an arbitrary cutoff of _____ MDI when no preclinical information is available. It was noted that this same IVAX product is marketed in Europe and many other parts of the world. In addition, other approved products have used the same valve and valve gasket and may have similar leachables, and may or may not be qualified, but IVAX does not have access to that data. The Division, therefore, considered the available human safety information in making a determination to allow qualification of these leachables in the post-marketing setting. Qualification of the _____ leachables in question will require a 90-day preclinical study in a single species. A validated test methodology for quantitative determination of leachables and extractables will be submitted.

Trade Name: _____



Labeling: Labeling was addressed in this cycle, and revised labeling for the package insert (PI) and patient leaflet were agreed upon. Please see the FDA fax dated October 26, 2004 and the IVAX fax/email dated October 28, 2004 for the latest PI, patient leaflet, carton, label, and actuator design labels. Several specifics should be noted about the label for this drug product. We reviewed the labels from all currently approved albuterol HFA drug products for best-practice and most accurate wording rendition, and the labeling language for this PI was modified as deemed appropriate. Previous albuterol HFA inhalational aerosol drug products have resulted from a CFC to HFA "switch" development program, and the clinical trials therefore included the same manufacturer's CFC drug product. For those labels, the Division included efficacy information from the CMC drug product to assure the medical community that switching from the CFC to the HFA formulation would not result in any loss of efficacy. This was the first instance of an albuterol HFA inhalation aerosol development program with the active comparator in the clinical trials being a different manufacturer's albuterol HFA inhalational aerosol. After careful consideration, the Division felt that inclusion of the clinical trial results for the "active comparator HFA-134a albuterol inhaler" was appropriate and necessary, again to assure the medical community re efficacy of this drug product. Language was included in the PI to discourage patients or physicians from interchanging this drug product's actuator or canister with the actuator or canister from any other inhalational aerosol drug products.

DIVISION DIRECTOR'S MEMORANDUM

Date: November 28, 2003
To: NDA 21-457
From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Drug products, HFD-570
Product: Volare HFA (albuterol sulfate) Inhalation Aerosol
Applicant: Ivax Research, Inc.,

Administrative, Introduction, and Regulatory History

Ivax Research submitted NDA 21-457 for Volare HFA Inhalation Aerosol as a 505(b)(2) application for the treatment or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease

The NDA was received by the Agency on January 31, 2003. The PDUFA due date on this application is November 30, 2003. At present there are two approved HFA based albuterol products in the United States, Schering's Proventil HFA, and GSK's Ventolin HFA. When approved, Volare HFA would provide patients with another choice of non-CFC based albuterol for inhalation use. This drug product was originally developed by Zenith Goldline

At the same time the applicant (subsequently changed to Ivax) decided to change the actuator design to make this drug product identical to the one that is currently approved in the United Kingdom. The actuator orifice size of 0.22 mm. This change increased the respirable dose to 50% and the respirable fraction to 0.60.

The Division and the applicant had met on several occasions, and discussed and agreed upon a clinical program that would support filing of a NDA application. The clinical program consists of eight studies, of which four are considered to be pivotal. These studies support the approval of this application. However, there are several outstanding chemistry and manufacturing issues that will preclude approval of this application in this review cycle.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

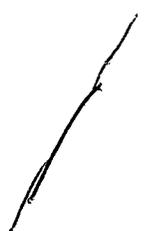
The active component of Volare Inhalation Aerosol is albuterol sulfate. The formulation for this suspension uses HFA-134a (1,1,1,2-tetrafluoroethane). This propellant has minimal or no ozone-depleting potential. The drug product _____

_____ The CMC review team has identified several deficiencies that will preclude approval of this application at this review cycle. The CMC review team has recommended an approvable action because of these deficiencies, and I concur with the recommendation. One of the major deficiency relate to lack of control of particle size distribution. The applicant has not provided adequate controls for the drug substance particle size distribution _____ This parameter is important because aerodynamic particle size distribution of the emitted dose is linked to control at the drug substance properties. There are other deficiencies relating to impurity specification, stability data, and control of drug substance and drug product manufacturing process. These are detailed in CMC discipline review. In addition, the site involved in micronization of the drug substance is not scheduled for inspection until December 15, 2003. The site is located _____

Clinical and Statistical

The clinical program was based on eight studies of which four are considered to be pivotal. Two of the pivotal studies (BNP-301-4-167, and BNP-301-4-105) supported efficacy and safety, and two (IX-101-105, and IXR-107-1-105) supported only safety. BNP-301-4-167 was a six-week, randomized, placebo-controlled multiple dose study. BNP301-4-105 was a randomized, placebo-controlled single dose crossover study. Both studies included Proventil HFA as an active comparator. IX-101-105 was an ex-US 12-week safety study using a related breath-operated device (Volare HFA BOI), but included PEFr as an efficacy measure. IXR-107-1-105 was a three-period cumulative dose crossover safety study. The submitted studies are reviewed in detailed in Dr. Starke's excellent review. Based on the review of the submitted data, Dr. Starke concluded that the applicant has demonstrated Volare HFA to be consistency superior to placebo and reasonably comparable to Proventil HFA and has recommended approval, and I concur with his conclusion and recommendation.

Studies BNP-301-4-167 and BNP-301-4-105 has showed that Volare HFA at a dose of 180 mcg demonstrates efficacy compared to placebo with a net increase in FEV1 AUC 0-6hr in the range of 1.04 to 1.14 L.Hr in mild to moderate asthmatics. The serial FEV1 curve also demonstrated consistent efficacy over placebo and comparable to Proventil HFA. There were no safety issues identified in the clinical studies.



Clinical Pharmacology and Biopharmaceutics, and Clinical

There are no outstanding clinical pharmacology issues with this application. Pharmacokinetic analyses show that systemic exposure to albuterol delivered by Volare HFA was comparable to that delivered by Proventil HFA. The Office of Clinical Pharmacology and Biopharmaceutics reviewer has recommended approval of this application, and I concur with this recommendation.

Pharmacology and Toxicology

The applicant did not conduct any new preclinical studies for this application because albuterol is a well studied and approved product and the applicant is referring the Agency's previous determination on albuterol under the 505(b)(2) paradigm. The applicant has right of reference to the HFA preclinical and other relevant data.

Data Quality, Integrity, and Financial Disclosure

The DSI conducted audit of three sites involved in study BNP-301-4-105 and four sites involved in study BNP-301-4-167. Two of the sites were common between the two studies. The DSI did not identify any major problem with the conduct of the studies in these sites that would preclude approval. Also during the review of the NDA no irregularities were identified that would question the quality of the data or data integrity. All studies were conducted in accordance with accepted ethical standards. No financial disclosure issues are present.

Pediatric Consideration

The applicant is proposing indication down to the age of 12 years for this product;

Product Name

will be addressed at a subsequent review cycle.

This issue

Labeling

The product label was not extensively reviewed in this cycle because the product is not heading towards approval. Ivax submitted a label that has language very similar to other approved albuterol labels, including Proventil HFA label. This is generally acceptable. The label that was submitted does not conform to the sections and heading outlined in 21 CFR 201.56(d). Ivax will be asked to resubmit the label conforming to the regulation.

Action

The clinical efficacy, safety, and pharmacokinetic data support approval of the application. There are outstanding CMC issues that need to be resolved before the application can be approved. Therefore, the action on this application will be APPROVABLE.

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Badrul Chowdhury
10/29/04 05:14:03 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION: NDA 21-457, N-000 **TRADE NAME:** Not available / Undecided
APPLICANT/SPONSOR: Ivax Research, Inc. **USAN NAME:** Albuterol sulfate HFA MDI
4400 Biscayne Boulevard
Miami, FL 33137
MEDICAL OFFICER: Peter Starke, MD **CATEGORY:** Beta agonist
DATE: 29 October 2004 **ROUTE:** Orally inhaled

SUBMISSIONS REVIEWED IN THIS DOCUMENT

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
15 March 2004			Complete response as of 30 April 2004
06 October 2004		Fax/email	Patient leaflet
19 October 2004		Fax/email	Revised Package Insert (PI) and patient leaflet
27 October 2004		Fax/email	Revised PI and patient leaflet
28 October 2004		Fax/email	Revised PI, patient leaflet, carton, label, and actuator design labels

RELATED APPLICATIONS

<u>Document Date</u>	<u>Application</u>	<u>Comments</u>
31 January 2003	NDA 21-457, N-000	First submission of NDA for Albuterol sulfate HFA pMDI NDA for Albuterol sulfate HFA pBOI

REVIEW SUMMARY:

This is review of the complete response to an Approvable action taken on November 28, 2003, for a 505(b)(2) NDA application from IVAX Research, Inc., of Miami, Florida. The drug product is a pressurized metered dose inhaler (pMDI) formulation of racemic albuterol sulfate with a hydrofluoroalkane (HFA) propellant. The drug product was developed and will be manufactured by Ivax Pharmaceuticals, Inc., located in Waterford, Ireland, a wholly owned subsidiary of IVAX Corporation. The active comparator drug product used in the clinical trials in support for the application was Proventil HFA Inhalation Aerosol. As of the previous action, the remaining unresolved issues were drug product quality (CMC), trade name, and labeling issues. Other than labeling, there were no clinical issues to be addressed in this cycle. All three issues were addressed in this cycle.

OUTSTANDING ISSUES:

Agreements for post-approval submission of several CMC validations, methodologies, qualifications, etc. within specified time periods, as outlined in a fax of October 21, 2004 and agreed to in a teleconference of October 25, 2004.

RECOMMENDED REGULATORY ACTION

NDA: X **APPROVAL** **APPROVABLE** **NOT APPROVABLE**
OTHER ACTION:

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION: NDA 021-457, N-000	TRADE NAME: Volare HFA Inhalation Aerosol
APPLICANT/SPONSOR: Ivax Research, Inc. 4400 Biscayne Boulevard Miami, FL 33137	USAN NAME: Albuterol sulfate HFA MDI
	CATEGORY: Bronchodilator
	ROUTE: Orally inhaled
MEDICAL OFFICER: Peter Starke, MD	PDUFA DATE: 30 November 2003
DIVISION DIRECTOR: Badrul Chowdhury, MD	REVIEW DATE: 21 November 2003

SUBMISSIONS REVIEWED IN THIS DOCUMENT

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
30 January 2003	31 January 2003		Paper NDA & electronic dataset submission
5 May 2003			Resubmission of electronic datasets
6 June 2003	9 June 2003		120-day safety update report
18 July 2003	21 July 2003	N-000 BM	Partial response to questions posed at teleconference of 9 July 2003.
5 August 2003	6 August 2003		Partial response to questions posed at teleconference of 9 July 2003 and answers to statistical questions of 25 July 2003.
7 August 2003	8 August 2003		Partial response to questions of 4 August 2003
29 August 2003	2 September 2003		Response to questions of 15 August 2003
15 October 2003			Request for proprietary or trade name change to

RELATED APPLICATIONS

<u>Document Date</u>	<u>Application</u>	<u>Comments</u>
		Albuterol sulfate HFA BOI

REVIEW SUMMARY:

This is a 505(b)(2) NDA application from IVAX Research, Inc., of Miami, Florida for a metered dose inhaler (MDI) formulation of racemic albuterol sulfate with an hydrofluoroalkane (HFA) propellant. While albuterol sulfate is the official generic name for the drug in the United States, the World Health Organization recommended name is salbutamol sulfate. The proposed trade name is Volare™ HFA (Albuterol Sulfate, USP) Inhalation Aerosol. While IVAX Research, Inc., of Miami, Florida submitted the application, Volare was developed and will be manufactured by Ivax Pharmaceuticals, Inc., located in Waterford, Ireland. Both companies are wholly owned subsidiaries of IVAX Corporation.

Four clinical trials are reviewed, two for efficacy and four for safety. All studies submitted were in support of the indication of treatment or prevention of bronchospasm with reversible obstructive airway disease in adults and children 12 years of age and older. While the clinical program to support marketing approval for Albuterol-HFA-MDI was small, the studies do support approval for this indication. Both studies BNP-301-4-167 and BNP-301-4-105 showed that Albuterol-HFA-MDI at a dose of 180 mcg (2 inhalations) demonstrates efficacy when compared to placebo, with a net increase in FEV₁ AUEC₀₋₆ in the range of 1.04 to 1.14 L•Hr in mild-to-moderate asthmatics. The clinical program supports comparable pharmacodynamics and clinical safety to the marketed Proventil HFA drug product. The PK study also appears to show comparability of systemic exposure between the HFA-MDI product and Proventil HFA. Tachyphylaxis was seen with chronic use, and was roughly similar for all drugs.

Evaluation of pharmacologic effects including systolic and diastolic blood pressure, serum glucose and potassium, and ECG parameters of heart rate, QT and QTc intervals revealed no unexpected or new safety information regarding the effects of albuterol or the specific drug products being evaluated.

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION: NDA 021-457, N-000	TRADE NAME: Volare HFA Inhalation Aerosol
APPLICANT/SPONSOR: Ivax Research, Inc. 4400 Biscayne Boulevard Miami, FL 33137	USAN NAME: Albuterol sulfate HFA MDI
	CATEGORY: Bronchodilator
	ROUTE: Orally inhaled
MEDICAL OFFICER: Peter Starke, MD	PDUFA DATE: 30 November 2003
DIVISION DIRECTOR: Badrul Chowdhury, MD	REVIEW DATE: 21 November 2003

Review Summary continued:

There were no unusual trends in adverse events in any of the studies, and no safety trends were identified during the course of this review. Safety was derived from combined clinical information for both the Albuterol-HFA-MDI and HFA-BOI drug products. While pharmacokinetic (PK) and pharmacodynamic (PD) parameters for the Albuterol-HFA-MDI drug product were comparable to the marketed drug product Proventil HFA, PK and PD parameters for the Albuterol-HFA-BOI drug product revealed less systemic exposure with the HFA-BOI than with the HFA-MDI drug product. However, differences were considered not significant with respect to the safety findings in the review, allowing review and inclusion of safety information from the HFA-BOI drug product in this application.

OUTSTANDING ISSUES:

CMC issues preclude approval on this cycle. These issues include specifications for the drug substance particle size and stability testing of the drug product. Please see the CMC review for further details.

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Adequacy of testing of device performance remains an open issue that has not been completely addressed by the applicant. As noted in the Device Performance section, eight patients were withdrawn from study BNP 301-4-167 due to an inhaler malfunction, of whom two of the malfunctions were in the MDI drug product, one of which contained active drug product and one contained placebo drug product. The defect analysis revealed that one (placebo) inhaler had malfunctioned due to a deformed actuator orifice, in turn due to excessive pressure that had been used to actuate canister. No problem could be found with the second (active) returned device. No information was provided for the six BOI canisters returned due to a malfunction.

~~_____~~

The proposed product label follows non-standard ordering for section headings. The product label should follow the order shown in 21 CFR 201.56(d)(1) and (2).

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS: <input checked="" type="checkbox"/> APPROVAL	<input type="checkbox"/> APPROVABLE	<input type="checkbox"/> NOT APPROVABLE
OTHER ACTION: <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

CLINICAL REVIEW

NDA 021-457, N-000, Volare HFA Inhalation Aerosol

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CLINICAL REVIEW OF NDA 021-457, N-000

EXECUTIVE SUMMARY

1. RECOMMENDATIONS

1.1. Recommendation on Approvability

It is recommended that this NDA for Albuterol HFA-MDI be approved for the indication of treatment or prevention of bronchospasm with reversible obstructive airway disease in adults and children 12 years of age and older. _____

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

One Phase 4 study is recommended. While all devices in the pivotal 6-week trial were inspected, and all patients completed a questionnaire, the number of devices evaluated for particle size distribution and delivery dose uniformity though life-of-the-device was limited to _____. It is suggested _____

2. SUMMARY OF CLINICAL FINDINGS

2.1. Background and Administrative Issues

This is a 505(b)(2) NDA application from IVAX Research, Inc., of Miami, Florida for a metered dose inhaler (MDI) formulation of racemic albuterol sulfate with an hydrofluoroalkane (HFA) propellant. While albuterol sulfate is the official generic name for the drug in the United States, the World Health Organization recommended name is salbutamol sulfate. While IVAX Research, Inc., of Miami, Florida is submitting the application, Albuterol-HFA-MDI was developed and will be manufactured by Ivax Pharmaceuticals, Inc., located in Waterford, Ireland. Both companies are wholly owned subsidiaries of IVAX Corporation. Albuterol-HFA-MDI is currently licensed for marketing in 32 countries worldwide.

Albuterol sulfate is a sympathomimetic amine with a primary effect on the lungs as a beta-adrenergic bronchodilator. The proposed indication is for the treatment or prevention of bronchospasm with reversible obstructive airway disease _____ in adults and children 12 years of age and older. The proposed dosage

for treatment of acute episodes of bronchospasm or prevention of asthmatic symptoms is two inhalations repeated every 4 to 6 hours.

2.2. Brief Overview of Clinical Program

A total of eight efficacy, safety, PK, and PD studies were submitted with this application. Four of those studies were intensively reviewed as pivotal studies (BNP-301-4-167, BNP-301-4-105, IX-101-105, and IXL 107-1-105), and four were not. Reviews of the pivotal studies as well as synopses of the supporting studies may be found in the Appendix of this review.

To support efficacy, the applicant submitted two US studies as pivotal efficacy studies (BNP-301-4-167 and BNP-301-4-105), along with two ex-US supporting efficacy studies (IX-105-105 and IX-100-105). BNP-301-4-167 was a six-week, randomized, evaluator-blind, placebo-controlled multiple dose study, whereas BNP-301-4-105 was a randomized, evaluator-blind, placebo-controlled single dose crossover pharmacodynamic (PD) study. In addition to placebo control, both studies incorporated active control arms, allowing comparisons to the marketed Proventil HFA. Supportive study IX-105-105 was primarily a safety study performed in patients 7-18 years, since PEFr (the primary efficacy measure) was measured at each clinic visit. Study IX-100-105 was a 4-period cumulative dose crossover study which compared the IVAX HFA-MDI and HFA-BOI products with the CFC-MDI and Ventolin CFC MDI products, but did not include a placebo control. For these reasons, only the two primary studies were reviewed for efficacy.

To support safety, the applicant submitted two studies as pivotal safety studies, BNP-301-4-167 and IX-101-105. BNP-301-4-167 was a six-week US efficacy and safety study (described above), and IX-101-105 was a 12-week randomized, placebo-, and active-controlled multiple dose study. IX-101-105 had been performed as a therapeutic equivalence study comparing the HFA-BOI and CFC-MDI products to support European registration. However, it did incorporate a comparison with placebo-HFA-BOI. Despite the fact that this study did not have an HFA-MDI arm, it was included as a safety study at the Division's suggestion. To allow incorporation of the HFA-BOI safety database information from this study in the HFA-MDI program required an estimation of comparability of the two products via evaluation of the PK/PD links provided by the applicant. Therefore, although it was submitted as a supportive safety study, the high-dose PK and extrapulmonary safety study (IXL 107-1-105) was reviewed as a pivotal study to support the evaluation of systemic safety. It was judged that the HFA-BOI drug product, while producing slightly less systemic (PK) and local (PD) exposure than the HFA-MDI drug product, was associated with sufficient exposure to allow inclusion of the safety information from the HFA-BOI drug product in the safety review.

2.3. Efficacy

All studies submitted were in support of the indication of treatment or prevention of bronchospasm with reversible obstructive airway disease in adults and children 12 years of age and older. While the clinical program to support marketing approval for Albuterol HFA-MDI was small, the studies do support approval for this indication. Both studies BNP-301-

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4-167 and BNP-301-4-105 showed that Albuterol-HFA-MDI at a dose of 180 mcg (2 inhalations) demonstrates efficacy when compared to placebo, with a net increase in FEV₁ AUEC₀₋₆ in the range of 1.04 to 1.14 L·Hr in mild-to-moderate asthmatics. In addition, the clinical program based on pharmacodynamic parameters supports comparability but not bioequivalence to the marketed Proventil HFA drug product. The pharmacokinetic study also appears to show comparability between the HFA-MDI product and Proventil HFA with regard to systemic absorption of albuterol. However, there was less systemic exposure with the HFA-BOI drug product than with either Albuterol-HFA-MDI or Proventil HFA. Tachyphylaxis was seen with chronic use, and was roughly similar for all drugs.

Proposed labeling was reviewed during this cycle for overall inclusion and exclusion of safety information, but not for specific wording. The proposed labeling for the CLINICAL TRIALS section of the product label is primarily based on the pivotal efficacy and safety study, BNP-301-4-167.

_____ is not appropriate for the label. This information should be communicated to the applicant.

Inclusion of

2.4. Safety

No safety trends were identified during the course of this review. There were no unusual trends in adverse events, laboratory events, vital signs, physical examinations, or other safety parameters in any of the studies. The incidence of adverse events was comparable among all albuterol treatment groups (Albuterol HFA-MDI, Albuterol HFA-BOI, and Proventil HFA).

Since the safety database for Albuterol-HFA-MDI alone was very small, safety was derived from combined clinical information for both the Albuterol-HFA-MDI and HFA-BOI drug products. This required assessing whether the two products were similar enough to allow inclusion of this safety information. While pharmacokinetic (PK) parameters for the Albuterol-HFA-MDI drug product were comparable to the marketed drug product Proventil HFA, PK parameters for the Albuterol-HFA-BOI drug product revealed less systemic exposure with the HFA-BOI than with the HFA-MDI drug product. However, differences were not considered significant with respect to the safety findings in the review, allowing review and inclusion of safety information from the HFA-BOI drug product in this application.

Executive Summary

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Evaluation of extrapulmonary pharmacologic effects including systolic and diastolic blood pressure, serum glucose and potassium, and ECG parameters of heart rate, QT and QTc intervals revealed no unexpected or new safety information regarding the effects of albuterol or the specific drug products being evaluated.

However, adequacy of testing of device performance remains an open issue that has not been completely addressed by the applicant. As noted in the Device Performance section, eight patients were withdrawn from study BNP 301-4-167 due to an inhaler malfunction, of whom two of the malfunctions were in the MDI drug product, one of which contained active drug product and one contained placebo drug product. Neither of these malfunctions, if investigated, was discussed in the study report or in the summary of safety. This information should be provided by the applicant.

2.5. Dosing

The pharmacologic and pharmacodynamic effects of orally inhaled albuterol are well characterized. No dosing, regimen, or administration issues were raised for the Albuterol-HFA-MDI device during this review. For the indication of treatment or prevention of bronchospasm with reversible obstructive airway disease in adolescents and adults ≥ 12 years of age and older, the dosing, regimen, and administration of the Albuterol-HFA-MDI is similar to other orally inhaled albuterol drug products, and is supported by the clinical trials submitted to this application. It is recommended that the applicant's suggested dose of 2 inhalations repeated every 4-6 hours be the approved dose.

2.6. Special Populations

Review of the demographics of patients enrolled in the multiple dose studies revealed that the majority of patients were females, and an overwhelming majority was White. There were very few patients randomized in the 12 to 18 and the ≥ 65 year old age ranges. However, the limited numbers in certain age or races should not raise any safety concerns. Since the pharmacological and pharmacodynamic effects of albuterol are well characterized, it was not expected that either safety or efficacy would be affected by these demographic parameters, and further data regarding use in these groups was not considered necessary to support this application.

Except for a supporting study, IX-105-105, performed in patients 7-18 years of age, pediatric studies were not submitted with this application.

Albuterol was not studied in pregnant women in the clinical program. Information is supplied from the labeling for Proventil HFA regarding class labeling as Pregnancy Category C. Since the pharmacological and pharmacodynamic effects of orally inhaled albuterol are well characterized, data regarding use in other populations was not considered necessary to support this application.

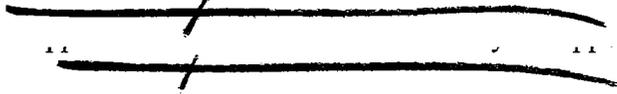
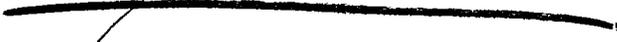
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2.7. Comments to Applicant

It is suggested that the following comments be conveyed to the applicant at the end of this review cycle:

1. 
2. The CLINICAL TRIALS section of the proposed product label 

 Revise the proposed product label to remove this information.
3. The proposed product label follows non-standard ordering for section headings. The product label should follow the order shown in 21 CFR 201.56(d)(1) and (2).
4. Because of the timelines involved, we were unable to address your request of October 15, 2003, for a name change from Volare HFA Inhalation Aerosol to 
 during this review cycle. Please resubmit this request with your complete response.

APPEARS THIS WAY
ON ORIGINAL

CLINICAL REVIEW**1. INTRODUCTION AND BACKGROUND****1.1. Established and Proposed Trade Name of Drug, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups**

This is a 505(b)(2) NDA application from IVAX Research, Inc., of Miami, Florida for a metered dose inhaler (MDI) formulation of racemic albuterol sulfate with an hydrofluoroalkane (HFA) propellant. While albuterol sulfate is the official generic name for the drug in the United States, the World Health Organization recommended name is salbutamol sulfate. While IVAX Research, Inc., of Miami, Florida is submitting the application, Volare was developed and will be manufactured by Ivax Pharmaceuticals, Inc., located in Waterford, Ireland. Both companies are wholly owned subsidiaries of IVAX Corporation.

Albuterol sulfate is a sympathomimetic amine with a primary effect on the lungs as a beta-adrenergic bronchodilator. The proposed indication is for the treatment or prevention of bronchospasm with reversible obstructive airway disease _____ in adults and children 12 years of age and older. The proposed dosage for treatment of acute episodes of bronchospasm or prevention of asthmatic symptoms is two inhalations repeated every 4 to 6 hours. _____

1.2. State of Armamentarium for Indication(s)

While there are many albuterol sulfate MDI products marketed with chlorofluorocarbons (CFCs) as the propellant, the CFCs used in these products are scheduled to be phased out in the next several years and replaced by hydrofluoroalkane (HFA) propellants. Only one albuterol HFA MDI is currently approved, Proventil[®] HFA Inhalation Aerosol, marketed by Schering.

The main difference between the proposed drug product and the currently marketed (reference) product (Proventil[®] HFA) is the absence of the surfactant oleic acid in the proposed formulation. Other differences between Ivax's drug product and Proventil[®] HFA include the ethanol concentration of _____ (compared to _____ for Proventil HFA) and the actuator orifice size of 0.22 mm (compared to 0.29 mm for Proventil HFA).

1.3. Important Milestones in Product Development

1.3.1. Regulatory History

The IND for albuterol-HFA-MDI was originally submitted by Zenith Goldline

~~_____~~

IND 60,549 was passed with Amendments to the Division of Pulmonary and Allergy Drug Products (DPADP) for evaluation in July of 2000. At the same time, Baker Norton changed the drug product actuator design from the original drug product. Rather than manufacturing a product with an _____, Baker Norton used an actuator with a smaller orifice size (0.22 mm) that is currently approved for use with this product in the United Kingdom. Baker Norton stated that the change in actuator increased the respirable dose _____ to 50%, and the respirable fraction _____ to 0.60.

The Baker Norton albuterol-HFA-MDI is marketed in Europe with two different actuators, one push-and-breathe (MDI), and the other breath-actuated (BOI). Both drug products contain the same canister and drug formulation of albuterol with HFA propellant. _____

~~_____~~

When the IND was passed with Amendments to the Division of Pulmonary and Allergy Drug Products (DPADP) in July of 2000, Baker Norton indicated that it would await the suggestions of this Division prior to initiation of any studies. A teleconference was held with Baker Norton on August 15, 2000, to discuss the IND proposal. Results of that discussion are contained in the Medical Officer's Review of August 22, 2000. At that time the Division agreed that it was safe to proceed with the proposed IND study, but discussed with Baker Norton the need for a drug development plan _____

Baker Norton met with the Division on October 13, 2000 to discuss their drug development plan. At the time, deficiencies in the plan included limited long-term (12-week) data that could be used to support efficacy and safety. In particular, the 12-week European study used only the BOI product. In addition, the plan did not include information on device performance evaluations _____

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The Division met with IVAX for a pre-NDA meeting on November 8 and 14, 2001. At that time, the Division stated that an ISS that was part of a common technical document was acceptable. The Division stated that a full ISE should include all the pivotal studies with a full rationale and explanation of efficacy, including differences between the two drug products and differences with the comparator drug product. The nature of the proposed application was deemed "minimalistic," since it lacked a 12-week efficacy and safety study. Therefore, the Division strongly suggested that IVAX include the 12-week European safety and efficacy study as a pivotal study, even though the study used the BOI product. —

1.3.2. Foreign Marketing History

Both the Albuterol-HFA-MDI and Albuterol-HFA-BOI product configurations were approved for marketing in the United Kingdom starting in April of 2000. A limited marketing history was submitted with the initial application, consisting of a table with a listing of the number of units of Albuterol-HFA-MDI (under the brand names *Salamol CFC Free MD*, *Salamol HFA MDI*, or *Alamol CFC Free MDI*, and the generic name *Salbutamol HFA MDI*) sold by country. Nine countries were listed, as shown in Table 1, under the column of Number of Units Sold. The submission states that units of Albuterol-HFA-MDI were sold in Europe in 2001 through August 2002 [M2, v1.3, p 200103].

The Division requested an updated foreign marketing history and received the same listing in the submission dated August 7, 2003. The Division again requested this information and received a full listing of worldwide approval, marketing authorization dates, and launch dates in a submission dated August 27, 2003. That submission showed that Albuterol-HFA-MDI is currently licensed for marketing in 32 countries worldwide. Table 1 combines the information from all submissions and provides a listing of countries in which marketing approval has been obtained for the HFA-MDI product.

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Table 1. Foreign marketing history of Albuterol-HFA-MDI

Country	Product Name	Units Sold*	Date of Marketing Approval
Argentina	Salamól		June, 2002
Belgium	Salbutamol Norton		January, 2002
Bulgaria	Salbutamol Norton		June, 2001
Cyprus	Salamol		N/A
Czech Republic	Alamol CFC Free MDI 100 mcg	/	July, 2000
	Ecosal		
	Salamol CFC Free MDI 100 mcg (brand name) Salbutamol HFA MDI 100 mcg (generic name)		
Estonia	Ecosal		February, 2002
Fiji	Salamol		N/A
Germany	Salabu-Azu	/	July, 2002
	Salbutamol HFA MDI 100 mcg		
Hong Kong	Salamol CFC Free		September, 2002
Hungary	Ecosal		March, 2002
Ireland	Salamol CFC Free MDI 100 mcg		May, 2001
Jamaica	Salamol CFC Free MDI 100 mcg		January, 2000
Kazakhstan	Ecosal		August, 2002
Kenya	Salamol		April, 2002
Latvia	Ecosal		January, 2001
Lithuania	Ecosal		August, 2001
Malta	Salamol CFC Free MDI 100 mcg		N/A
Mauritius	Salamol CFC Free MDI 100 mcg		N/A
Mexico	Salamol		May, 2002
Netherlands	Salbutamol Norton	/	July, 2001
	Salamol HFA MDI 100 mcg		
Panama	Salamol		January, 2002
Philippines	Asmalin / Libretin		August, 2002
Qatar	Salamol		N/A
Russia	Salamol		August, 2002
Singapore	Salamol		January, 2003
Trinidad, Tobago	Salamol		December, 2001
Ukraine	Salamol		December, 2001
United Arab Emirates	Salamol		April 2002
United Kingdom	Salamol CFC Free MDI 100 mcg (brand name)	/	April 2000
	Salbutamol HFA MDI 100 mcg (generic name)		
Uruguay	Salamol		March, 2002
Uzbekistan	Ecosal		July, 2002
Venezuela	Salamol		March, 2002

* Number of units sold as of the time submission of NDA 21-457

Sources: M1, V1.1, Tab 1.2.11, p 100001; Submission of 8/7/03, Tab 1; Submission of 8/29/03, Tab 4

1.4. Other Relevant Information

There is no other relevant information.

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1.5. Important Issues with Pharmacologically Related Agents

Albuterol sulfate is a sympathomimetic amine with selective beta-2 adrenergic agonist properties, and pharmacological effects similar to terbutaline. When administered by inhalation or by the oral route, the primary effect is on the bronchial smooth muscle in the lungs acting as a bronchodilator. The onset of action is short, with significant effect by 15 minutes and demonstrable effects for 3 to 4 hours. There are many years of clinical experience with this drug, and the side effects have been well characterized. Since there is a population of beta-2 receptors in the human heart, the primary side effects are cardiovascular in nature. These may include increases in pulse rate and blood pressure, symptoms, and/or electrocardiographic changes.

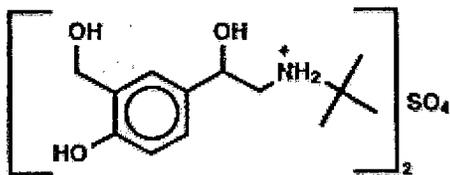
There are no other important issues with pharmacologically related agents.

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2. CLINICALLY RELEVANT FINDINGS FROM OTHER REVIEWS

2.1. Chemistry, Manufacturing, and Controls

The active component of Volare (albuterol sulfate) Inhalation Aerosol is albuterol sulfate, USP, the racemic form of albuterol. While the World Health Organization recommended name for the drug is salbutamol sulfate, the U.S. official generic name for the drug is albuterol sulfate. Albuterol sulfate is a relatively selective beta₂-adrenergic bronchodilator. The chemical name is: α^1 -[(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylene- α,α' -diol sulfate (2:1) (salt). The chemical structure is shown below.



The molecular weight of albuterol sulfate is 576.7, and the empirical formula is $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$. Albuterol sulfate is a white to off-white crystalline powder. It is soluble in water and slightly soluble in ethanol.

Under the terms of the Montreal Protocol, use of CFC propellants is to be phased out due to their ozone-depleting potential. Accordingly, IVAX developed a CFC-free albuterol inhaler that utilizes a hydrofluoroalkane (HFA) propellant, HFA-134a (1,1,1,2-tetrafluoroethane). This propellant is predicted to have minimal or no ozone-depleting potential.

Manufacturing site for Albuterol-HFA-MDI is IVAX Pharmaceuticals, Ireland. This site includes manufacturing, quality control, analytical testing, and research and development. Volare Inhalation Aerosol is formulated as a pressurized metered-dose aerosol unit for oral inhalation. Each inhaler canister contains a microcrystalline suspension of albuterol sulfate in propellant HFA-134a and ethanol. The canister is matched to a metering valve and an actuator. The actuator is of a press-and-breathe type, although IVAX has developed a breathe-operated (BOI) device utilizing the same canister and metering valve, but with a different breath-operated actuator. Each drug product canister is formulated to provide 200 inhalations. Each actuation delivers 120 mcg albuterol sulfate, USP from the canister valve and 108 mcg albuterol sulfate, USP, from the actuator mouthpiece (equivalent to 90 mcg of albuterol base from the mouthpiece). IVAX recommends priming the inhaler before the first use and when the inhaler has not been used for more than 2 weeks. Priming is performed by releasing "test sprays" into the air, away from the face.

It should be noted that there are a number of differences between the IVAX Albuterol-HFA and marketed reference Proventil HFA albuterol metered dose inhaler. Unlike Proventil HFA, the formulation of the IVAX Albuterol-HFA does not contain the surfactant oleic acid. In addition, the actuator orifice size of 0.22 mm differs from that for Proventil HFA (0.29 mm).

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Because chemistry, manufacturing, and controls (CMC) deficiencies, the CMC reviewer feels that there are insufficient CMC data to warrant approval on this cycle. The major CMC review findings may be summarized as follows:

- There is no control of the particle size distribution (PSD) of [REDACTED]. The acceptance criteria for PSD for the micronized drug substance are inadequate to assess batch-to-batch reproducibility.
- Stability data provided for the drug product are considered insufficient for the proposed expiry dating of [REDACTED]. Stability data are available from [REDACTED] lots. [REDACTED] of the [REDACTED] lots included data from both the previous (not-to-be-marketed) [REDACTED] actuator as well as from the to-be-marketed [REDACTED] actuator. [REDACTED] of the [REDACTED] lots extend to [REDACTED] of data at 25°, and [REDACTED] of data at 40°, and [REDACTED] lot contains information of less extent. Stability data on the [REDACTED] lots extend to [REDACTED] of data.
- For APSD (through life of the canister) testing, none of the non-stressed lots were tested from the beginning to the end of the canister life, but rather only at the middle of the canister life. As a result, the drug product performance in terms of mass deposition into the lungs through the full life of the canister could not be assessed. Although stressed lots were tested for beginning and end of canister life, the data are limited to only [REDACTED] and are insufficient to ensure consistent product performance.
- There is [REDACTED]. This [REDACTED] may be due to [REDACTED].

2.2. Animal Pharmacology and Toxicology

As a 505(b)(2) application, the applicant submitted published literature to support the animal pharmacology and toxicology safety of this drug. There were no issues raised by the Pharmacology/Toxicology reviewer.

2.3. Microbiology

Microbial controls at the drug substance and drug product levels include [REDACTED]. Although the media (HFA, as well as ethanol) is not expected to promote bacterial growth, the specifications did not include a statement that the drug substance and drug product are free of pathogenic bacteria. The CMC reviewer will be requesting that the specifications be revised to include these specifications.

2.4. Statistics

The statistical reviewer participated in the review of the six-week primary efficacy and safety study, BNP-301-4-167. The primary efficacy analysis was able to be verified. In addition, the statistical reviewer verified the primary analysis for the single-dose study BNP-301-4-105. Efficacy analyses were not verified for the other studies submitted.

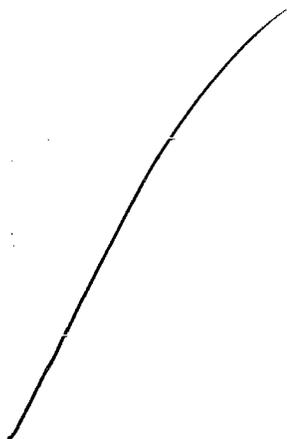
Clinically Relevant Findings from Other Reviews

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2.5. Product Name Consult



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3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

3.1. Pharmacokinetics

One of the studies in this application (IXR-107-1-105) included PK information and was reviewed by the Clinical Pharmacology and Biopharmaceutics reviewer as well as by myself in this document. Study IXR-107-1-105 was a cumulative-dose, single-dose, 3-way crossover, PK and extrapulmonary effect safety study of Albuterol HFA MDI and BOI compared to Proventil HFA MDI. Because the study was also reviewed in this document, all relevant information from the PK findings were placed within the body and/or discussion section of that study review, which may be found in the Appendix of this document on page 129. These results are also discussed within the Efficacy and Safety sections of this review, and are therefore not repeated here.

3.2. Pharmacodynamics

Pharmacodynamic information was the primary information submitted in support of this application. Study reviews addressing pharmacodynamics may be found within the individual study reviews in the Appendix of this document.

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4. DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1. Sources of Clinical Data

This is a paper NDA submission comprising 102 volumes. The document was submitted in the Common Technical Document (CTD) format. The clinical sections are Modules 1 and 2, and part of Module 5. The datasets are submitted electronically.

In the originally submitted document, the indexes and references were confusing and incomplete. The primary difficulties were with the Master, Module, and subsidiary Tables of Contents (TOCs). Because of these deficiencies, it was difficult to find everything within the application to perform the Filing and Planning review process. Nevertheless, when the reviewer tried to find an item it appeared to be present. These issues were discussed with the applicant on several occasions during the course of the preparation of the Filing and Planning review, and IVAX made a firm commitment in writing to address all the issues raised and in particular to correct any deficiencies in the jacketing, tabulation, and TOCs. Some of the other areas which needed to be addressed included the lack of a complete foreign marketing history, the need for a statistical reviewer's guide, and the lack of a study report for study BNP-301-4-167 within Module 5.

To address these issues, the applicant replaced all the original TOCs and Tabs with new ones in June of 2003, providing new Module/Volume numbers as well as new TOCs in each volume and new Tabs between sections within each volume. The electronic information for statistical review was also resubmitted. All issues were addressed.

4.2. Overview of Clinical Trials

A total of eight efficacy, safety, PK, and PD studies were submitted with this application. To support efficacy, the applicant submitted two US studies as pivotal efficacy studies (BNP-301-4-167 and BNP-301-4-105), along with two ex-US supporting efficacy studies (IX-105-105 and IX-100-105). BNP-301-4-167 was a six-week, randomized, evaluator-blind, placebo-controlled multiple dose study, whereas BNP-301-4-105 was a randomized, evaluator-blind, placebo-controlled single dose crossover study. In addition to placebo control, both studies incorporated active control arms, allowing comparisons to the marketed Proventil HFA. Supportive study IX-105-105 was primarily a safety study performed in patients 7-18 years, although PEFr (the primary efficacy measure) was measured at each clinic visit. Study IX-100-105 was a 4-period cumulative dose crossover study which compared the IVAX HFA-MDI and HFA-BOI products with the CFC-MDI and Ventolin CFC MDI products, but did not include a placebo control. In addition, many of the supporting studies tried to establish so-called "therapeutic equivalence" of test and reference drug products. However, such claims of therapeutic equivalence are not considered relevant in a 505(b)(2) application. For these reasons, only the two primary studies were reviewed for efficacy.

To support safety, the applicant submitted two studies as pivotal safety studies, BNP-301-4-167 and IX-101-105. BNP-301-4-167 was a six-week US efficacy and safety study (described above), and IX-101-105 was a 12-week randomized, placebo-, and active-

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controlled multiple dose study. IX-101-105 had been performed as an therapeutic equivalence study comparing the HFA-BOI and CFC-MDI products to support European registration. However, it did incorporate a comparison with placebo-HFA-BOI. Despite the fact that this study did not have an HFA-MDI arm, it was included as a safety study at the Division's suggestion.

The applicant also submitted six supporting safety studies (IXL-106-1-105, IXL 107-1-105, BNP-301-4-105, IX-100-105, IX-105-105, and SAMM57). Although it was submitted as a supportive safety study, the high-dose PK and extrapulmonary (pharmacologic) effects safety study (IXL 107-1-105) was reviewed as a pivotal study to support safety. IXL-106-1-105, an almost identical study to IXL 107-1-105 but with a shorter interval between treatment periods, was a failed PK and extrapulmonary effects safety study since the PK data revealed albuterol in 56% of pre-dose blood samples. BNP-301-4-105 was submitted primarily as an efficacy study, but did contain single-dose safety data, which was reviewed. IX-100-105 was an ex-US, cumulative dose, single dose study without PK data, and IX-105-105 was an ex-US pediatric safety study. Neither of these studies was reviewed in depth, although the information from these studies that the applicant submitted to the Summary of Clinical Safety was reviewed. One uncontrolled open label safety study, SAMM57 was submitted but not reviewed.

Of the eight submitted studies, a total of four studies were reviewed as pivotal in support of either efficacy and/or safety, as shown in Table 2. In-depth reviews of the four individual reviewed studies may be found in the Appendix: Detailed Study Reviews section of this review. Other submitted supporting studies are shown in Table 3, and synopses may be found in the Appendix of this review.

Table 2. Summary of Pivotal* Efficacy and Safety Studies

Study Type	Design / Population	Formulation	Dose (mcg)	N	Efficacy/Safety Notes
BNP 301-4-167 Efficacy & Safety US (32)	6-week, multi-center, randomized, double-blind / double-dummy vs placebo, evaluator-blind vs Proventil HFA, placebo- and active-controlled, parallel group multiple-dose study, incorporating two 3-week life-of-device tests Mild-to-moderate asthmatics (FEV ₁ 50-85% predicted) with airway reversibility FEV ₁ ≥12% after 180 mcg albuterol, ≥12y	Placebo-HFA-BOI/MDI	QID	345	Primary efficacy: FEV ₁ AUEC ₀₋₆ on Days 1, 22, 43
		Albuterol-HFA-BOI	180 QID	58	
		Albuterol-HFA-MDI	180 QID	173	
		Albuterol-HFA-MDI	180 QID	58	
		Proventil®-HFA	180 QID	56	
BNP 301-4-105 Efficacy & Safety US (5)	Multi-center, randomized, evaluator-blind, placebo- and active-controlled, 7-sequence, 7-period, single-dose crossover study Moderate to severe asthmatics (FEV ₁ 50-75% predicted) with airway reversibility FEV ₁ ≥15% after 180 mcg albuterol, 18-50y	Placebo-HFA-MDI	0	47	Primary efficacy: FEV ₁ AUEC ₀₋₆ Safety: As a single-dose study, the only safety analysis was AEs
		Albuterol-HFA-MDI	90		
		Albuterol-HFA-MDI	180		
		Albuterol-HFA-MDI	270		
		Proventil®-HFA	90		
		Proventil®-HFA	180		
		Proventil®-HFA	270		
IX-101-105 Safety	12-week, multi-center, randomized, placebo- and active-controlled,	Placebo-HFA-BOI	QID	203	Efficacy: FEV ₁ AUEC ₀₋₆
				55	

Description of the Clinical Data Sources

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Study Type	Design / Population	Formulation	Dose (mcg)	N	Efficacy/Safety Notes
Russia (10) Poland (5)	double-blind, double-dummy, parallel group multiple-dose study Mild-to-moderate asthmatics (FEV ₁ 50-80% predicted) with airway reversibility FEV ₁ ≥15% after 200 mcg albuterol, 18-65y	Albuterol-HFA-BOI Albuterol-CFC-MDI	200 QID 200 QID (200mcg ex-valve)	61 66	at 0, 3, 6, 9, 12 weeks Evaluated as a safety study
IXR-107-1-105 PK/PD US	Single-center, randomized, evaluator-blind, active-controlled, 3-period, cumulative-dose crossover study in healthy subjects	Albuterol-HFA-MDI Albuterol-HFA-BOI Proventil®-HFA 2 + 4 + 6 actuations	180 + 360 + 540 = 1080 mcg	16	Safety: High-dose PK/PD for albuterol vs: QT, QTc, K ⁺ , glucose

* Studies considered to be 'pivotal' by the Division

'Source: Module 5, volume 1.1B

Table 3. Summary of Supporting Studies

Study	Design / Population	Formulation	Dose (mcg)	N	Notes
IXL-106-1-105 PK/PD US	Single-center, randomized, evaluator-blind, active-controlled, 3-period, cumulative-dose crossover study in healthy subjects	Albuterol-HFA-MDI Albuterol-HFA-BOI Proventil®-HFA 2 + 4 + 6 actuations	180 + 360 + 540 = 1080 mcg	16	Invalid PK data: Albuterol found in 56% of pre-dose blood samples
IX-100-105 PD South Africa	Single-center, randomized, evaluator-blind, active-controlled, 4-period, cumulative-dose crossover study in mild-to-moderate asthmatics 1 + 2 + 4 + 8 actuations	Albuterol-HFA-MDI Albuterol-HFA-BOI Ventolin®-CFC-MDI Albuterol-CFC-MDI	100 + 200 + 400 + 800 = 1600 mcg ex-valve	25	No placebo control, No PK
IX-105-105 Safety Russia (8)	6-week randomized, placebo-controlled, active-controlled study in mild-to-moderate asthmatics age 7-18 years	Placebo-HFA-MDI Albuterol-HFA-MDI Albuterol-CFC-MDI	QID 200 QID 200 QID	138	Pediatric safety study, PEFR only
SAMM57 Safety UK	12-week open-label, general practice, observational cohort study with 3:1 allocation ratio HFA:CFC in mild-to-moderate asthmatics age ≥ 7 years	Albuterol-HFA-MDI Albuterol-CFC-MDI	At the patient's existing prescribed dose	1009	Open label study

4.3. Postmarketing Experience

Postmarketing experience with Albuterol-HFA-MDI is reported from nine countries (see Post-Marketing section of this review). The NDA submission states that ~~1~~ units of Albuterol-HFA-MDI were sold in Europe in 2001 through August 2002 [M2, v1.3, p 200103]. A 120-day safety update report was submitted June 6, 2003, and updated in the submission of August 7, 2003. All data from these submissions were reviewed.

4.4. Literature Review

No literature review was performed as part of the review of this application.

5. CLINICAL REVIEW METHODS

5.1. Conduct of the Review

The review included in-depth evaluations of four trials that were considered pivotal to support either the efficacy and/or safety of Albuterol-HFA-MDI (Table 2). The reviews of these studies may be found in the Appendix of this document. Other supportive studies were not reviewed, but synopses may also be found in the Appendix of this document.

To support efficacy, the applicant submitted two US studies as pivotal studies (BNP-301-4-167 and BNP-301-4-105), along with two ex-US supporting efficacy studies (IX-105-105 and IX-100-105) [M2, v 1.3, p 200020]. Both compared Albuterol-HFA-MDI to placebo and a marketed comparator, Proventil[®]-HFA. The two pivotal efficacy studies are briefly summarized below. In addition, the six-week clinical study included the Albuterol-HFA-BOI product that IVAX is developing.

To support safety, the applicant submitted two studies as pivotal studies (BNP-301-4-167 and IX-101-105). These studies were reviewed. The applicant also submitted six supporting safety studies (IXL-106-1-105, IXL 107-1-105, BNP-301-4-105, IX-100-105, IX-105-105, and SAMM57). BNP-301-4-105 was submitted primarily as an efficacy study, but did contain single-dose safety data which was reviewed. In addition, the Division considered the high-dose PK/PD safety (IXL 107-1-105) critical to evaluation of safety, and reviewed this study as a pivotal safety study despite the fact that the study did not include a placebo treatment arm. Therefore, a total of four studies were evaluated for safety. IXL-106-1-105 was a PK/PD study, but was considered a failed study, as the PK data revealed albuterol in 56% of pre-dose blood samples. Study IXL 107-1-105 (listed above) was a repeat of this study with longer intervals between treatments. IX-100-105 was an ex-US, cumulative-dose, single-dose therapeutic equivalence PD study without PK data, and IX-105-105 was an ex-US pediatric safety study. Neither of these studies was reviewed in depth, although the information from these studies that the applicant submitted to the Summary of Clinical Safety was reviewed. One uncontrolled open label safety study, SAMM57 was submitted but not reviewed.

The four trials that were reviewed are briefly summarized below.

BNP-301-4-167 was a six-week, multi-center, randomized, double-blind / double-dummy vs placebo, evaluator-blind vs Proventil HFA, placebo- and active-controlled, parallel group multiple-dose study, incorporating two 3-week life-of-device tests, conducted in mild-to-moderate asthmatics (FEV_1 50-85% predicted) ≥ 12 years of age. This study was reviewed for as a pivotal study for both efficacy and safety. The Biometrics reviewer was able to duplicate the applicant's primary efficacy results.

BNP-301-4-105 was a multi-center, randomized, evaluator-blind, placebo- and active-controlled, 7-sequence, 7-period, single-dose crossover study in moderate to severe asthmatics (FEV_1 50-75% predicted) 18-50 years of age. This study was reviewed primarily for efficacy and secondarily for safety. The Biometrics reviewer was able to duplicate the applicant's primary efficacy results.

IXR-107-1-105 was a cumulative-dose, single-dose PK and pharmacologic effect 3-way crossover, safety study of Albuterol HFA MDI and BOI compared to the reference product Proventil HFA. This study was not placebo controlled, and was reviewed primarily as a pivotal safety study. The primary reason for review of this study was to evaluate systemic exposure of both the HFA-MDI and HFA-BOI drug products, thus allowing consideration of safety data from the HFA-BOI product during the review of safety. Since this study contained PK rather than PD information the results were evaluated by the Clinical Pharmacology and Biopharmaceutics reviewer.

IX-101-105 was a 12-week, ex-US, multi-center, randomized, placebo- and active-controlled, double-blind, double-dummy, parallel group multiple-dose study in mild-to-moderate asthmatics (FEV₁ 50-80% predicted) ages 18-65y who showed airway reversibility FEV₁ ≥15% after 200 mcg albuterol. Since this study did not include the HFA-MDI but did include the HFA-BOI drug product, this study was reviewed as a safety study.

5.2. Materials Consulted

This is a paper NDA submission comprising 102 volumes. The entire clinical submission was evaluated as part of this review. Electronic datasets were provided and reviewed by the appropriate Biopharmaceutics or Biometrics reviewers, and their feedback is incorporated into this review.

5.3. Referencing and Documentation

Referencing within this NDA review is based on the revised TOCs. Each reference includes a Module, Volume, and Page number, as indicated by M# (where # = the CTD module, and the clinical modules include modules 1, 2, and 5), V n.mm (where n = the submission number, and mm is the volume within the module for that submission), P pppppp (where pppppp is the page number). For simplicity, whereas the abbreviation for the Module number is capitalized, the abbreviations for the volume and page numbers are not capitalized. For example, a typical reference might look like [M5, v 1.17, p 500001-8; v 1.25, p 500275-88], where the text sites two volumes and sets of pages within Module 5.

5.4. Data Quality and Integrity

A Division of Scientific Investigations (DSI) audit was requested and conducted for this NDA. Because of difficulties finding information in the NDA prior to IVAX providing new Tables of Contents, the Division was unable to suggest sites for audit. Therefore, DSI requested information directly from IVAX. This information included a list of study sites, with the CI name/address, number enrolled, number evaluable, number with AEs/SAEs, number of protocol violations, number of premature withdrawals, and number who had a positive outcome without any statistical calculations. Based on this submission (May 15, 2003), DSI chose the sited listed in Table 4. Unfortunately, site 3314 in study BNP-301-4-167 was not chosen for audit. At this site, nine patients were inadvertently dosed using a new inhaler instead of their used inhaler on Day 22, and one patient had an inhaler labeling error. These protocol deviations were not uncovered until well into the review cycle. In

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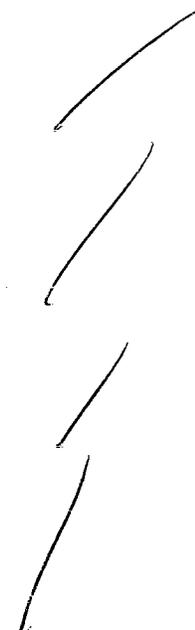
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addition, it was felt that these protocol deviations did not affect the study results, and therefore no attempt was made to add this site to the DSI audit.

Although the DSI consult was performed, the results were not collated and available for review prior to completion of this document. The results are expected to be available prior to the PDUFA due date.

Table 4. NDA 21-457 (VOLARE HFA) Proposed Sites for Inspection (Total of 5 Sites)

Protocol	Clinical Investigator	ID Number	Location	Total Enrolled Subjects	Reason for Selection
BNP-301-4105 (N=46)	Miller	3275	MA	19	
	Lumry	3281	TX	9	
	Finn	3272	SC	12	
BNP-301-4-167 (N=345)	Lumry	3281	TX	6	
	LeDoux	3319	WA	18	
	Miller	3275	MA	12	
	Berkowitz	3306	GA	17	

5.5. Ethical Standards

No ethical issues were raised during the course of this review. All study reports had statements that they were conducted in compliance with Good Clinical Practices and all applicable regulatory requirements, including, where applicable, the Declaration of Helsinki.

5.6. Financial Disclosure

There were no financial disclosure issues in this application. The applicant submitted Form 4354 in compliance with 21 CFR part 54, a financial disclosure certification statement. The statement includes the three U.S. studies that were reviewed as pivotal for efficacy or safety. [M1, v 1.1, p 100001-8]

6. INTEGRATED REVIEW OF EFFICACY

6.1. Brief Statement of Conclusions

All studies submitted were in support of the indication of treatment or prevention of bronchospasm with reversible obstructive airway disease in adults and children 12 years of age and older.

6.2. General Approach to the Efficacy Review

All studies were evaluated and/or received an in-depth review. A review of each of the four studies that were received an in-depth review may be found in the Appendix of this document.

6.3. Summary of Trials by Indication

The proposed indication is for the treatment or prevention of bronchospasm with reversible obstructive airway disease in adults and children 12 years of age and older. The applicant submitted studies to support the indication of treatment or prevention of bronchospasm with reversible obstructive airway disease in adults and children 12 years of age and older.

6.3.1. Indication of Treatment or Prevention of Bronchospasm with Reversible Obstructive Airway Disease in Adults and Children 12 Years of Age and Older

To support efficacy, the applicant submitted two US studies as pivotal studies (BNP-301-4-167 and BNP-301-4-105), along with two ex-US supporting efficacy studies (IX-105-105 and IX-100-105) [M2, v 1.3, p 200020]. Both pivotal studies compared Albuterol-HFA-MDI to placebo and a marketed comparator, Proventil[®]-HFA. In addition, BNP-301-4-167 (the six-week clinical study) included the Albuterol-HFA-BOI product that IVAX is developing. Study IX-105-105 was an ex-US study performed in patients 7-18 years and older. The study included both Albuterol-HFA-BOI and Albuterol-HFA-MDI arms as well as two approved comparators, but it did not include a placebo arm and measured PEFR at each clinic visit. It was therefore considered only as a safety study. Study IX-100-105 was a 4-period cumulative dose (1500 mcg) crossover study which compared the IVAX Albuterol HFA-MDI and HFA-BOI products with the CFC-MDI and Ventolin CFC MDI products, but did not include a placebo control or PK data. For these reasons, only the two primary studies summarized below were reviewed for efficacy. The Biometrics reviewer was able to duplicate the applicant's primary efficacy results for both pivotal clinical efficacy studies.

BNP-301-4-167 was a six-week, multi-center, randomized, double-blind / double-dummy vs placebo, evaluator-blind vs Proventil HFA, placebo- and active-controlled, parallel group multiple-dose study, incorporating two 3-week life-of-device tests, conducted in mild-to-moderate asthmatics (FEV₁ 50-85% predicted) ≥12 years of age. The study compared the efficacy of Albuterol HFA-MDI versus placebo-HFA-MDI, as

well as with Albuterol-HFA-BOI and the active comparator Proventil HFA, each dosed at two inhalations four times daily for six weeks. The Biometrics reviewer was able to duplicate the applicant's primary efficacy results.

BNP-301-4-105 was a multi-center, randomized, evaluator-blind, placebo- and active-controlled, 7-sequence, 7-period, single-dose crossover study in moderate-to-severe asthmatics (FEV_1 50-75% predicted) 18-50 years of age. The study compared Albuterol-HFA-MDI at doses of 90, 180, and 270 mcg with placebo HFA-MDI and the active comparator Proventil HFA (90, 180, and 270 mcg). The Biometrics reviewer was able to duplicate the applicant's primary efficacy results.

6.3.1.1. BNP-301-4-167

This was a six-week, multi-center, randomized, evaluator-blind, (double-blind, double-dummy vs placebo for the IVAX products), active- and placebo-controlled, parallel group multiple-dose study comparing the efficacy and safety of Albuterol-HFA-MDI and Albuterol-HFA-BOI with that of placebo and Proventil HFA administered to at 345 mild-to-moderate asthmatics ≥ 12 years of age. Eligibility requirements included an FEV_1 50-85% predicted and demonstration of reversible bronchoconstriction as evidenced by a $\geq 12\%$ increase in FEV_1 within 30 minutes following inhalation of albuterol 180 mcg (2 actuations). Eligible patients were randomized to receive Placebo HFA-BOI/MDI, Albuterol HFA-MDI, Albuterol-HFA-BOI, or Proventil HFA administered as 2 puffs (180 mcg) four times daily for 42 days. A double-dummy technique for the MDI and BOI inhalers allowed maintenance of a double-blind for the Placebo-HFA-BOI/MDI, Albuterol-HFA-MDI, and Albuterol-HFA-BOI arms. Because a Proventil HFA placebo was not available, the Proventil HFA arm could not be visually blinded, and therefore was only evaluator blinded.

A total of 345 patients were randomized, of whom 290 completed study treatment, and 251 (89% of the patients completing six weeks of treatment) completed evaluations on the final day of the study. Randomization was not equal, but was 1:3:1:1 for the Albuterol-HFA-MDI : Albuterol-HFA-BOI : Proventil HFA : Placebo groups. The unbalanced randomization was designed to provide greater information ~~for the Albuterol-HFA-BOI drug product~~ for the Albuterol-HFA-BOI drug product. The ITT population included 58, 173, 56, and 58 patients in the Albuterol-HFA-MDI, Albuterol-HFA-BOI, Proventil HFA, and placebo groups, respectively. Because of the unbalanced randomization, the number of patients who completed the study Albuterol-HFA-MDI and placebo groups was quite small: 52 and 47 patients, respectively. Treatment groups were otherwise relatively well balanced at randomization, except that there was a higher percent of males in the placebo group than the other groups. Overall there were more females (61%) than males (39%) enrolled, and Whites were in the large majority (81%), with Asians and 'Other' races poorly represented.

6.3.1.1.1. Primary Efficacy

The primary efficacy analysis was a comparison of the mean difference between Albuterol-HFA-MDI and placebo for the $AUEC_{0-6}$ of baseline-adjusted FEV_1 at Day 43 or last observation was statistically significant (LS mean difference = 1.04 L·Hr, $p = <0.0001$). Analyses performed using both pre-specified and actual assessment times were almost

identical (shown in Table 5). Other comparisons of interest between Albuterol-HFA-BOI and Proventil-HFA vs placebo were also significant (Albuterol-HFA-BOI vs placebo LS mean difference = 1.04, p = 0.0000, Proventil vs placebo LS mean difference = 0.97, p = 0.0001). There were minor and not statistically significant differences among active treatments, with the largest numerical difference between the Albuterol-HFA-MDI and Albuterol-HFA-BOI products. Analysis by subgroups of age, race, and gender did not reveal any trends. Note that the devices used on Day 1 were new, whereas devices used on Days 22 and 43 were not cleaned prior to use and had been used for about 3 weeks with weekly cleaning at home.

Table 5. BNP-301-4-167, Primary Efficacy Variable: AUEC₀₋₆ (L•Hr) of baseline-adjusted FEV₁ at Day 43/LOCF, MITT

Treatment	N	LS Mean (STE)	LS Mean Diff (STE)	p-value
Analysis using pre-specified assessment times¹				
Albuterol HFA-MDI	58	1.28 (0.17)	1.04 (0.25)	0.0000
Placebo	58	0.23 (0.17)		
Analysis using actual assessment times²				
Albuterol HFA-MDI	58	1.28 (0.17)	1.04 (0.24)	<0.0001
Placebo	58	0.24 (0.17)		

1 Based on a one-way ANOVA model using the pre-specified assessment times

2 Based on a one-way ANOVA model using the actual assessment times

Source: M5, v 1.17, Table 14.2.1.1, p 500307

M2, v 1.3, Tables 2.1-2.2, p 200037-8

6.3.1.1.2. Secondary Efficacy

Secondary efficacy analyses included analyses of pulmonary function (spirometric and pharmacodynamic) parameters based on spirometric measurements performed during clinic visits at various timepoints throughout the study, ambulatory function parameters recorded on diary cards, and device performance as measured by an ease-of-use questionnaire at the end of the study. Secondary and pharmacodynamic parameters were supportive of efficacy of Albuterol-HFA-MDI, and the comparability of Albuterol-HFA-MDI with Proventil HFA. As expected, tachyphylaxis was seen with chronic use. These are outlined below.

6.3.1.1.2.1. Spirometric and pharmacodynamic parameters

The secondary comparisons of AUEC₀₋₆ of percent change in FEV₁ and AUEC₀₋₆ of baseline-adjusted percent predicted FEV₁ at Days 1, 22, and 43 by study day and treatment group showed a significant effect of study day, but the interaction of treatment and study day was not significant, implying that while there was a trend toward decreasing AUEC₀₋₆ over time, differences between treatment groups did not change. This trend was likely due to the development of tolerance (tachyphylaxis).

Hourly non-baseline-adjusted FEV₁ differed slightly from the baseline-adjusted FEV₁, which more clearly defined efficacy. In contrast, these results pointed toward the tendency of albuterol to produce tachyphylaxis when used routinely over periods of time.

Tachyphylaxis, a partial drug tolerance, is a well-known phenomenon associated with chronic use of all β₂-agonists. When used on a regular basis, tachyphylaxis may occur

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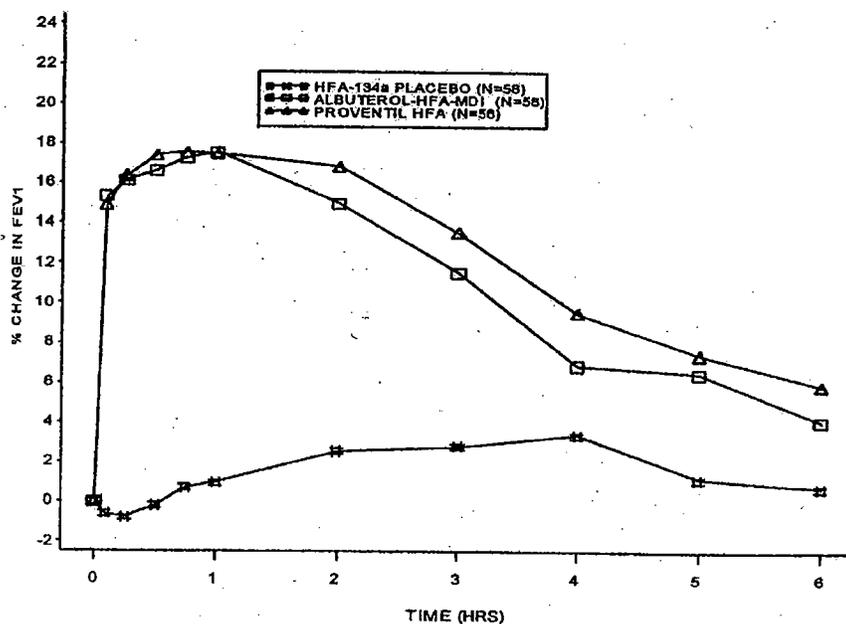
within days to weeks from the start of treatment, and this phenomenon continues without further reduction while routine treatment is continued. This presents as a limited reduction in efficacy, and is evidenced on PFTs more by a decrease in the duration rather than a decrease in the peak effect. However, prolonged therapy may lead to reduction in the control of asthma symptoms, and use in this manner is discouraged. PRN use of beta agonists, on the other hand, does not appear to be associated with clinically significant tolerance.

As expected, tachyphylaxis occurred during the course of this study. This phenomenon was noted for all active drugs, and may be seen by comparison of both the baseline-adjusted $FEV_{1\ 0-6}$ and the non-baseline-adjusted (raw) $FEV_{1\ 0-6}$ over the course of the study visits, but is more clearly seen in the latter results. On Day 1, non-baseline-adjusted FEV_1 increased by 200-300 ml and maintained a separation for up to 3-4 hours. By Day 43, non-baseline-adjusted FEV_1 increased by only 100-200 ml, and maintained separation for only 2-3 hours. Note that on Day 1, the Proventil HFA appeared to produce a higher FEV_1 with longer duration of response than [REDACTED] the Albuterol-HFA-MDI [REDACTED], which produced about the same FEV_1 response. On Day 43, the [REDACTED] roventil HFA produced a higher FEV_1 with longer duration of response than Albuterol-HFA-MDI.

Change from pre-dose baseline in FEV_1 was comparable among all active treatment groups on Day 1, 22, and 43. For all active treatments, differences between active and placebo were largest up to one hour, and steadily declined over the six-hour period. Whereas there was some visual separation of the active treatment groups from placebo throughout the 6-hour period on Day 1, on Days 22 and 43 the differences between active and placebo became quite small after 4 hours. On Day 43, Albuterol-HFA-MDI appeared to give a higher mean change from baseline (as measured either by mean FEV_1 in L or by % change in FEV_1) than [REDACTED] or Proventil HFA (Figure 1).

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Day 1



Day 43

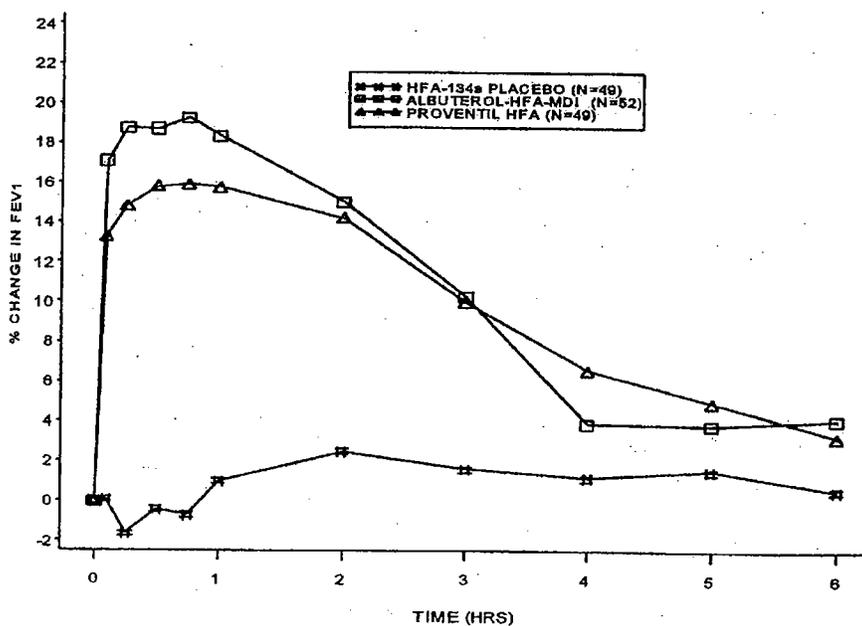


Figure 1. BNP-301-4-167, FEV₁ as a mean percent change from test-day pre-dose on Day 1 and Day 43

Source: M2, v 1.3 Figure 6, p 200026

Baseline-adjusted maximum FEV₁ and baseline adjusted maximum percent predicted FEV₁ overall, and at Days 1, 22, 43 were evaluated in a mixed-effect ANOVA model with treatment, study day, and treatment-by-study-day interaction as fixed effects and patient as a random effect. Both sets of analyses showed similar results. The main effect of treatment was statistically significant ($p \leq 0.0001$ for both), with the effect of study day less so ($p = 0.0517$ and $p = 0.0484$, respectively). Treatment by study day interaction effect was not significant. Pairwise comparisons of each of the treatment group with placebo remained statistically significant ($p \leq 0.0001$) for all comparisons over time. There was a marginal decrease in baseline-adjusted maximum FEV₁ and percent predicted FEV₁ over time for the _____ Proventil HFA groups, but not the Albuterol HFA-MDI group. This decrease resulted in minor differences between treatment groups which emerged over time (seen visually in Figure 1), although the active treatment groups were not statistically different from each other on any study day ($p > 0.12$ and $p > 0.09$, respectively).

Median time (in minutes) to baseline-adjusted maximum FEV₁ for the active treatment groups ranged from 46.8 to 54.0 minutes on Day 1, to 46.2 to 49.8 minutes on Day 22, to 31.2 to 49.2 minutes on Day 43. For the placebo group, median times were at least 2 hours on each study day. Differences among active treatment groups were not statistically significant ($p > 0.05$ for hazard ratios), but differences between active and placebo were statistically significant ($p < 0.05$).

Time to response onset was defined in the protocol as the time to an increase from baseline in FEV₁ $\geq 15\%$. All active treatment groups were significantly different than placebo. For each active treatment group, the number of patients who responded decreased from Day 1 to Day 43. The median time to a 15% response in FEV₁ increased from Day 1 to Day 43 for the _____ the Proventil HFA groups, but not for the Albuterol HFA-MDI group. Differences primarily were due to increases in the range of time to onset of response, i.e. fewer patients reached a 15% response in FEV₁, and more patients took longer to respond to this level.

Since the response rate was lower than the applicant expected, a *post-hoc* analysis using a 12% response rate was added. All active treatment groups were significantly different than placebo.

Duration of response, defined as the duration from the onset of a 15% response in FEV₁ to the time of offset of response was evaluated for responders only. On Days 1 and 43, no difference between the active treatment groups was noted. On Day 22, the Albuterol HFA-MDI group had duration times that were significantly shorter than the other two active treatment groups. While tachyphylaxis was not seen in the duration of response as measured by a 15% response, there was a trend noted when measured by the duration of a 12% response.

6.3.1.1.2.2. Dairy parameters

Dairy parameters included pre-dose AM PEF, daytime asthma scores, number of nocturnal awakenings, and number of puffs of rescue medication. Mean daily PEF per week showed

no significant changes during treatment for any of the active treatment groups, and no significant differences from placebo. Curiously, the placebo group started with the highest PEF (LS mean 371), and dropped to the lowest of any of the groups (340-345) during each weekly treatment interval. Asthma symptom scores averaged by week showed a slight mean improvement for all treatment groups, with no statistically significant differences among the groups. In general, the group with the lowest symptom scores was the Albuterol-HFA-MDI group. Change from baseline for asthma symptom scores was largest for the Albuterol-HFA-MDI group (mean = -0.19), Proventil HFA (mean = -0.12), and placebo (mean = -0.07). Nighttime awakenings due to asthma requiring rescue medication showed minimal changes over time and no clear trends. The number of puffs of rescue medication per day differed among treatment groups during the baseline run-in period (Albuterol-HFA-MDI 2.6, Proventil HFA 2.9, placebo 2.6). During the treatment period, use of rescue medication decreased for all active treatment groups, but not for placebo (Albuterol-HFA-MDI 1.5, Proventil HFA 1.5, placebo 2.5). When adjusted for baseline differences, the change from baseline compared to placebo was significant for Albuterol-HFA-MDI ($p = 0.003$) and Proventil HFA ($p = 0.001$).

6.3.1.2. BNP-301-4-105

This was a multi-center, randomized, evaluator blind, placebo-controlled, seven-treatment-seven-period, seven-sequence, single-dose crossover bronchodilation study comparing Albuterol-HFA-MDI 90, 180, or 270 mcg, Proventil HFA 90, 180, or 270 mcg, and placebo administered at 2 to 7 day intervals in 47 moderate to moderately severe asthmatics (FEV_1 50-75% predicted with reversible bronchoconstriction of $\geq 15\%$). The primary variable was the baseline-adjusted change in FEV_1 average area-under-the-effect curve over 0-6 hours following dosing ($AUEC_{0-6}$). The secondary variable was the baseline-adjusted maximum FEV_1 value observed post-dose (FEV_{1max}). Both the primary and secondary analyses were based on a per-protocol population, and included comparisons of the mean difference between each active group and placebo at each dose level, the mean difference between active groups at each dose level, and the within-product difference of 1 versus 2, 1 versus 3, and 2 versus 3 actuations (i.e. dose response). In addition, the dose-response of Albuterol-HFA-MDI was compared to Proventil HFA.

Fifty-eight patients were randomized, 19 males (32.8%) and 39 females (67.2%), predominantly Whites (81% Whites, 14% Blacks, and 5% "Other"). Forty-seven completed the study, of whom 16 did not complete every treatment (14 due to bronchospasm). The frequency of concomitant use of inhaled corticosteroids was not stated.

The primary efficacy analyses and treatment comparisons for the baseline-adjusted mean FEV_1 $AUEC_{0-6}$ for the per-protocol population were statistically significant ($p < 0.0001$) for all dose comparisons between Albuterol-HFA-MDI and placebo (Table 6) as well as between Proventil HFA and placebo. Comparison between similar doses of active drugs showed only small differences which were not statistically significant. Comparison of doses within each drug product showed a trend to more effect with higher doses. For Albuterol-HFA-MDI there was no statistically significant differences between doses, but for the Proventil HFA, there was a statistically significant difference between the 270 mg dose

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compared to both the 90 mg ($p = 0.0006$) and 180 mg ($p = 0.0290$) doses. Results for gender subgroups were statistically significant for all active treatments compared to placebo.

Table 6. BNP-301-4-105, Primary Efficacy, Baseline-adjusted FEV₁ AUEC₀₋₆ (L•Hr) and treatment comparisons, PP population

Treatment / Comparison group	Dose / Comparison	LS mean (SE)	LS mean difference (SE)	p-value
Placebo	0	0.45 (0.20)		
Albuterol-HFA-MDI	90	1.45 (0.20)	1.00 (0.17)	<0.0001
	180	1.59 (0.20)	1.14 (0.17)	<0.0001
	270	1.70 (0.20)	1.25 (0.17)	<0.0001
	90 vs 270		0.58 (0.17)	0.0006
	180 vs 270		0.36 (0.17)	0.0290
1 Baseline-adjustment = each post-dose FEV ₁ minus the average of the two baseline FEV ₁ s.				
2 LS means and p-values derived from a mixed effects model with fixed effects of sequence, period, and treatment group and random effect of subject within sequence.				

Source: M5, v 1.10, Table 11.4.1.2(1), p 500060; Table 14A.2.2.1-3, p 500097-9

The secondary efficacy analyses and treatment comparisons for the baseline-adjusted maximum FEV₁ (L) for the per-protocol population were statistically significant ($p < 0.0001$) for all dose comparisons between Albuterol-HFA-MDI and placebo as well as between Proventil HFA and placebo. Comparison between similar doses of active drugs showed only small differences which were not statistically significant. Comparison of doses within each drug product showed a trend to higher maximum FEV₁ with increasing doses. For Albuterol-HFA-MDI there was no statistically significant differences between doses, but for the Proventil HFA, there was a statistically significant difference between the 90 mg and the 270 mg dose ($p = 0.0052$).

The applicant also sought, but was unable to show, bioequivalence between the test (Albuterol-HFA-MDI) and reference (Proventil HFA) products. The potency ratio (with 90% confidence intervals) was calculated to be 1.13, but the derived confidence intervals of 0.77-1.91 exceeded the protocol-defined confidence intervals of 0.67-1.50. Therefore, in this study, bioequivalence between Albuterol-HFA-MDI and Proventil HFA could not be established based on the FEV₁ AUEC₀₋₆ data.

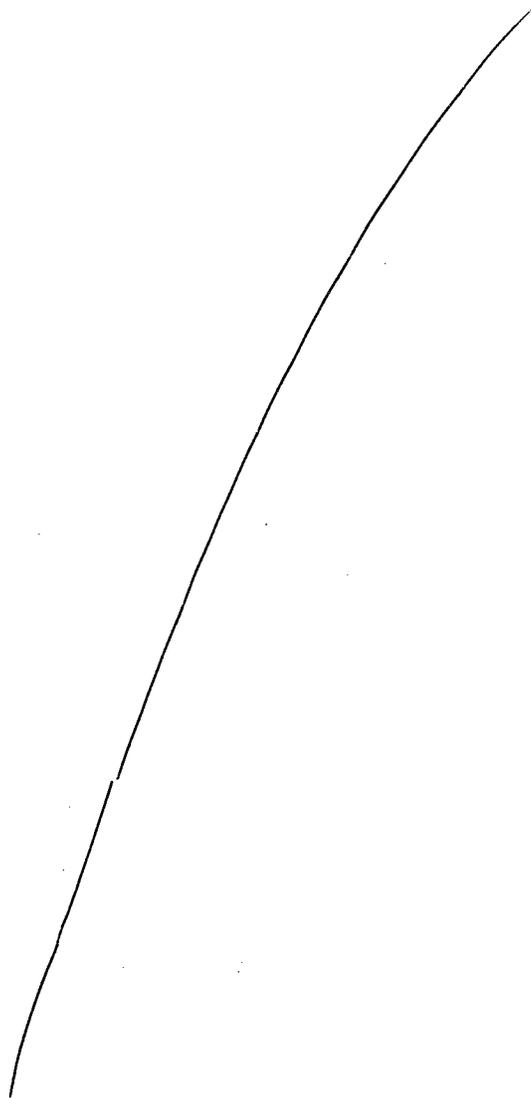
The applicant also performed a number of post-hoc efficacy analyses, comparing Albuterol-HFA-MDI with Proventil HFA. These analyses included baseline-adjusted percent predicted FEV₁ AUEC₀₋₆, baseline-adjusted maximum percent predicted post-dose FEV₁, time to maximum FEV₁, time to response onset (15% increase in FEV₁ over baseline), and duration of response as measured both from the time of dosing and the time of response onset. The baseline-adjusted percent predicted FEV₁ AUEC₀₋₆, and baseline-adjusted maximum percent predicted post-dose FEV₁ analyses yielded no new information. There were no significant differences between products for time to maximum FEV₁ or time to response onset. The paired raw median time to maximum response was 0.98 and 0.76 hours, 0.90 and 1.01 hours, and 0.88 and 0.76 hours for the 90, 180, and 270mg doses of Albuterol-HFA and Proventil HFA, respectively. The paired raw median time to response onset was 0.36 and 0.31 hours, 0.20 and 0.28 hours, and 0.25 and 0.14 hours for the 90, 180, and 270mg doses of Albuterol-HFA and Proventil HFA, respectively. There were no significant

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differences between products for duration of response either from the time of dosing or from the time of response onset.



6.4. Efficacy Discussion and Conclusions

All studies submitted were in support of the indication of treatment or prevention of bronchospasm with reversible obstructive airway disease in adults and children 12 years of age and older. While the clinical program to support marketing approval for Albuterol-HFA-MDI was small, the studies do support approval for this indication. Both studies BNP-301-4-167 and BNP-301-4-105 showed that Albuterol-HFA-MDI at a dose of 180 mcg (2

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inhalations) demonstrates efficacy when compared to placebo, with a net increase in FEV₁ AUEC₀₋₆ in the range of 1.04 to 1.14 L·Hr in mild-to-moderate asthmatics. The clinical program supports comparability but not bioequivalence to the marketed Proventil HFA drug product. The PK study also appears to show comparability between the HFA-MDI product and Proventil HFA. However, there was less systemic exposure with the HFA-BOI drug product than with either Albuterol-HFA-MDI or Proventil HFA. Tachyphylaxis was seen with chronic use, and was roughly similar for all drugs.

Proposed labeling was reviewed during this cycle for overall inclusion and exclusion of safety information, but not for specific wording. The proposed labeling for the CLINICAL TRIALS section of the product label is primarily based on the pivotal efficacy and safety study, BNP-301-4-167. However, the applicant has included _____

_____ Inclusion of information _____ is deemed not appropriate for the label. This information should be communicated to the applicant.

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7. INTEGRATED REVIEW OF SAFETY

7.1. Brief Statement of Findings

No safety trends were identified during the course of this review. Safety was derived from combined clinical information for both the Albuterol-HFA-MDI and HFA-BOI drug products. While pharmacokinetic (PK) and pharmacodynamic (PD) parameters for the Albuterol-HFA-MDI drug product were comparable to the marketed drug product Proventil HFA, PK and PD parameters for the Albuterol-HFA-BOI drug product revealed slightly less exposure with the HFA-BOI than with the HFA-MDI drug product. However, differences were not considered significant with respect to the safety findings in the review, allowing review and inclusion of safety information from the HFA-BOI drug product in this application.

Evaluation of systemic safety (pharmacological effects) including systolic and diastolic blood pressure, serum glucose and potassium, and ECG parameters of heart rate, QT and QTc intervals revealed no unexpected or new safety information regarding the effects of albuterol or the specific drug products being evaluated. There were no unusual trends in adverse events in any of the studies.

However, adequacy of testing of device performance remains an open issue that has not been completely addressed by the applicant. As noted in the Device Performance section, eight patients were withdrawn from study BNP 301-4-167 due to an inhaler malfunction, of whom two of the malfunctions were in the MDI drug product, one of which contained active drug product and one contained placebo drug product. Neither of these malfunctions, if investigated, was discussed in the study report or in the summary of safety. This information should be provided by the applicant.

7.2. Methods and Content (Materials Utilized in Review)

Four studies were evaluated for safety information. These include two clinical studies of six and twelve weeks duration, one active-controlled cumulative dose PK/PD safety study, and one active- and placebo-controlled single-dose PD study. The studies are summarized below:

BNP-301-4-167 was a six-week, multi-center, randomized, double-blind / double-dummy vs placebo, evaluator-blind vs Proventil HFA, placebo- and active-controlled, parallel group multiple-dose study, incorporating two 3-week life-of-device tests, conducted in mild-to-moderate asthmatics (FEV_1 50-85% predicted) ≥ 12 years of age. The study compared the efficacy of Albuterol HFA-MDI versus placebo-HFA-MDI, as well as with Albuterol-HFA-BOI and the active comparator Proventil HFA, each dosed at two inhalations four times daily for six weeks.

IX-101-105 was a 12-week, ex-US, multi-center, randomized, placebo- and active-controlled, double-blind, double-dummy, parallel group multiple-dose study in mild-to-moderate asthmatics (FEV_1 50-80% predicted) ages 18-65y who showed airway reversibility $FEV_1 \geq 15\%$ after 200 mcg albuterol. Since this study did not include the HFA-MDI but did include the HFA-BOI drug product, this study was considered to

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contain important safety information that might relate to both drug products, and reviewed as a safety study.

IXR-107-1-105 was a cumulative-dose, single-dose PK/PD 3-way crossover, safety study of Albuterol HFA MDI and BOI compared to the reference product Proventil HFA. This study included both PK and extrapulmonary pharmacologic parameters, and therefore was reviewed as a pivotal safety study.

BNP-301-4-105 was a multi-center, randomized, evaluator-blind, placebo- and active-controlled, 7-sequence, 7-period, single-dose crossover study in moderate to severe asthmatics (FEV₁ 50-75% predicted) 18-50 years of age. The study compared Albuterol-HFA-MDI at doses of 90, 180, and 270 mcg with placebo HFA-MDI and the active comparator Proventil HFA (90, 180, and 270 mcg). This study yielded minimal, single-dose safety information.

7.3. Description of Patient Exposure

Overall, 1810 patients were exposed to albuterol formulations in the clinical program: 941 to Albuterol-HFA-MDI, 266 Albuterol-HFA-BOI, and 540 to commercially approved comparators (131 to Proventil HFA, 409 to Albuterol-CFC). Including all the safety studies and the postmarketing study SAMM-57, the number of patients and subjects exposed by study and formulation is shown in Table 7. The number of patient-days of exposure is shown in Table 8. The duration of exposure to active drug in the placebo-controlled, multiple dose studies is shown in Table 9. Note that the pivotal efficacy and safety study, BNP 301-4-167 only included 58 patients exposed to Albuterol-HFA-MDI, with only 49 patients exposed for 6 weeks, and the two placebo-controlled multiple-dose studies involved far more exposure to Albuterol-HFA-BOI than to Albuterol-HFA-MDI. Most of the patient exposure to Albuterol-HFA-MDI was in the uncontrolled, open-label, 12-week SAMM-57 study. [M2, v 1.3, p 200070]

Patient withdrawals are shown in Table 10. Demographics of patient exposure are discussed in Section 9 of this review, Use in Special Populations, but the demographics of patients who were withdrawn from multiple dose studies is shown in Table 11.

Table 7. Number of patient and subjects exposed to albuterol by study and formulation

Study	Albuterol-HFA-MDI	Albuterol-HFA-BOI	Placebo	Comparators
BNP 301-4-167^a	58	173	58	56
IX-101-105 ^b		69	66	68
BNP 301-4-105 ^c	52		51	50
IX-100-105 ^d	25	24		25
IX-105-105 ^e	68			70
SAMM-57 ^f	738			271
Total Patients	941	266	174	540
IXL 106-1-105 ^g	16	15		15
IXL 107-1-105	16	15		15
Total Subjects	32	30		30

a Pivotal 6-week safety and efficacy study is shown in **bold**
b 12-week therapeutic efficacy and safety study
c Single-dose crossover study

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- | |
|---|
| d Cumulative-dose crossover study |
| e 6-week safety study in patients 7-18 years of age, no placebo group |
| f 12 week, open-label, safety study |
| g Failed PK/PD study |

Source: M2, v 1.3, Table 14, p 200070

Table 8. Number of patient days of exposed to albuterol by study and formulation

Study	Albuterol-HFA-MDI	Albuterol-HFA-BOI	Placebo	Comparators
BNP 301-4-167 *	2357	6816	2317	2299
IX-101-105		5124	4620	
BNP 301-4-105	153		51	150
IX-100-105	25	24		48
IX-105-105	2822			
SAMM-57	76088			
Total Patient-days	81455	11964	6988	2497

* Pivotal 6-week safety and efficacy study is shown in bold

Source: M2, v 1.3, Table 15, p 200070

Table 9. Duration of exposure to active drug in placebo-controlled, multiple dose studies *

Weeks of Exposure	Number of patients			
	BNP 301-4-167			IX-101-105
	Alb-HFA-MDI	Alb-HFA-BOI	Proventil HFA	Alb-HFA-BOI
1	55	169	57	69
2	55	168	57	69
3	54	163	57	68
4	51	155	51	67
5	50	150	51	67
6	49	144	50	67
7				66
8				65
9				62
10				61
11				61
12				60

* Mean daily exposure was between 7.3 and 8.0 puffs per day

Source: M2, v 1.3, Table 16, p 200072

Table 10. Reason for patient withdrawal in multiple-dose studies

Study / Treatment	N	Withdrawn		Patient Request	Protocol Violation	AE	Lost	Other
		N	%					
BNP 301-4-167								
Placebo HFA	58	11	19	3 (27)		3 (27)	1 (9)	4 (36)
Alb-HFA-MDI	58	6	10		1 (17)	4 (67)		1 (17)
Alb-HFA-BOI	173	32	18	3 (9)	2 (6)	17 (53)	4 (13)	8 (25)
Proventil HFA	56	6	11	1 (17)		2 (33)		3 (50)
IX-101-105								
Placebo HFA	66	11	17	2 (18)	4 (36)	4 (36)		1 (9)

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Study / Treatment	N	Withdrawn		Patient Request	Protocol Violation	AE	Lost	Other
		N	%					
Alb-HFA-BOI	69	8	12	3 (37)	1 (13)	3 (38)	1 (13)	1 (12)

Source: M2, v 1.3, Table 2.4.1, p 200117

Table 11. Patient disposition and demographics in multiple-dose studies *

Study / Treatment	N	Withdrawn		Males	Females	<65	>65	White	Black
		N	%						
BNP 301-4-167									
Placebo HFA	58	11	19	7/29 (24)	4/29 (14)	10/56 (18)	1/2 (50)	8/47 (17)	2/6 (33)
Alb-HFA-MDI	58	6	10	2/20 (10)	4/38 (11)	6/57 (11)	0/1 (0)	5/45 (11)	1/10 (10)
Alb-HFA-BOI	173	32	18	12/65 (19)	20/108 (19)	29/160 (18)	3/13 (23)	25/142 (18)	6/25 (24)
Proventil HFA	56	6	11	1/22 (5)	5/34 (15)	6/53 (11)	0/3 (0)	6/48 (13)	0/6 (0)
IX-101-105									
Placebo HFA	66	11	17	5/23 (22)	6/43 (14)	11/66 (17)		11/66 (17)	
Alb-HFA-BOI	69	8	12	3/24 (13)	5/45 (11)	8/69 (12)		8/69 (12)	

* Demographics shown: Number of patients withdrawn/Number of patients in that subgroup (Percent withdrawn in that subgroup). Other ethnic groups not shown.

Source: M2, v 1.3, Table 2.3, p 200116

7.4. Safety Findings from Clinical Studies

7.4.1. Systemic safety (Study IXR-107-1-105)

Both pharmacokinetic data and extrapulmonary safety were evaluated in study IXR-107-1-105. The data from this study are presented in this section.

This was a single-center, randomized, evaluator-blind, active-controlled, three-treatment, three-period, three-sequence, cumulative-dose crossover comparison safety study evaluating the extrapulmonary and pharmacokinetic profiles of Albuterol-HFA-MDI, Albuterol-HFA-BOI, and Proventil HFA in 15 healthy subjects. Eligible subjects were randomized to receive 2 + 4 + 6 actuations administered at 30 minutes intervals (180 + 360 + 540 for a total treatment dose of 1080 mcg) of Albuterol-HFA-MDI, Albuterol-HFA-BOI, or Proventil HFA, with a minimum of 6 days between treatments. Sixteen subjects were randomized, one withdrew, and 15 subjects completed the study (per protocol population). Even though this was a single-dose study with no placebo control, the high-dose PK/PD safety data captured in the study makes it a 'pivotal' study. The study contained comparative data between Albuterol-HFA-MDI and Proventil HFA drug products, as well as between the HFA-MDI and HFA-BOI drug products. While the former comparative PK and pharmacologic data supported the overall 505(b)(2) program, the latter PK data allowed linkage of systemic exposure between the HFA-MDI and HFA-BOI drug products, permitting inclusion of the safety data from the BOI drug product in the MDI datasets. The study was reviewed by both the Division's Pharmacology & Biopharmaceutics and Medical Reviewers.

7.4.1.1. Pharmacokinetics

There were no significant differences among treatment groups in PK parameters at baseline. With treatment, the concentration-time curves for all three products substantially

overlapped, suggesting that the PK parameters are comparable. There were no statistically significant differences between Albuterol-HFA-MDI and Proventil HFA for any parameters. Administration of Albuterol-HFA-BOI resulted in a slightly earlier T_{max} , lower C_{max} , and lower total exposure (AUC_{0-t} and AUC_8) than either Albuterol-HFA-MDI or Proventil HFA. The differences between Albuterol-HFA-BOI and Proventil HFA for AUC_{0-t} and AUC_8 were statistically significant. There were also statistically significant differences between Albuterol-HFA-MDI and Albuterol-HFA-BOI for AUC_{0-t} , and AUC_8 , and C_{max} . However, the 90% confidence intervals for the ratios between all evaluated PK parameters were within 80-120%, implying that these drug products are comparable and that any differences noted may not be clinically relevant.

7.4.1.2. Extrapulmonary (Pharmacologic) Parameters

Extrapulmonary pharmacologic parameters included systolic and diastolic blood pressure, serum glucose and potassium, and ECG parameters of heart rate, QT, and QTc intervals. All changes in pharmacologic parameters were expected based on the known physiologic effects of albuterol drug substance. Mean changes in systolic and diastolic BP and serum glucose and potassium were comparable among products. Mean changes in heart rate, QT, and QTc intervals were comparable between Albuterol-HFA and Proventil HFA, but not between Albuterol-HFA-BOI and the other products. Albuterol-HFA-BOI raised the heart rate less and had more negative effect on QT interval than the other two products, producing a very small net increase in QTc (+5.00) 15 minutes after the third (1080 mcg) dose. In contrast, the net increase in QTc for Albuterol-HFA and Proventil HFA peaked at 25.4 to 33.3 msec 15-30 minutes after the third dose. The smaller effect on QTc interval noted for Albuterol-HFA-BOI compared to either Albuterol-HFA-MDI or Proventil HFA is likely due to the high variability of QTc results and the fact that there was only one baseline ECG measurement prior to each treatment, making the baseline measurements far less reliable (generally at least three baseline measurements are recommended). In fact, two subjects had elevated baseline QTc intervals >440 msec prior to Albuterol-HFA-BOI administration but not prior to other treatment periods. These differences may have influenced the QTc results for the Albuterol-HFA-BOI treatment group, while not affecting the ECG parameters for the Albuterol-HFA-MDI or Proventil HFA treatment groups.

Analysis of QTc outliers (QTc \geq 440 msec with a >10 msec change) did not show any differences among groups. Adverse events were comparable among treatments, although both Albuterol-HFA-MDI and Albuterol-HFA-BOI were associated with a slightly higher incidence of tremor than Proventil HFA.

7.4.2. Adverse Events

Because of the paucity of safety data for the HFA-MDI drug product, adverse events for the HFA-BOI product were evaluated and are included in the tables below. It was felt that the systemic exposure safety data from study IXR-107-1-105 showed similar enough exposure to allow consideration of the HFA-BOI in the overall safety evaluation.

Adverse events from the multiple dose studies were pooled. To do so required pooling of only the first six weeks of adverse events from the 12-week study, IX-101-105, with the adverse events from the six-week efficacy and safety study, BNP-301-4-167. These are

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shown in Table 12, whereas the adverse events occurring in study BNP-301-4-167 are shown in Table 13. Note that this study enrolled patients to Albuterol-HFA-BOI and Placebo, but not to Albuterol-HFA-MDI, so the incidence of adverse events from patients treated with Albuterol-HFA-MDI in the two tables are the same, but the incidence of placebo adverse events differs slightly. No unusual or unexpected trends in adverse events, including serious or unexpected adverse events, were noted.

Table 12. Adverse events incidence of $\geq 2\%$ of patients in a treatment group occurring within the first 6 weeks of multiple-dose studies

	Albuterol- HFA-MDI n = 58 (%)	Albuterol- HFA-BOI n = 242 (%)	Proventil HFA n = 56 (%)	Pooled Placebo n = 124 (%)
Body as a Whole				
Abdominal pain	0	1 (0.4)	3 (5.4)	2 (1.6)
Back pain	2 (3.4)	0	2 (3.6)	3 (2.4)
Flu syndrome	0	3 (1.2)	1 (1.8)	4 (3.2)
Headache	4 (6.9)	12 (5.0)	3 (5.4)	4 (3.2)
Cardiovascular system				
Tachycardia	2 (3.4)	1 (0.4)	1 (1.8)	0
Musculo-skeletal system				
Pain	2 (3.4)	2 (0.8)	0	0
Nervous system				
Dizziness	2 (3.4)	0	0	0
Respiratory system				
Asthma	4 (6.9)	19 (7.9)	3 (5.4)	5 (4.0)
Bronchitis	0	5 (2.1)	1 (1.8)	4 (3.2)
Cough increased	2 (3.4)	2 (0.8)	0	3 (2.4)
Dyspnea	1 (1.7)	1 (0.4)	0	4 (3.2)
Infection	2 (3.4)	4 (1.7)	2 (3.6)	2 (1.6)
Pharyngitis	8 (13.8)	22 (9.1)	4 (7.1)	6 (4.8)
Rhinitis	3 (5.2)	3 (1.2)	2 (3.6)	1 (0.8)

Source: M2, v. 13, Table 24, p 200079-81

Table 13. BNP-301-4-167, Adverse events with an incidence of $\geq 3\%$ of patients

	Albuterol- HFA-MDI n = 58 (%)	Albuterol- HFA-BOI n = 173 (%)	Proventil HFA n = 56 (%)	Placebo n = 58 (%)
Total patients with an AE	23 (39.7)	71 (41.0)	20 (35.7)	22 (37.9)
Body as a Whole				
Abdominal pain	0	1 (0.6)	3 (5.4)	0
Back pain	2 (3.4)	0	2 (3.6)	3 (5.2)
Flu syndrome	0	0	1 (1.8)	2 (3.4)
Headache	4 (6.9)	11 (6.4)	3 (5.4)	1 (1.7)
Cardiovascular system				
Tachycardia	2 (3.4)	1 (0.6)	1 (1.8)	0
Musculo-skeletal system				
Pain	2 (3.4)	2 (1.2)	0	0
Nervous system				
Dizziness	2 (3.4)	0	0	0

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	Albuterol- HFA-MDI n = 58 (%)	Albuterol- HFA-BOI n = 173 (%)	Proventil HFA n = 56 (%)	Placebo n = 58 (%)
Respiratory system				
Asthma	4 (6.9)	17 (9.8)	3 (5.4)	4 (6.9)
Bronchitis	0	5 (2.9)	1 (1.8)	2 (3.4)
Cough increased	2 (3.4)	1 (0.6)	0	2 (3.4)
Infection	2 (3.4)	4 (2.3)	2 (3.6)	2 (3.4)
Pharyngitis	8 (13.8)	22 (12.7)	4 (7.1)	5 (8.6)
Rhinitis	3 (5.2)	3 (1.7)	2 (3.6)	1 (1.7)

Source: Source: M2, v 1.3, Table 4.3.13, p 200196

7.4.3. Device performance

At the End of Phase 2 meeting, the Division had requested evaluating device performance in the pivotal clinical trial, BNP 301-4-167. The Division requested an evaluation of device performance at the end of device use i.e. at the end of each three week period. The length of the clinical trial, six weeks, would then provide two life-of-the-device periods. The Division specifically requested that this include an evaluation of both clogging and spray pattern. The Division also requested information regarding frequency of jamming of the BOI device. The applicant submitted information regarding visual inspection of canisters at the end of the study, a sampling of canisters sent for *in vitro* testing, and results of a patient satisfaction device performance questionnaire.

The inhaler mouthpiece was visually inspected for all devices when returned at Days 22 and 43. Greater than 98.5% of the inhalers were returned at each visit. Patient instructions had been to clean the inhalers weekly. For the MDI device, deposits were observed in 9.9% and 14.6% of inhalers on Days 22 and 43, respectively. For the BOI device, deposits were observed in 8.7% and 7.5% of inhalers on Days 22 and 43, respectively. None of the deposits were associated with any reported device malfunctions.

In the clinical study, the applicant sought to measure patient satisfaction with device performance by a non-validated questionnaire. The questionnaire had been developed by the applicant and was completed by each patient at Day 43 or at early termination. The MDI and BOI devices were compared for ease of use, ease of learning to use, ease of breathing, overall opinion, and preference for the device. While most patients rated both products very easy to use, a comparison of ease of use

However, among patients randomized to active treatment with the MDI device, the overall opinion was evenly split between the two devices, whereas among those randomized to active treatment with the BOI device,

Eight (8) patients were discontinued during study BNP 301-4-167 due to an inhaler malfunction (6 BOI and 2 MDI). Not all of the devices that malfunctioned contained active drug (i.e. some were placebo inhalers given to patients randomized to other treatments). The

study tables attributed withdrawal to the study drug to which the patient was randomized. Three of the eight malfunctioning inhalers contained active drug (2 BOI and 1 MDI). No explanation was given as why these patients were discontinued as opposed to dispensing new inhalers and allowing continuation in the study. Review of the listing of inhalers sent for *in vitro* testing reveals that none of these were part of the 24 inhalers sent for evaluation of the drug delivery profile and particle size distribution. The defect analysis revealed that one (placebo) inhaler had malfunctioned due to a deformed actuator orifice, in turn due to excessive pressure that had been used to actuate canister. When the canister was tested with a new actuator, no problem was noted. No problem could be found with the second (active) returned device. No information was provided for the six BOI canisters returned due to a malfunction.

There were no device performance measurements or *in vitro* testing of canisters in any of the other clinical trials that were reviewed, and no device failures or clinical issues regarding device performance were noted in any of those clinical trials.

Only 24 canisters for 12 patients (12 MDI and 12 BOI) were sent for post-study *in vitro* testing. This included 6 of each for evaluation of dose content uniformity and 6 of each for evaluation of particle size distribution. None of the canisters were out of specification. However, the drug product for one patient assigned to MDI treatment was sent for post-study testing and was found to contain placebo; active drug was found in the patient's BOI device canister. The number sent for testing is below the current recommendation for post-use *in vitro* testing. Therefore, it is suggested that the applicant provide data from at least 100 canisters post-use as a Phase 4 commitment.

7.5. Miscellaneous Studies

No safety information from other studies was reviewed.

7.6. Literature Review of Safety

No literature review of safety was provided in this application.

7.7. Postmarketing Surveillance

In the submissions to this NDA, the applicant indicates that Albuterol-HFA-MDI is being marketed in nine countries (see Post-Marketing section of this review). The submission states that units of Albuterol-HFA-MDI were sold in Europe in 2001 through August 2002. No adverse events had been reported from Cyprus, Czech Republic, Germany, Netherlands, Malta, Jamaica, or Mauritius. However, in the UK, a total of 15 people reported one or more adverse events, shown in Table 14. Note that one patient reported an adverse event of a failed inhaler. Another 10 patients reported adverse events with Albuterol-HFA-BOI, including lack of efficacy in seven, wheezing in three, gagging in three, and nausea in two patients. [M2, v1.3, p 200103-4]

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Table 14. Post-marketing Adverse Events with Albuterol-HFA-MDI

Age / Sex	Adverse Event	Outcome
29 / NK	Exacerbation of asthma	Unknown
60 / NK	Bronchospasm, Cough, Drug ineffective	Recovered
16 / M	Muscle cramps, Creatinine phosphokinase increased	Recovered
46 / F	Angioedema, Face edema	Recovering
57 / F	Taste perversion, Glossitis, Tongue ulceration	Recovered
35 / F	Aggravated bronchospasm	Recovered
28 / F	Exacerbation of asthma	Recovered
MK / F	Inhaler failed	Recovered
NK / NK	Lack of efficacy	Recovered
74 / M	Depression	Recovered
15 / M	Erythematous rash, Pain, Blister, Akinesia, Maladministration of drug	Unknown
NK / M	Photosensitivity	Recovered
4 / M	Aggression, Agitation, Drug abuse, Hallucinations	Recovered
45 / M	Exacerbation of asthma, Drug ineffective	Not recovered
27 / F	Tongue edema, Face edema, Pyrexia	Recovered

Source: M2, v1.3, Table 38, p 200103-4

In addition, there were two studies involving Albuterol-HFA-MDI that were either ongoing or were initiated after the time of submission of NDA 21-457 [6/6/03, Tab 2.7; 8/7/03, Tab 1, p 100001]. The studies are:

BNP-201-4-167: This is a double-blind, double-dummy, placebo-controlled, dose-ranging, 5-period, single-dose crossover efficacy study comparing Albuterol-HFA-BOI and Albuterol-HFA-MDI with placebo in asthmatics 18-50y with FEV₁ 50-75% predicted. Of the 40 patients enrolled, there were no serious events. One patient discontinued due to an adverse event, severe bronchitis.

IXR-202-4-167: This is an open-label, 2-period, single-dose crossover efficacy comparison of Albuterol-HFA-BOI and Albuterol-HFA-MDI in asthmatics ≥18y with poor inhaler coordinating ability. Of the 12 patients enrolled, there have been no serious adverse events, and no discontinuations due to adverse events.

7.8. Safety Update

A 120-day safety update report was submitted June 6, 2003, and updated in the submission of August 7, 2003. Other adverse events listed through April of 2003 include reports of lack of efficacy, gagging, nausea, burning in the throat, and lightheadedness as shown in Table 15. Note that the applicant submitted reports for both the HFA-MDI and HFA-BOI products, since both use the same canister. The applicant states that the spectrum of events is similar to that of the post-marketing reports submitted to the NDA. [8/7/03, Tab 1, p 100001].

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Table 15. 120-day Safety Update: Adverse Events up to April 7, 2003

Reference Number	Age / Sex	Adverse Event	Outcome
Albuterol-HFA-MDI			
1264	NK / F	Lack of efficacy, breathlessness	Resolved
1279	NK / F	Lack of efficacy	Resolved
1286	NK / M	Lack of efficacy	Resolved
1298	NK / M	Lack of efficacy	Resolved
1278	5 / F	Gagging, nausea	Resolved
Albuterol-HFA-BOI			
1232	NK / NK	Lack of efficacy	Resolved
1241	NK / NK	Lack of efficacy	Resolved
1242	NK / NK	Lack of efficacy	Resolved
1255	NK / NK	Lack of efficacy	Resolved
1283	NK / F	Lack of efficacy leading to hospitalization	Resolved
1287	NK / F	Lack of efficacy	Resolved
1296	NK / F	Lack of relief	Resolved
1303	NK / F	Lack of relief	Resolved
1198	NK / NK	Wheeziness	Resolved
1199	NK / NK	Wheeziness; lack of relief	Resolved
1200	NK / NK	Wheeziness, no relief	Resolved
1206	NK / NK	Gagging, lack of efficacy	Resolved
1207	NK / NK	Gagging, nausea	Resolved
1208	NK / NK	Gagging, nausea	Resolved
1265	NK / NK	Burning sensation in the throat	Resolved
1281	NK / M	Lightheadedness	Resolved
1272	NK / NK	Nausea	Resolved

Source: 6/6/03, Tab 2.7.4

7.9. Drug Withdrawal, Abuse, and Overdose Experience

There were no instances of overdosage noted in the clinical program [M2, v 1.3, p 200102]. The clinical program included several studies that evaluated the pharmacokinetic, pharmacodynamic, and/or pharmacologic effects of high cumulative doses of albuterol. In studies IXL-106-1-105 and IXL-107-1-105, healthy subjects were exposed to three cumulative doses of 1080 mcg of albuterol, and in study IX-100-105, patients were exposed to four cumulative doses of 1500 mcg of albuterol. There were no unexpected adverse events, and the pharmacological effects noted were all effects that were expected of albuterol.

There are a few reports of intentional or unintentional overdosage with albuterol. Most involve oral formulations with accidental ingestion by children or excessive ingestion by persons with a history of depression. A few cases of abuse of inhaled albuterol have been published. Most are in young asthmatics. Since this has also been reported with other inhaled drugs such as beclomethasone and terbutaline, the applicant states (and provides several references to this effect) that this is likely due to addiction to the fluorocarbons. Since there is no evidence that HFA-134a induces central nervous system stimulation, the applicant states that the likelihood of abuse is small, and no more than for Albuterol-CFC products. The applicant states that in post-marketing surveillance there was one case report

of a four-year old boy in the UK found to be abusing Albuterol-HFA (manufacturer unknown). This child had aggression, agitation, and hallucinations, which resolved upon withdrawal of the drug. [M2, v 1.3, p 200102]

Proposed labeling for the Overdosage section of the product label is identical to that for Proventil HFA. Based on the information provided in this application, the proposed labeling for this section is acceptable.

7.10. Adequacy of Safety Testing

Safety testing for this application was considered to be borderline but probably adequate. There were two issues regarding adequacy of safety testing: the numbers of patients exposed, and the adequacy of testing of device performance.

Two multiple dose studies were submitted in support of this application, only one of which dosed patients with the HFA-MDI drug product for up to six weeks (study BNP 301-4-167). The second study was submitted at the Division's request primarily because of the paucity of safety data from the 58 patients randomized to Albuterol-HFA-MDI treatment in study BNP 301-4-167. This second study, IX-101-105, was a 12-week placebo-controlled study that evaluated the HFA-BOI drug product. This study was accepted as a safety study in an effort to increase the database for both drug products, with the assumption that the applicant could link the two drug products by PK and PD data.

The linkage comes from two studies, one providing PD data and one providing PK data. The PD data comes from study BNP 301-4-167 (study BNP-301-4-105 did not use the HFA-BOI drug product), and PK data comes from study IXR-107-1-105. The combined data supports the conclusion that there is slightly less systemic exposure with use of the HFA-BOI drug product than the HFA-MDI drug product. In study BNP 301-4-167, the AUEC₀₋₆ (L•Hr) of baseline-adjusted FEV₁ at Day 43/LOCF was 1.28 and 1.17 for Albuterol HFA-MDI and Albuterol HFA-BOI, respectively. In study IXR-107-1-105, administration of Albuterol-HFA-BOI resulted in a slightly earlier T_{max}, lower C_{max}, and lower total exposure (AUC_{0-t} and AUC₈) than Albuterol-HFA-MDI. The differences between Albuterol-HFA-MDI and Albuterol-HFA-BOI were statistically significant for AUC_{0-t}, AUC₈, and C_{max}. It can be concluded that these drug products (despite the fact that the canister and actuator orifice are identical) yield slightly different clinical PD and PK results, with the HFA-BOI drug product yielding slightly lower systemic exposure. However, it is not felt that these differences are clinically relevant with respect the safety information to be derived from the two clinical studies provided in this application. Therefore, the safety information from both studies does provide adequate information to support this application.

However, adequacy of testing of device performance remains an open issue that has not been completely addressed by the applicant. As noted in the Device Performance section above, eight patients were withdrawn from study BNP 301-4-167 due to an inhaler malfunction, of whom two of the malfunctions were in the MDI drug product, one of which contained active drug product and one contained placebo drug product. Neither of these malfunctions, if investigated, was discussed in the study report or in the summary of safety. This information should be provided by the applicant.

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7.11. Labeling Safety Issues and Postmarketing Commitments

The pharmacological and pharmacodynamic effects of orally inhaled albuterol are well characterized. There are no specific labeling issues raised during the course of this review.

Therefore no postmarketing commitments are recommended.

The proposed ADVERSE REACTIONS section of the label was reviewed for overall inclusion and exclusion of safety information, but not for specific wording. The primary safety information in this section includes a description of the pivotal safety and efficacy study, BNP-301-4-167, followed by a table of adverse events based on the 58 patients enrolled in the Albuterol-HFA-MDI arm, the 58 patients in the placebo arm, and the marketed active comparator Proventil HFA (trade name omitted). In addition, adverse events from the 173 patients enrolled in the Albuterol-HFA-BOI arm of this study are included in a separate paragraph. Information is also included about adverse reactions in cumulative dose studies. Based on this safety review, inclusion of this information is considered appropriate. In addition, the applicant has proposed

Information from these studies is of borderline usefulness, but may remain in the label.

**APPEARS THIS WAY
ON ORIGINAL**

8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

The pharmacological and pharmacodynamic effects of orally inhaled albuterol are well characterized. No dosing, regimen, or administration issues were raised for the Albuterol-HFA-MDI device during this review. For the indication of treatment or prevention of bronchospasm with reversible obstructive airway disease in adolescents and adults ≥ 12 years of age and older, the dosing, regimen, and administration of the Albuterol-HFA-MDI is similar to other orally inhaled albuterol drug products, and is supported by the clinical trials submitted to this application. It is recommended that the applicant's suggested dose of 2 inhalations repeated every 4-6 hours be the approved dose.

Proposed labeling for the DOSAGE and ADMINISTRATION section of the product label is almost identical to that for Proventil HFA. The differences are discussed in the bullets below. Based on the information provided in this application, the proposed labeling for this section is acceptable except for inclusion of EIB.

- The proposed Albuterol-HFA-MDI PI includes dosage and administration information ~~_____~~ this information should be removed from the Dosage and Administration section.
- The proposed Albuterol-HFA-MDI PI recommends the release of ~~_____~~ test sprays as compared to the Proventil HFA PI which suggests four test sprays. Unless the CMC reviewer suggests otherwise, this is acceptable from a clinical perspective.

**APPEARS THIS WAY
ON ORIGINAL**

9. USE IN SPECIAL POPULATIONS

9.1. Evaluation of Applicant's Gender, Age, Race, or Ethnicity Efficacy and Safety Analyses and Adequacy of Investigation

The demographics of patients enrolled in the multiple dose studies are shown in Table 16. There were very few patients randomized in the 12 to 18 and the ≥65 year old age ranges. The majority of patients were females, and an overwhelming majority was White. However, the limited numbers in certain age or races should not raise any safety concerns. Since the pharmacological and pharmacodynamic effects of albuterol are well characterized, it was not expected that either safety or efficacy would be affected by these demographic parameters, and further data regarding use in these groups was not considered necessary to support this application.

Table 16. Patient demographics and baseline characteristics of multiple dose studies*

Demographic	BNP 301-4-167				IX-101-105	
	Alb-HFA-MDI n = 58	Alb-HFA-BOI n = 173	Proventil HFA n = 56	Placebo n = 58	Alb-HFA-BOI n = 69	Placebo n = 66
Age, years: (mean)	39.4	38.7	40.1	39.8	42.4	40.6
≥12 to <18 years	8 (13.8)	23 (13.3)	4 (7.1)	3 (5.2)		
≥18 to <40 years	18 (31.0)	67 (38.7)	27 (48.2)	29 (50.0)	23 (33.3)	30 (45.5)
>40 to <65 years	31 (53.5)	70 (40.5)	22 (39.3)	24 (41.4)	46 (66.7)	36 (54.5)
≥65 years	1 (1.7)	13 (7.5)	3 (5.4)	2 (3.5)		
Gender:						
Males	20 (34.5)	65 (37.6)	22 (39.3)	29 (50.0)	24 (34.8)	23 (34.8)
Females	38 (65.5)	108 (62.4)	34 (60.7)	29 (50.0)	45 (65.2)	43 (65.2)
Race:						
White	45 (77.6)	142 (82.1)	48 (60.7)	47 (81.3)	69 (100)	66 (100)
Black	10 (17.2)	25 (14.5)	6 (60.7)	6 (10.3)		
Asian	2 (3.5)	5 (2.9)	1 (1.8)	1 (1.7)		
Other	1 (1.7)	1 (0.6)	1 (1.8)	4 (6.9)		

* Table shows mean for age in years, N (%) for other results. Mean ages are taken from study reports, as they differ slightly from what is reported in the ISS

Source: M2, v 1.3, Table 20, p 200075 and study reviews in Appendix

9.2. Pediatric Program

Except for a supporting study, IX-105-105, performed in patients 7-18 years of age, pediatric studies were not submitted with this application.

9.3. Comments on Data Available or Needed in Other Populations (Such as Renal or Hepatic Compromised Patients, Use in Pregnancy)

Albuterol was not studied in pregnant women in the clinical program. Information is supplied from the labeling for Proventil HFA regarding class labeling as Pregnancy

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Category C [M2, v 1.3, p 200100]. Since the pharmacological and pharmacodynamic effects of orally inhaled albuterol are well characterized, data regarding use in other populations was not considered necessary to support this application.

9.4. Proposed Labeling

IVAX has created a new section of their proposed product

This section includes information about use in labor and delivery, by nursing mothers, in pediatric patients, and in the geriatric population. The information and wording of these subsections are identical to similar sections in the Proventil HFA label

Consequently, although the wording is the same, the location may not make the information as clear as in the Proventil HFA label. The applicant should address this issue in future labeling.

**APPEARS THIS WAY
ON ORIGINAL**

Use in Special Populations

10. CONCLUSIONS AND RECOMMENDATIONS

10.1. Conclusions Regarding Safety and Efficacy

All studies submitted were in support of the indication of treatment or prevention of bronchospasm with reversible obstructive airway disease in adults and children 12 years of age and older. While the clinical program to support marketing approval for Albuterol HFA-MDI was small, the studies do support approval for this indication. Both studies BNP-301-4-167 and BNP-301-4-105 showed that Albuterol HFA-MDI at a dose of 180 mcg (2 inhalations) demonstrates efficacy when compared to placebo, with a net increase in FEV₁ AUEC₀₋₆ in the range of 1.04 to 1.14 L·Hr in mild-to-moderate asthmatics. The clinical program supports comparability but not bioequivalence to the marketed Proventil HFA drug product. The PK study also appears to show comparability between the HFA-MDI product and Proventil HFA. However, there was less systemic exposure with the HFA-BOI drug product than with either Albuterol HFA-MDI or Proventil HFA. Tachyphylaxis was seen with chronic use, and was roughly similar for all drugs.



No safety trends were identified during the course of this review. Safety was derived from combined clinical information for both the Albuterol HFA-MDI and HFA-BOI drug products. While pharmacokinetic (PK) and pharmacodynamic (PD) parameters for the Albuterol HFA-MDI drug product were comparable to the marketed drug product Proventil HFA, PK and PD parameters for the Albuterol HFA-BOI drug product revealed slightly less systemic exposure with the HFA-BOI than with the HFA-MDI drug product. However, differences were not considered significant with respect to the safety findings in the review, allowing review and inclusion of safety information from the HFA-BOI drug product in this application.

Evaluation of pharmacologic effects including systolic and diastolic blood pressure, serum glucose and potassium, and ECG parameters of heart rate, QT and QTc intervals revealed no unexpected or new safety information regarding the effects of albuterol or the specific drug products being evaluated. There were no unusual trends in adverse events in any of the studies.

However, adequacy of testing of device performance remains an open issue that has not been completely addressed by the applicant. As noted in the Device Performance section, eight patients were withdrawn from study BNP 301-4-167 due to an inhaler malfunction, of whom two of the malfunctions were in the MDI drug product, one of which contained active drug product and one contained placebo drug product. The defect analysis revealed that one

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(placebo) inhaler had malfunctioned due to a deformed actuator orifice, in turn due to excessive pressure that had been used to actuate canister. No problem could be found with the second (active) returned device. No information was provided for the six BOI canisters returned due to a malfunction. Life-of-the-device, post-use device performance evaluations were limited to [REDACTED] canisters. Therefore, I would suggest [REDACTED]

10.2. Recommendations on Approvability

It is recommended that this NDA for Albuterol HFA-MDI be approved for the indication of treatment or prevention of bronchospasm with reversible obstructive airway disease in adults and children 12 years of age and older. [REDACTED]

10.3. Labeling

Proposed labeling was reviewed during this cycle for overall inclusion and exclusion of safety information, but not for specific wording. The proposed labeling for the CLINICAL TRIALS section is primarily based on the six-week safety and efficacy study BNP-301-4-167, [REDACTED]. The proposed ADVERSE REACTIONS section of the label includes safety information based on the pivotal efficacy and safety study as well as non-pivotal studies. However, many sections of the proposed label are identical to their counterparts in the Proventil HFA product label. Since the application is a 505(b)(2) application for a drug product with well characterized pharmacological and pharmacodynamic effects, inclusion of virtually identical wording in many of these sections is considered appropriate. Specific information relating to various sections of the proposed labeling are addressed below.

While the content is present, the proposed product label follows non-standard ordering for section headings. The product label should follow the order shown in 21 CFR 201.56(d)(1) and (2).

The proposed [REDACTED]

The proposed labeling for the CLINICAL TRIALS section of the product label is primarily based on the pivotal efficacy and safety study, BNP-301-4-167. [REDACTED]

[REDACTED] Inclusion of information [REDACTED] is deemed not appropriate for the label. This information should be communicated to the applicant.

The proposed ADVERSE REACTIONS section of the label includes safety information based on the pivotal efficacy and safety study, BNP-301-4-167. A description of the study is followed by table of adverse events is based on the 58 patients enrolled in the Albuterol-

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HFA-MDI arm, the 58 patients in the placebo arm, and the marketed active comparator Proventil HFA (trade name omitted). In addition, adverse events from the 173 patients enrolled in the Albuterol-HFA-BOI arm of this study are included in a separate paragraph. Information is also included about adverse reactions in cumulative dose studies. Based on this safety review, inclusion of this information is considered appropriate. In addition, the applicant has proposed _____ n
_____ Information
from these studies is of borderline usefulness, but may remain in the label.

The proposed labeling for the DOSAGE and ADMINISTRATION section of the product label is almost identical to that for Proventil HFA. The differences are discussed in the bullets below. Based on the information provided in this application, the proposed labeling for this section is acceptable except for inclusion of EIB.

- The proposed Albuterol-HFA-MDI PI includes _____

- The proposed Albuterol-HFA-MDI PI recommends the release of _____ test sprays as compared to the Proventil HFA PI which suggests four test sprays. Unless the CMC reviewer suggests otherwise, this is acceptable from a clinical perspective.

IVAX has created a new section of their proposed product label. _____
_____ This section includes information about use in labor and delivery, by nursing mothers, in pediatric patients, and in the geriatric population. The information and wording of these subsections are identical to similar sections in the Proventil HFA label.

Consequently, although the wording is the same, the location may not make the information as clear as in the Proventil HFA label. The applicant should address this issue in future labeling.

10.4. Comments to Applicant

It is suggested that the following comments be conveyed to the applicant at the end of this review cycle:

1. _____

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2. The CLINICAL TRIALS section of the proposed product label include

Revise the proposed product label to remove this information.

3. The proposed product label follows non-standard ordering for section headings. The product label should follow the order shown in 21 CFR 201.56(d)(1) and (2)

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APPENDIX

11. DETAILED STUDY REVIEWS OF PIVOTAL STUDIES

11.1. Study BNP-301-4-167: Six-week efficacy and safety study comparing Albuterol HFA-MDI and -BOI to Proventil HFA MDI and placebo in mild-to-moderate asthmatics

Protocol #: BNP-301-4-167

Title: Chronic-dose comparison of the efficacy and safety of Albuterol-HFA-MDI (), Albuterol-HFA-BOI (), and Proventil® HFA in mild-to-moderate asthmatics

Study Dates: August 1, 2001 to February 25, 2002

Sites: 32 sites in the US

IRB: Sterling Institutional Review Board
6300 Powers Ferry Road, Suite 600-351
Atlanta, GA 30339

Western IRB
3535 Seventh Avenue, SW
Olympia, WA 98502-5010

The Copernicus Group
118 MacKenan Drive, Suite 400
Cary, NC 27511

Source: M5, v 1.17, p 500001; v 1.25, p 502845-50

11.1.1. Protocol

11.1.1.1. Objective/Rationale

The primary objective of this study was to evaluate the efficacy and safety of Albuterol-HFA-MDI and Albuterol-HFA-BOI relative to placebo and Proventil® HFA, the reference product, when administered to mild-to-moderate asthmatics for 42 days. The secondary objective was to compare the efficacy and safety of Albuterol-HFA-MDI with that of Albuterol-HFA-BOI. An additional objective was to evaluate the performance of the BOI device during repeated use. [M5, v 1.17, p 500021; v 1.24, p 502749]

11.1.1.2. Summary of the Study Design

This was a six-week, multi-center, randomized, evaluator-blind, (double-blind, double-dummy vs placebo for the IVAX products), placebo-controlled, parallel group study comparing the efficacy and safety of Albuterol-HFA-MDI and Albuterol-HFA-BOI with that of placebo and Proventil HFA administered to at 345 mild-to-moderate asthmatics ≥ 12 years of age. Eligibility requirements included an FEV₁ 50-85% predicted and demonstration of reversible bronchoconstriction as evidenced by a $\geq 12\%$ increase in FEV₁

within 30 minutes following inhalation of albuterol 180 mcg (2 actuations). Eligible patients were randomized to receive Placebo HFA-BOI/MDI, Albuterol HFA-MDI, Albuterol-HFA-BOI, or Proventil HFA administered as 2 puffs (180 mcg) four times daily for 42 days. A double-dummy technique for the MDI and BOI inhalers allowed maintenance of a double-blind for the Placebo-HFA-BOI/MDI, Albuterol-HFA-MDI, and Albuterol-HFA-BOI arms. Because a Proventil HFA placebo was not available, the Proventil HFA arm could not be visually blinded, and therefore was only evaluator blinded.

11.1.1.3. Population

11.1.1.3.1. Inclusion criteria [M5, v 1.17, p 500023-5, v 1.24, p 502755-9]

Patients were included in the study if they met each of the following criteria:

1. Male, or non-pregnant, non-nursing females, ≥ 12 years of age at screening. Females of childbearing potential were included if practicing an acceptable method of birth control (barrier methods, oral birth control pills, progesterone implanted rods, IUDs, or Depo-Provera) and have a negative serum pregnancy test at screening. Pre-menarchal patients were required to have a pregnancy test if they became post-menarchal while participating in the study.
2. Had asthma for a minimum of six months duration that was stable for at least four weeks prior to the screening visit as defined by clinical history, and which was mild-to-moderate severity (FEV₁ 50-85% predicted for age, height, gender, and race) at the screening visit. The diagnosis of asthma was made in accordance with the American Thoracic Society (ATS) definition. Study-qualifying FEV₁ values were obtained between 6AM and 11AM, using the highest of three valid pulmonary function tests (PFTs), of which the two highest FEV₁ values could not differ by more than 0.2 L.
Comment: In addition to what is stated in the protocol, the study report states that if the specified reproducibility was not met, then up to five additional PFTs could be performed until the difference between the two highest did not exceed 0.2L [M5, v1.17, p 500034].
3. Had the ability to perform spirometry reproducibly and to be trained in the correct usage of a conventional MDI and the BOI.
4. Had the ability to perform peak expiratory flow (PEF) determinations with a handheld peak flow meter.
5. Had reversible bronchoconstriction as verified by a 12% increase in FEV₁ within 30 minutes following inhalation of albuterol 180 mcg (2 actuations) [Amendment 2].
6. Could tolerate withdrawal of applicable medications including methyl xanthines, antileukotrienes, anticholinergics, and oral or long-acting β_2 -agonists, for qualification at screening. Use of these medications was not permitted throughout the study.
7. Otherwise healthy individuals with a clinically acceptable medical history, physical examination, vital signs, and 12-lead ECG.
8. Non-smokers for at least 12 months prior to the screening visit, with maximum smoking histories of ten pack-years.
9. Provided written informed consent.

Additional pre-randomization inclusion criteria following the pre-study run-in period included:

10. The patient's asthma did not exacerbate at any time during the run-in period. For a patient to be excluded, the exacerbation required modification of the patient's treatment and/or increase in daily albuterol intake beyond 12 puffs.
11. The patient provided complete diary data for four out of the seven days during each of the two weeks of the run-in period.
12. The clinical laboratory parameters obtained at screening were within the clinically acceptable range.
13. The chest x-ray was consistent with asthma and showed no evidence of other active pulmonary disease. The chest x-ray may have been obtained at any time within the 52 weeks prior to the screening visit, unless a change in the clinical status warranted a repeat x-ray. All female patients were required to have a negative pregnancy test prior to any required x-ray.

11.1.1.3.2. Exclusion criteria [M5, v 1.17, p 500025-6, v 1.24, p 502757-8]

Patients were not eligible for enrollment in the pre-study run-in period if they met any of the following criteria at baseline:

1. Inability to tolerate or unwillingness to comply with required washout period for all applicable medications and xanthine-containing foods and beverages prior to the screening visit.
2. Hospitalization for acute exacerbation of asthma more than two times in the past year.
3. Treatment in an emergency room for asthmatic symptoms or hospitalization for asthmatic symptoms within three months prior to the screening visit.
4. An upper respiratory tract infection and/or sinusitis associated with exacerbation of asthmatic symptoms that did not resolve within three weeks prior to the screening visit.
5. A history and/or presence of any clinically significant non-asthmatic acute or chronic disease, including but not limited to bronchitis, emphysema, active tuberculosis, bronchiectasis, cystic fibrosis, clinically significant cardiovascular disease (including cardiac arrhythmias and uncontrolled hypertension), clinically significant hepatic, renal, or endocrine disorders, and neoplastic disease other than basal cell carcinoma of the skin.
6. Known or suspected substance abuse (e.g. alcohol, marijuana, etc.) and/or any other medical or psychological conditions that in the investigator's opinion should preclude study enrollment.
7. Allergy or sensitivity to albuterol, or to other components of the formulation used in the clinical trial materials.
8. Exposure to investigational drugs within 30 days prior to the screening visit.
9. Previous enrollment in a Baker-Norton or an IVAX-sponsored asthma study.

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11.1.1.3.3. Concomitant, Excluded, and Rescue Medications, Washout Periods

Permitted concomitant medications included [M5, v1.17, p 500026, 500031-32; v 1.24, p 502757, 502785-6]:

1. Oral contraceptives for female patients.
2. Low-dose aspirin for cardiovascular-event prophylaxis.
3. Non-prescription analgesics (acetaminophen only), antacids, and anti-diarrheals as necessary.
4. Inhaled corticosteroids, cromolyn and/or nedocromil, as long as the prescribed dose regimen was stable for at least four weeks prior to the screening visit. Patients requiring subsequent changes in the prescribed dose regimen of these drugs were discontinued.

Excluded medications included:

1. Currently required continuous treatment with β -blockers (administered by any route), MAO (monoamine oxidase) inhibitors, tricyclic antidepressants, and/or systemic corticosteroids.
2. Treatment with oral or injectable corticosteroids within the previous six weeks.
3. No continuously administered asthma/allergy medications except: 1) inhaled corticosteroids, cromolyn and/or nedocromil, and 2) intranasal corticosteroids and/or cremones. These medications were not subject to any formal pre-visit washout restrictions. However, they were withheld the morning of a study visit, and delayed until the end of the visit.
4. Certain medications required washout periods prior to the screening period or prior to the on-site treatment visit, as described below.

Table 17. BNP-301-4-167, Washout periods prior to the screening visit

Drug	Washout Period
Inhaled β_2 -agonists ¹	
Short-acting (e.g. albuterol, pirbuterol, terbutaline) ¹	6 hours
Long-acting (e.g. salmeterol) ^{2,3}	2 weeks
Oral and injectable corticosteroids ²	6 weeks
Oral and intranasal decongestants	6 hours
Oral theophyllines ²	1 week
Antileukotrienes (e.g. zileuton, zafirlukast, montelukast) ²	1 week
Oral β_2 -agonists ^{2,3}	2 weeks
Anticholinergics	
Inhaled (e.g. ipratropium) ²	12 hours
Oral ²	1 week
Antihistamines	6 hours
Aspirin and other non-steroidal anti-inflammatory drugs ⁴	1 week

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¹ Short-acting inhaled β_2 -agonists, other than the study and rescue medications, not permitted post-screening. However, use of nebulized albuterol permitted for treatment of asthma exacerbations occurring between Day 1 and Day 43 visits when used in accordance with procedures described in the rescue medication section.

² Must be withdrawn for the entire duration of patients participation in the study.

³ Patients receiving oral or long-acting inhaled β_2 -agonists may be switched to short-acting inhaled β_2 -agonists during the pre-screening visit washout period.

⁴ No washout required for routine daily low-dose aspirin for cardiovascular-event prophylaxis.

Source: M5, v 1.24, p 502808

Table 18. BNP-301-4-167, Restrictions and washout periods prior to each on-site treatment (Days 1, 22, 43)

Restriction	Washout
Strenuous physical exercise/exertion	Morning of visit
Cold air exposure	Morning of visit
Rescue medications ¹	6 hours
Oral and intranasal decongestants	6 hours
Antihistamines	6 hours
Aspirin and other non-steroidal anti-inflammatory drugs ²	1 week
Alcohol	24 hours
Xanthine-containing foods and beverages	8 hours
Meals	1 hour
¹ Use of nebulized albuterol permitted for treatment of asthma exacerbations occurring between the Day 1 and Day 43 visits when used in accordance with the procedures described in the rescue medication section.	
² No washout required for routine daily low-dose aspirin for cardiovascular-event prophylaxis.	

Source: M5, v 1.24, p 502786, 502809; v1.17, 500032

Rescue medication included an Albuterol CFC-MDI inhaler (IVAX Pharmaceuticals, Inc., formerly Zenith Goldline Pharmaceuticals) for prn use both during the run-in and treatment phases [M5, v 1.17, p 500029; v1.24, p 502764]. The protocol states that patients were to be instructed to use no more than 2 puffs (180 mcg) at any one time, while the study report does not discuss rescue medication dosage. In addition, the protocol states that rescue albuterol was to be labeled with dosing instructions for emergency use, allowing self-administration of 2 puffs every 20 minutes to a maximum of six puffs for any given episode while attempting to obtain medical assistance [M5, v1.24, p 502764].

Comment: The statement regarding labeling for emergency use was in the protocol, but not in the study report.

Exacerbations during a clinic visit were treated with 2 puffs of rescue albuterol. If this treatment failed, treatment included a course of 2.5 mg of albuterol by nebulization four times daily for 5 days during which time period treatment with study medication was withheld. If this treatment was successful, the patient could resume CTM treatment and remain in the study. However, if this treatment was not successful, additional treatment was provided, and patients were discontinued from the study. [M5, v1.24, p 502768-9; v1.17, p 500036]

Management of off-site exacerbations during the treatment phase (Days 1-43) was similar to on-site management. This consisted of a course of nebulized albuterol (2.5 mg) four timed daily for five days, during which time study medication was withheld. If successful, patients

remained in the study, but did not come to the clinic for the next treatment evaluation until six days or more after completion of the course of albuterol by nebulization. If not successful, additional treatment was provided, and patients were discontinued from the study. [M5, v1.24, p 502768-9; v1.17, p 500036]

11.1.1.3.4. Subject withdrawal [M5, v 1.17, p 500027, v 1.24, p 502790]

Patients were to be discontinued from the study if any of the following occurred:

1. Occurrence of any adverse event sufficiently severe to warrant withdrawal as judged by the Principal Investigator or Sponsor.
2. Onset of any serious condition (including exacerbation of asthma requiring administration of steroids) or the need to administer any medication that might pose a hazard to the patient or affect the validity of the efficacy data.
3. Any changes in the dosage of the patient's allowable concomitant asthma medications.
4. Loss or malfunction of one of more inhalers necessitating shortening of the dosing duration.
5. Desire by the patient to withdraw at any time for any reason.
6. Non-compliance with the protocol and/or lack of willingness or commitment to cooperate in all phases of the study.

Patients who did not complete all study-related procedures and evaluations were to be considered to have discontinued prematurely from the study.

11.1.1.3.5. Protocol amendments

The protocol was amended twice, on June 8, 2001 and August 29, 2001. The first amendment was recommended by the investigators and their staff, and made prior to study initiation. The changes primarily involved allowing entry of pre-menarchal females with a negative pregnancy test, easing drug washout and other restrictions, permitting greater flexibility regarding the role of the dosing administrator in the conduct of the study, simplification of the run-in period procedures (elimination of placebo treatment during run-in), and modification of the order in which vital signs were undertaken during on-site six-hour post-dose evaluations [M5, v 1.24, p 502674-5]. The second protocol amendment was made approximately one month after commencement of the study. The changes included a relaxation of the entry criteria for reproducibility of FEV₁ to 0.2L (previously 5% or 0.1L) and for airway reversibility of 12% (rather than 12% and 200 mL as was previously permitted), formalization of allowable windows for post-screening clinic visits, and correction of the upper limit of the acceptable range for alkaline phosphatase for all age groups [M5, v 1.24, p 502743].

11.1.1.4. Conduct/Study Procedures/Blinding

The study was divided into two periods, a 14-day pre-randomization run-in period, and a 42-day treatment period. During the run-in period, patients received rescue medication to be used if needed, but did not receive either active or placebo study medications. On Day 1, each patient was randomized to receive one of four treatments administered four times a day, as shown in Table 19. Patients were instructed to take 2 puffs four times a day from each of the two provided inhalers: one MDI inhaler and one BOI inhaler. As shown, this

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double-dummy technique allowed maintenance of a double-blind for the Placebo-HFA-BOI/MDI, Albuterol-HFA-MDI, and Albuterol-HFA-BOI arms. Because a Proventil HFA placebo was not available, the Proventil HFA arm could not be visually blinded, and therefore was only evaluator blinded. This was accomplished by providing a Dosing Administrator to each study site, limiting other study personnel from being aware of the patient's assigned treatment. Patients were instructed to refrain from discussing aspects of their assigned treatment with study personnel or other patients. An independent monitor not otherwise connected with the study undertook the monitoring of drug accountability. [M5, v 1.17, p 500027-31]

Since neither the protocol nor the study report discussed blinding of the positive control Proventil HFA product, this information was requested, and the applicant responded in the submission of July 18, 2003. There was no attempt made to disguise the Proventil product. The can and the actuator were over-labeled with the clinical research label. The investigator was blinded via the use of a dosing administrator. [Submission of 7/18/03, p 1]

Each patient was given two inhalers per treatment period, numbered Inhaler No. 1 and Inhaler No. 2, both on the canister and on the actuator. This was done so that if the two components became separated, they could be paired correctly. The labels were not color-coded. [Submission of 8/7/03, p 2]

A study flow chart is shown in Table 20. Lots used in the study are shown in Table 21.

Table 19. BNP-301-4-167, Dosing and Blinding Methodology

Treatment	Dose	Inhalers	Dose Regimen	Blinding
Placebo-HFA-BOI/MDI	0 mcg albuterol QID	Placebo-HFA-MDI Placebo-HFA-BOI	2 actuations QID 2 actuations QID	Double-blind
Albuterol-HFA-MDI	180 mcg albuterol QID	Albuterol-HFA-MDI Placebo-HFA-BOI	2 actuations QID 2 actuations QID	Double-blind
Albuterol-HFA-BOI	180 mcg albuterol QID	Placebo-HFA-MDI Albuterol-HFA-BOI	2 actuations QID 2 actuations QID	Double-blind
Proventil HFA	180 mcg albuterol QID	Proventil HFA Placebo-HFA-BOI	2 actuations QID 2 actuations QID	Evaluator-blind

Source: M5, v 1.17, p 500028

Table 20. BNP-301-4-167, Study Flow Chart

Event	Screen	Run-in	Day 1	Daily	Day 22	Day 43
Written informed consent	✓					
Study-qualifying spirometry (FEV ₁)	✓					
Reversible bronchoconstriction	✓					
Medical / 6-week medication history	✓					
Physical examination / vital signs	✓					✓ ^a
Routine laboratory tests (non-fasting) ^h	✓					✓ ^a
Serum pregnancy test	✓ ^b					✓ ^b
12-lead ECG	✓					✓ ^a
Chest x-ray	✓ ^b					
PEF training	✓					
Inhalation / dosing technique training	✓		✓ ^b		✓ ^b	
Inhalation / dosing assessment			✓		✓	✓
Dispense peak flow meter	✓					

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Event	Screen	Run-in	Day 1	Daily	Day 22	Day 43
Dispense rescue medication	✓		✓ ^b		✓ ^b	
Dispense run-in diary	✓					
Retrieve run-in diary			✓			
Dispense post-randomization diary			✓		✓	
Retrieve post-randomization diary					✓	✓
Study medication dosing			✓	✓ ^f	✓	✓
Dispense study medications			✓		✓ ^c	
Retrieve dispensed study medications					✓	✓
PFTs (6-hour serial FEV ₁)			✓ ^d		✓ ^d	✓ ^d
Serial vital signs			✓ ^e		✓ ^e	✓ ^e
Asthma symptom assessments		✓		✓ ^f		
Pre-AM PEF ./ rescue medication use		✓		✓ ^f		
Nocturnal awakenings		✓		✓ ^f		
Concomitant medications	✓	✓	✓	✓ ^f	✓	✓
Adverse events		✓	✓	✓ ^f	✓	✓
Device-use assessments / questionnaire						✓ ^g

a Follow-up physical examination, 12-lead ECG, and clinical laboratory evaluations were conducted at the end of the Day 43 visit or at the time of early discontinuation.

b If applicable. If needed, retraining was performed at the end of a study visit.

c Fresh study medication inhalers were dispensed at the end of the Day 22 visit following completion of assessments.

d Assessments were made 0.5 hours prior to dosing, and immediately prior to, and 0.083 (5 minutes), 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, and 6 hours after completion of the dosing. Respiratory rate and oral temperature measurements were excluded post-drug. The Day 22 assessments were made using the inhaler(s) dispensed at the Day 1 visit, and the Day 43 assessments were made with those dispensed at the Day 22 visit.

e Assessments were made 0.5 hours prior to dosing, and immediately prior to the FEV₁ measurements, at approximately 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, and 6 hours after completion of the dosing. Respiratory rate and oral temperature measurements were excluded post-drug. The Day 22 assessments were made using the inhaler(s) dispensed at the Day 1 visit, and the Day 43 assessments were made with those dispensed at the Day 22 visit.

f For Days 2-21 and 23-42, patients were instructed to make daily assessments and record them in a diary. PEF measurements were made prior to the first dose of the day. Recording of nocturnal awakenings and nightly albuterol use were made prior to the morning PEF measurement.

g Completed at the end of Day 43 or at the time of early discontinuation.

h Clinical laboratory tests included a complete blood count with differential and serum chemistries: glucose, sodium, potassium, chloride, creatinine, total protein, albumin, total bilirubin, calcium, phosphorous, alkaline phosphatase, ALAT (SGPT), and ASAT (SGOT).

Sources: M5, v1.17, p 500050; v1.24, p 502271, 502804

Table 21. BNP-301-4-167, Investigational Product Lots

Product	Strength/Quantity per Actuation	Manufacturer	Lot/Batch Number	Expiry Date
Placebo-HFA-BOI/MDI	0	IVAX Pharmaceuticals, Ireland	ABF75A	N/A
Albuterol-HFA-MDI	90 mcg	IVAX Pharmaceuticals, Ireland	AAW13A	6/02
Albuterol-HFA-BOI	90 mcg	IVAX Pharmaceuticals, Ireland	AAW13A	6/02
Proventil HFA	90 mcg	3M Pharmaceuticals (Distributed by Key Pharmaceuticals, Inc.)	GBD002A & 000535	4/02 6/02
MDI Actuators			01R0010	N/A
BOI Actuator Unit			00R0159	N/A

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Product	Strength/Quantity per Actuation	Manufacturer	Lot/Batch Number	Expiry Date
			00R0156	N/A

Source: M5, v 1.17, p 500029

11.1.1.5. Safety Evaluations

Safety evaluations included screening history, physical examination, chest x-ray, 12-lead ECG, and routine clinical laboratory evaluations which included a serum pregnancy test for females of childbearing potential. Screening physical examinations included height, weight, sitting vital signs (oral temperature, respiratory rate, heart rate, and blood pressure). Screening also included spirometry, with an FEV₁, FEV₁ percent predicted, and an assessment of the percent reversibility by administration of 180 mcg of albuterol. All laboratory measurements were performed at a centralized laboratory [M5, v 1.17, p 500053]. [M5, v 1.17, p 500034-7]

Through the course of the study, morning peak flow (PEF) measurements were performed by patients at home using a peak flow meter. PEFs during the run-in period were used to establish the 'personal best' PEF for each patient. The patient diary also captured daytime asthma symptom scores, nocturnal asthma awakenings, use of rescue medication, and adverse events.

Spirometry and vital signs were performed during each treatment period as part of the safety profile assessment as shown in Table 20. Spirometric data included the highest FEV₁ obtained from three acceptable maneuvers at each measurement. Safety evaluations also included a physical examination, 12-lead ECG, and non-fasting laboratory evaluations at the end of Day 43 or at the time of early discontinuation from the study.

A device use questionnaire was completed at the end of the last day of the study, or at study discontinuation. The device questionnaire included questions regarding ease of use, ease of learning to use, ease of inhaling, and overall opinion for each of the MDI and BOI inhalers, as well as a question regarding preference between the two inhaler types. However, the questionnaire did not include information regarding blockages or malfunctions of the inhalers. [M5, v 1.24, p 502807]

11.1.1.6. Efficacy and Compliance Evaluations

Efficacy and compliance evaluations included spirometry at each clinic visit and daily diary information. Diaries included information on the daily AM PEF measurements prior to dosing (the highest of three values was recorded), nocturnal awakenings requiring rescue medication (recorded each AM), daytime asthma symptom scores (recorded each PM before bed), number of puffs of rescue albuterol used (recorded twice daily in the AM and PM), and number of puffs of study medication used (recorded each PM). [M5, v 1.17, p 500035]

The assessment of daytime asthma symptoms (reflective for the previous 12-14 hours) each evening included the symptoms of wheeze, shortness of breath, cough, and tightness of chest, each scored on a 0-3 scale, where:

0 = No symptoms

1 = Symptom occurred but did not interfere with daily activity

- 2 = Symptom occurred but was sometimes annoying or interfered with daily activity
- 3 = Symptom occurred even at rest and was annoying or interfered with daily activity.

11.1.1.7. Pharmacokinetic Evaluations

No pharmacokinetic evaluations were performed in this study. [M5, v 1.17, p 500051]

11.1.1.8. Statistical Plan

11.1.1.8.1. Definition of study populations

The protocol defined a modified intent to treat (MITT) population for the primary analysis, consisting of study-eligible patients who received at least one dose of study medication. The study report states that all randomized patients were considered study eligible. [M5, v 1.17, p 500053; v 1.24, p 502794]

11.1.1.8.2. Primary endpoint and analysis

The primary efficacy variable was the baseline-adjusted area under the FEV₁-versus time curve over 6 hours (AUEC₀₋₆) at Day 43. Baseline adjustment was made by subtracting the average of the two pre-dose FEV₁ measurements from each post-dose FEV₁ measurement. The primary analysis was a mixed-effects analysis of variance with fixed effect of treatment group. The following comparisons were made:

- The mean difference between Albuterol-HFA-MDI and placebo
- The mean difference between Albuterol-HFA-BOI and placebo
- The mean difference between Proventil-HFA and placebo
- The mean difference between Albuterol-HFA-MDI and Proventil-HFA
- The mean difference between Albuterol-HFA-BOI and Proventil-HFA
- The mean difference between Albuterol-HFA-MDI and Albuterol-HFA-BOI

AUEC₀₋₆ was calculated using the linear trapezoidal rule. The analysis was carried out with early discontinuations carried forward and with a two-sided significance level of 0.05. No attempt was made to adjust for multiple comparisons. [M5, v 1.17, p 500054; v 1.24, p 502791-5]

11.1.1.8.3. Secondary endpoints and analyses

Secondary analyses included [M5, v 1.17, p 500054-5; v 1.24, p 502792-6]:

- AUEC₀₋₆ at Days 1, 22, and 43.
- Baseline-adjusted maximum FEV₁ at Days 1, 22, 43, and last observed value. The analysis and comparisons were similar to the primary analysis.
- Weekly pre-dose AM PEF and weekly daytime asthma scores. Comparisons were derived from a mixed-effect ANOVA with fixed effects of baseline, treatment group, study week, and random patient effect. Baseline was the last seven days of the run-in period.
- Number of nocturnal awakenings, and number of puffs of rescue medication. Comparisons were made between treatment groups using a Chi-square test derived

from a generalized estimating equation (GEE) for Poisson random variables, with effect of treatment group, baseline average count over the 14-day run-in, observation period (Days 1 to 21 or 23 to 42), and offset variable equal to the number of days with reported data in each of the two observation periods.

- Time (in minutes) to response onset (defined as an increase from baseline in FEV₁ ≥15%), time to maximum FEV₁, and response duration for responders (defined as the number of minutes from the time of dosing to response offset: change from baseline <15%). Comparisons were made between treatment groups via the Cox's proportional hazard model with effects for treatment group.
- Device performance for each measure from the device questionnaire, items 1-4. Comparison was made between devices via chi-squared tests derived from a generalized linear model for a multinomial ordinal response with the effect of treatment group and device (BOI or MDI). Device performance data for both the MDI and BOI inhalers in the Proventil HFA treatment group were summarized separately.
- Distribution of device preference (BOI, MDI, or no preference) from the device questionnaire, item C. Individual 95% confidence intervals (CIs) were generated for proportion of patients reporting each device preference, unadjusted for multinomial correlations. Device preference data for both the MDI and BOI inhalers in the Proventil HFA treatment group were summarized separately.

11.1.1.8.4. Other endpoints and analyses

Additional summaries and analyses included [M5, v 1.17, p 500055-6; v 1.24, p 502796-7]:

- Mean and mean changes from baseline in FEV₁ and vital signs at each study time point.
- Weekly or tri-weekly ambulatory function measures by treatment group.
- Two-way cross-classification of paired responses to the device performance measures by treatment group for each response item.
- Overall incidence of adverse events, as well as the incidence of treatment-emergent adverse events, summarized by treatment group, body system, and preferred COSTART term.
- Use of concomitant medication, by treatment group.
- Patterns of missing diary data, summarized by treatment group and sites, classified by quartile (<25%, 25 to <50%, 50 to 75%, >75%).

11.1.1.8.5. Sample size considerations

Sample size was based on a previous Baker Norton albuterol study, [REDACTED] In that study, a between-patient standard deviation (SD) of 1.23 L•hr in AUEC₀₋₆ was observed. Mean differences for active minus placebo were all greater than 1.25 L•hr, with very small differences between active dose groups (0.08 L•hr). Based on the above information, the applicant chose a between treatment difference in AUEC₀₋₆ of 0.75 L•hr as the minimally clinically relevant difference. Assuming an SD in AUEC₀₋₆ of 1.23 L•hr, a sample size of at least 44 patients was needed for the two-sample t-test to attain at least 80% power at a two-sided 0.05 significance level. [REDACTED]

11.1.2. Results

11.1.2.1. Description of Study Population

11.1.2.1.1. Disposition

A total of 630 patients were screened, of whom 345 were randomized to treatment, and 290 completed (as opposed to having been discontinued from) the study. Patient disposition is shown in Table 22, with reasons for discontinuation shown in descending order of frequency. Note that the randomization was not equal, but was 1:3:1:1 for the Albuterol HFA MDI : Albuterol HFA BOI : Proventil HFA : Placebo groups. The applicant states that a post-hoc Pearson chi-squared test with three degrees of freedom showed no significant differences in discontinuation rates among the treatment groups. On Day 22, 315 patients (91.3% of MITT) had FEV₁ evaluations, of whom 290 (89%) completed the evaluations that day. On Day 43, 291 patients (84.3% of MITT) had FEV₁ evaluations, of whom 259 (89%) completed evaluations that day. Data was incomplete for 32 patients at the Day 43 visit, of whom data was incomplete due to bronchoconstriction in 14 patients. Therefore, while the number of patients considered to have completed the study was 290, the actual number of patients who completed the study for whom complete data was available for Day 43 was 259. [M5, v 1.17, p 500061-3]

Eight (8) patients were discontinued during study BNP 301-4-167 due to an inhaler malfunction (6 BOI and 2 MDI). Table 22 below is misleading in that the withdrawal is attributed to the study drug to which the patient was randomized. However, not all of the devices that malfunctioned were those that contained active drug (i.e. some were placebo inhalers given to patients randomized to other treatments). No further information was given regarding the nature of the malfunctions. [M2, v1.3, Table 2.4.2, p 2000118]

Table 22. BNP-301-4-167, Patient disposition*

Disposition	Alb-HFA-MDI	Alb-HFA-BOI	Proventil HFA	Placebo	Total
ITT population	58	173	56	58	345
Completed study ^a	52 (89.7%)	141 (81.5%)	50 (89.3%)	47 (81%)	290 (84%)
FEV ₁ measurement on Day 43 ^a	52	141	49	49	291
Complete FEV ₁ on Day 43	46	131	43	39	259
Incomplete FEV ₁ on Day 43	6	10	6	10	32
Due to bronchoconstriction	3	6	2	3	14
Discontinued ^b	6 (10.3%)	32 (18.5%)	6 (10.7%)	11 (19%)	55 (16%)
Adverse event	4	17	2	3	26
Onset of a serious condition ^c	3	12	2	2	19
Malfunction of inhaler	1	3	3	1	8
Consent withdrawn	0	3	1	3	7
Lost to follow-up	0	4	0	1	5
Protocol violation	1	2	0	0	3
Change in dosage of allowable	0	1	0	0	1

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Disposition	Alb-HFA-MDI	Alb-HFA-BOI	Proventil HFA	Placebo	Total
asthma medications Other ^d	0	4	0	3	7

a The data source for the number of patients who completed the study was based on the end-of-study form. The number of patients who had an FEV₁ on Day 43 was slightly different. The data source for this information comes from the spirometry database. One patient in the Proventil group (2174) was listed as having completed the study, but no spirometry data was available for Day 43. Two patients in the placebo group (2097, 2299) had spirometry on Day 43, but were excluded from the study due to use of prohibited medications. [Submission of 7/18/03, p 2]

b Patients may have had more than one reason for discontinuation.

c Includes asthma exacerbations requiring corticosteroid treatment, or need to administer any medication that might pose a hazard or affect validity of the study.

d The Other group included: Placebo: leaving for school, need to start non-steroidal anti-inflammatory, and took prohibited medication; Alb-HFA-BOI: study drug non-compliance, use of a large amount of rescue medication, study medication stolen patient request, and failure to follow the protocol.

Sources: M5, v 1.17, Table 10-2, p 500062; Table 14.1.1.1, p 500187-8
Submission of 7/18/03, p 2

11.1.2.1.2. Demographics and baseline characteristics

Demographics and baseline characteristics of the study population are shown in Table 23. Treatment groups were relatively well balanced at randomization, except that there was a higher percent of males in the placebo group than the other groups. Overall there were more females (61%) than males (39%) enrolled, and Whites were in the large majority (81%), with Asians and 'Other' races poorly represented.

FEV₁ and % predicted FEV₁ at screening and at baseline were comparable within each treatment group. Baseline FEV₁ was comparable between the Albuterol-HFA-MDI (2.34L) and Albuterol-HFA-BOI (2.35L) groups, with the Proventil HFA (2.42L) and Placebo (2.53L) slightly higher. Nevertheless, baseline % predicted FEV₁ was comparable between treatment groups (Table 23). Note that 138 patients were enrolled prior to Amendment 2, which changed the enrollment criterion for % reversibility of FEV₁ from 12% or 200 mL to solely 12% reversibility. Compared to the patients enrolled pre-Amendment 2, post-Amendment 2 patients had minimally increased % reversibility in all treatment groups except placebo, where there was a minimal decrease in % reversibility. Just over half the patients (54%) were on orally inhaled corticosteroids (ICS), but none were on systemic (oral or injectable) glucocorticoids/corticosteroids.

Review of the patient listings shows that baseline medical history, vital signs, physical examinations, and chest x-rays were comparable between treatment groups.

Table 23. BNP-301-4-167, Patient demographics and baseline characteristics

Disposition		Alb-HFA-MDI n = 58	Alb-HFA-BOI n = 173	Proventil HFA n = 56	Placebo n = 58	Total n = 345
Age, years:	Mean	39.4	38.7	40.1	39.8	39.2
≥12 to <18 years	N (%)	8 (13.8)	23 (13.3)	4 (7.1)	3 (5.2)	38 (11.0)
≥18 to <40 years	N (%)	18 (31.0)	67 (38.7)	27 (48.2)	29 (50.0)	141 (40.9)
>40 to <65 years	N (%)	31 (53.5)	70 (40.5)	22 (39.3)	24 (41.4)	147 (42.6)
≥65 years	N (%)	1 (1.7)	13 (7.5)	3 (5.4)	2 (3.5)	19 (5.5)
Gender:						

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Disposition		Alb-HFA-MDI n = 58	Alb-HFA-BOI n = 173	Proventil HFA n = 56	Placebo n = 58	Total n = 345
Males	N (%)	20 (34.5)	65 (37.6)	22 (39.3)	29 (50.0)	135 (39.4)
Females	N (%)	38 (65.5)	108 (62.4)	34 (60.7)	29 (50.0)	209 (60.6)
Race:						
White	N (%)	45 (77.6)	142 (82.1)	48 (60.7)	47 (81.3)	282 (81.7)
Black	N (%)	10 (17.2)	25 (14.5)	6 (60.7)	6 (10.3)	47 (13.6)
Asian	N (%)	2 (3.5)	5 (2.9)	1 (1.8)	1 (1.7)	9 (2.6)
Other	N (%)	1 (1.7)	1 (0.6)	1 (1.8)	4 (6.9)	7 (2.0)
Screening:						
FEV ₁ , L	Mean (SD)	2.34 (0.60)	2.32 (0.60)	2.44 (0.71)	2.50 (0.67)	2.37 (0.63)
% predicted FEV ₁	Mean (SD)	72.2 (9.4)	69.9 (9.5)	72.1 (8.7)	71.6 (9.2)	70.9 (9.4)
% reversibility	Mean (SD)	19.4 (10.7)	20.9 (11.7)	20.6 (12.3)	20.1 (8.8)	20.5 (11.2)
pre-Amendment 2	Mean (N)	17.6 (22)	20.7 (68)	20.1 (24)	20.8 (24)	20.2 (138)
post-Amendment 2	Mean (N)	20.6 (36)	210 (105)	21.0 (32)	20.0 (32)	20.8 (205)
Baseline (Day 1, randomization) ^a :						
FEV ₁ , L	Mean (SD)	2.34 (0.56)	2.35 (0.61)	2.42 (0.77)	2.53 (0.76)	2.39 (0.66)
% predicted FEV ₁	Mean (SD)	72.5 (9.9)	70.7 (11.2)	71.6 (11.7)	71.9 (12.1)	71.4 (11.2)
Baseline steroid use:						
Any steroids	N (%)	34 (59)	96 (55)	33 (59)	32 (55)	195 (57)
Orally inhaled	N (%)	33 (57)	90 (52)	33 (59)	31 (53)	187 (54)
Intranasal	N (%)	7 (12)	21 (12)	7 (13)	11 (19)	46 (13)
Oral or injectable	N (%)	0	0	0	0	0

a Baseline was defined as the average of the two pre-dose measurements

Source: M5, v 1.17, Table 11-1, p 500067; Tables 14.1.1.3-6, p 500209-16; Tables 14.1.7-9, p 500217-22; Tables 14.1.1.10-11, p 500223-6; Table 14.1.2, p 500227-31, Submission of 8/7/03, p2 and Tab 2

11.1.2.1.3. Eligibility Deviations and Protocol Violations

Eligibility deviations and protocol violations that occurred during the study are discussed below, and protocol violations are shown in Table 24. The deviations/violations were throughout the study population, and do not appear to have affected the outcomes of the study.

The study report states that following randomization, 50 patients were found to have eligibility deviations. Eligibility deviations included: laboratory or pulmonary function test not within the protocol specifications, inappropriate washout of pre-study medications, visit or qualification test not performed with the protocol-specified time window from the screening visit, and medical history included a condition disallowed by the protocol. Because the study report did not state what happened to these patients, a table of eligibility deviations was requested, and provided in a submission dated August 5, 2003. The eligibility deviations table lists 73 patients (rather than the 50 stated the study report) with at least one deviation. Of these, 12 patients took contraindicated medications. [M5, v 1.17, p 500064; submission of August 5, 2003, Section 2]

The most common protocol violations (called protocol deviations in the study report) during the course of the study most included pulmonary function tests performed outside the acceptable time windows, Visit 2-4 performed outside the acceptable time windows, missing diary entries, and inhalers cleaned on the wrong days. Because the study report did not state what happened to these patients, a table of protocol deviations/violations was requested, and

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provided in a submission dated August 5, 2003. There were 14 major protocol violations: 9 patients given a new inhaler prior to spirometry on Day 22, 3 patients with a lack of firewall between the dosing administrator and the evaluator/coordinator, 1 patient with an inhaler that was mislabeled, 1 patient whose canister was switched between actuators at some unknown time, and 1 patient whose placebo BOI canister malfunctioned. [M5, v 1.17, p 500064; submission of August 5, 2003, Tab 3; submission of August 29, 2003, Tab 2]

Discrepancies noted with use or labeling of study drug are listed below:

- Patient 2116 at site 3330 was randomized to MDI treatment. The active inhaler was selected for post-study testing, but no drug was found in the MDI inhaler, and drug was found in the BOI inhaler. It was determined that the canister from the MDI had been inserted in the BOI inhaler, and visa versa. Therefore, at Day 43, the patient was receiving active treatment from the BOI rather than the MDI. However, the patient was included in the statistical analysis for the MDI group.
- The study report states that at site 3314, 4 patients (2139, 2144, 2301, and 2303) were inadvertently given new inhalers for use on Day 22 prior to serial PFTs [M5, v 1.17, p 500064-5]. However, this is not correct, and it took several submissions and explanations to clarify the details. The correct number of patients who inadvertently were given new inhalers prior to PFTs was 9 patients. All occurred at site 3314. A table of protocol deviations submitted on August 5, 2003 expanded the list from 4 to 8 patients who were inadvertently given new inhalers for use on Day 22. These included 4 patients randomized to AlbuteroHFA-BOI (2139, 2140, 2142, and 2302), 2 patients randomized to AlbuteroHFA-MDI (2141, 2301), and one patient randomized to each of Proventil HFA (2144) and placebo (2143). Patient 2303 (randomized to Proventil HFA) was added to the listing in the submission of August 29, 2003. In addition, this patient also experienced a BOI device malfunction (discussed below), and was discontinued from the study. [Submission of 8/5/03, Tab 3, p 7-8; submission of 8/29/03, Tab 2, p 4]
- At site 3314, one patient had both inadvertent dosing with a new inhaler at Day 22, and a BOI device malfunction. Patient 2303, randomized to Proventil HFA, was inadvertently given a new inhaler for use on Day 22 prior to serial PFTs. The original submission stated that the patient had an inhaler labeling error, but the nature of the error was not specified. In response to the Division's queries regarding patients with protocol violations, the applicant submitted patient line listings. These submissions showed that the patient was discontinued early (after the Day 22 visit) due to a malfunction of the BOI inhaler. In addition, in the submission of August 29, 2003, the applicant clarified that this patient was also given a new inhaler prior to PFT determinations on Day 22. [Submission of August 5, 2003, Tab 3, p 8; Submission of August 29, 2003, Tab 2, p 4]
- At site 3314, one patient had an inhaler labeling error: Patient 2415D-N, randomized to AlbuteroHFA-BOI, received study medication that was mislabeled. The patient received a BOI inhaler labeled for patient 2412 from days 1 to 22. Kit 2412 at site 3281 was found to contain a BOI labeled for patient 2415. Kit 2412 was never used, as patient 2412 was never dosed. Unblinding after database lock revealed that 2412 and 2415 BOI inhalers both were active treatment with AlbuteroHFA-BOI.

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Table 24. BNP-301-4-167, Protocol deviations, ITT population

Disposition	Alb-HFA-MDI	Alb-HFA-BOI	Proventil HFA	Placebo
ITT population	58	173	56	58
Protocol violations †	18 (31.0)	78 (45.1)	21 (37.5)	30 (51.7)
Prohibited medication (Anti-asthmatic)	2 (3.4)	8 (4.6)	2 (3.6)	4 (6.9)
Prohibited medication (Misc)	0	10 (5.8)	5 (8.9)	4 (6.9)
Dosing error	3 (5.2)	7 (4.0)	2 (3.6)	2 (3.4)
Study eligibility *	1 (1.7)	7 (4.0)	4 (7.1)	5 (8.6)
Missing and/or mistimed screening evaluation	7 (12.1)	22 (12.7)	2 (3.6)	9 (15.5)
Visit mistiming	12 (20.7)	42 (24.3)	9 (16.17)	18 (31.0)

† Expressed as number of patients having deviation in category at least once, with denominator for percent derived from number of randomized patients per treatment. FEV₁ mistimings are not included in this table.
* Study eligibility deviations mainly restricted to medical history issues, out-of-range labs, and spirometry deviations.

Source: Submission of 8/29/2003, Tab 1

11.1.2.1.4. Compliance

Based on completion of a patient diary, 95% to 100% of patient diaries had less than 25% of data missing from the diary. A dosing compliance rate was not calculated in the initial submission, but was requested and submitted in July of 2003 (Table 25). In addition, a PEF compliance rate was also calculated for patients. Just as for the dosing compliance rates, PEF compliance overall was very high, with 90.9% for Albuterol-HFA-MDI, 92.6% for Albuterol-HFA-BOI, 95.6% for Proventil HFA-MDI, and 92.1% for placebo. [Submission of July 18, 2003]

Table 25. BNP-301-4-167, Dosing compliance rates, ITT population

Dosing Compliance	Alb HFA-MDI n = 58	Alb HFA-BOI n = 173	Proventil HFA n = 56	Placebo n = 58
Compliance rate* (mean)	91.7	92.2	95.6	90.5
n ≥ 90%	52	155	55	54
n >=85-90%	3	7	0	1
n < 85%	2	7	1	1
No data	1	4	0	2

* Compliance rate = the number of days with dairy information divided by the number of study days on the case report form.

Source: Submission of July 18, 2003

11.1.2.2. Efficacy Endpoint Outcomes

11.1.2.2.1. Primary efficacy measure

The primary efficacy analysis was a comparison of the mean difference between Albuterol-HFA-MDI and placebo for the AUEC₀₋₆ of baseline-adjusted FEV₁ at Day 43 or last observation (LOCF). Other comparisons of interest included the two other active drug products (Albuterol-HFA-BOI and Proventil-HFA) vs placebo, and between all three active drug products. Note that the devices used on Day 1 were new, whereas devices used on Days 22 and 43 were not cleaned prior to use and had been used for about 3 weeks with weekly cleaning [M5, v 1.17, p 500073].

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The primary efficacy analysis results are shown in Table 26 and Table 27, with the primary comparison of interest shown in **bold in each table**. Table 26 shows the results as the applicant submitted in the Study Report in Module 5, and Table 27 shows the results as submitted in the Tables for the Summary of Clinical Efficacy in Module 2. In the Study Report (Module 5), the applicant presented analyses based on the pre-specified timepoint for each FEV₁ measurement, whereas in the Tables for the Summary of Clinical Efficacy (Module 2) the analysis was based on the actual timepoint for each FEV₁ measurement. Either a methodology employing the actual timepoint or an interpolation based on actual timepoint of FEV₁ measurement is more accurate, and is therefore a preferred methodology. However, the results may be seen to be remarkably similar, and do not change any of the statistical conclusions. The FDA Biometrics Reviewer was able to duplicate both primary efficacy analyses using both datasets and methodologies. Since the results for the primary analysis were found to be almost identical, the Division did not request that the applicant resubmit all secondary and sub-group analyses that involved FEV₁ timepoints. Therefore, all secondary and sub-group analyses shown in this review are based on methodology employing the pre-specified FEV₁ timepoint rather than the actual timepoints of FEV₁ measurement for each patient.

The primary comparison of Albuterol HFA-MDI vs placebo was statistically significant (LS mean difference = 1.04, p = <0.0001), as were the comparisons for ~~_____~~ Proventil-HFA vs placebo (Albuterol HFA-BOI vs placebo LS mean difference = ~~_____~~ p = ~~_____~~ Proventil vs placebo LS mean difference = 0.97, p = 0.0001) (shown in Table 27). There were minor and not statistically significant differences among active treatments, with the largest numerical difference between the Albuterol HFA-MDI and Albuterol HFA-BOI products.

The primary efficacy analysis by subgroups of age, race, and gender are shown in Table 28, Table 29, and Table 30, respectively. While there was some variability within and among groups, there were no trends of note.

The primary efficacy analysis by subgroups of on or not on treatment with inhaled corticosteroids (ICS) is shown in Table 31. Not surprisingly, patients on ICS had higher mean AUEC₀₋₆ FEV₁ values than their untreated counterparts in all treatment groups.

Table 26. BNP-301-4-167, Primary Efficacy Variable: AUEC₀₋₆ (L·Hr) of baseline-adjusted FEV₁ at Day 43/LOCF, Analysis using pre-specified assessment times, MITT

Treatment	N	Mean (SD)	LS Mean (STE)	Treatment Comparison	LS Mean Diff (STE) ¹	p-value ¹
A) Albuterol HFA-MDI	58	1.28 (1.69)	1.28 (0.17)	A-D	1.04 (0.25)	0.0000
B) Albuterol HFA-BOI	173	_____)	B-D	_____	
C) Proventil HFA	56	1.20 (1.25)	1.20 (0.18)	C-D	0.97 (0.25)	0.0001
D) Placebo	58	0.23 (0.92)	0.23 (0.17)	A-C	0.07 (0.25)	0.7732
				B-C	_____	
				A-B	_____	
				Treatment		0.0000

¹ Based on a one-way ANOVA model using the pre-specified assessment times, not actual assessment times.

Source: M5, v 1.17, Table 14.2.1.1, p 500307

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Table 27. BNP-301-4-167, Primary Efficacy Variable: AUEC₀₋₆ (L•Hr) of baseline-adjusted FEV₁ at Day 43/LOCF, Analysis using actual assessment times, MITT

Treatment	N	Mean (SE)	LS Mean (STE)	Treatment Comparison	LS Mean Diff (STE) ¹	p-value ¹
A) Albuterol HFA-MDI	58	1.28 (0.22)	1.28 (0.17)	A-D	1.04 (0.24)	<0.0001
B) Albuterol HFA-BOI	173			B-D		
C) Proventil HFA	56	1.20 (0.17)	1.20 (0.18)	C-D	0.97 (0.25)	0.0001
D) Placebo	58	0.24 (0.12)	0.24 (0.17)	A-C	0.08 (0.25)	0.7594
				B-C		
				A-B		
				Treatment		<0.0001

¹ Based on a one-way ANOVA model using the actual assessment times, not pre-specified assessment times

Source: M2, v 1.3, Tables 2.1-2.2, p 200037-8

Table 28. BNP-301-4-167, AUEC₀₋₆ (L•Hr) of baseline-adjusted FEV₁ at Day 43/LOCF, by age group, MITT

Treatment	N	Mean (SD)	LS Mean (STE)	Treatment Comparison	LS Mean Diff (STE) ¹	p-value ¹
A) Albuterol HFA-MDI	58	1.28 (1.69)	1.28 (0.17)	A-D	1.04 (0.25)	0.0000
12 to <18 years	8	2.00 (1.00)	2.00 (0.15)		1.48 (0.98)	0.1414
18 to <40 years	18	1.42 (2.63)	1.42 (0.36)		1.20 (0.46)	0.0092
40 to <65 years	31	0.98 (0.99)	0.98 (0.20)		0.72 (0.30)	0.0182
≥65 years	1	2.12	2.12		2.34 (1.16)	0.0606
B) Albuterol HFA-BOI	173			B-D		
12 to <18 years	23					
18 to <40 years	67					
40 to <65 years	70					
≥65 years	13					
C) Proventil HFA	56	1.20 (1.25)	1.20 (0.18)	C-D	0.97 (0.25)	0.0001
12 to <18 years	4	1.11 (3.46)	1.11 (0.72)		0.58 (1.11)	0.6019
18 to <40 years	27	1.35 (0.89)	1.35 (0.22)		1.13 (0.41)	0.0062
40 to <65 years	22	1.15 (1.14)	1.15 (0.24)		0.90 (0.33)	0.0070
≥65 years	3	0.44 (0.42)	0.44 (0.55)		0.66 (0.86)	0.4544
D) Placebo	58	0.23 (0.92)	0.23 (0.17)			
12 to <18 years	3	0.52 (0.35)	0.52 (0.84)			
18 to <40 years	29	0.22 (1.05)	0.22 (0.28)			
40 to <65 years	24	0.26 (0.84)	0.26 (0.23)			
≥65 years	2	-0.22 (0.57)	-0.22 (0.67)			
				A-C	0.07 (0.25)	0.7732
				12 to <18y	0.89 (0.89)	
				18 to <40y	0.07 (0.46)	
				40 to <65y	-0.18 (0.31)	
				≥65y	1.68 (1.09)	
				B-C		
				12 to <18y		
				18 to <40y		
				40 to <65y		
				≥65y		
				A-B		

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Treatment	N	Mean (SD)	LS Mean (STE)	Treatment Comparison	LS Mean Diff (STE) ¹	p-value ¹
				12 to <18y 18 to <40y 40 to <65y ≥65y	/	

1 Based on a one-way ANOVA model using the pre-specified assessment times, not actual assessment times.

Source: M5, v 1.17, Table 14.2.1.1, p 500307; Tables 14.2.1.3-6, p 500318-21

Table 29. BNP-301-4-167, AUEC₀₋₆ (L•Hr) of baseline-adjusted FEV₁ at Day 43/LOCF, by race, MITT

Treatment	N	Mean (SD)	LS Mean (STE)	Treatment Comparison	LS Mean Diff (STE) ¹	p-value ¹
A) Albuterol HFA-MDI	58	1.28 (1.69)	1.28 (0.17)	A-D	1.04 (0.25)	0.0000
White	45	1.31 (1.87)	1.31 (0.20)		1.02 (0.29)	0.0004
Black	10	1.34 (0.78)	1.34 (0.36)		1.36 (0.58)	0.0238
Asian & Other	3	0.61 (0.53)	0.61 (0.47)		0.57 (0.63)	0.3843
B) Albuterol HFA-BOI	173	/	/	B-D	/	/
White	142	/	/		/	/
Black	25	/	/		/	/
Asian & Other	6	/	/		/	/
C) Proventil HFA	56	1.20 (1.25)	1.20 (0.18)	C-D	0.97 (0.25)	0.0001
White	48	1.22 (1.33)	1.22 (0.20)		0.94 (0.28)	0.0010
Black	6	1.09 (0.75)	1.09 (0.46)		1.11 (0.65)	0.0936
Asian & Other	2	1.11 (0.61)	1.11 (0.61)		1.07 (0.72)	0.1618
D) Placebo	58	0.23 (0.92)	0.23 (0.17)	A-C	0.07 (0.25)	0.7732
White	47	0.29 (0.95)	0.29 (0.20)	White	0.08 (0.28)	
Black	6	-0.03 (0.73)	-0.03 (0.46)	Black	0.25 (0.58)	
Asian & Other	5	0.04 (0.96)	0.04 (0.38)	Other ²	-0.50 (0.78)	
				B-C	/	/
				White	/	/
				Black	/	/
				Other ²	/	/
				A-B	/	/
				White	/	/
				Black	/	/
				Other ²	/	/

1 Based on a one-way ANOVA model using the pre-specified assessment times, not actual assessment times.

2 Asian and Other

Source: M5, v 1.17, Table 14.2.1.1, p 500307; Tables 14.2.1.7-9, p 500322-4

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Table 30. BNP-301-4-167, AUEC₀₋₆ (L•Hr) of baseline-adjusted FEV₁ at Day 43/LOCF, by gender, MITT

Treatment	N	Mean (SD)	LS Mean (STE)	Treatment Comparison	LS Mean Diff (STE) ¹	p-value ¹
A) Albuterol HFA-MDI	58	1.28 (1.69)	1.28 (0.17)	A-D	1.04 (0.25)	0.0000
Males	20	1.96 (1.40)	1.96 (0.30)		1.43 (0.39)	0.0003
Females	38	0.92 (1.73)	0.92 (0.21)		0.98 (0.31)	0.0021
B) Albuterol HFA-BOI	173	/	/	B-D	/	/
Males	65	/	/		/	/
Females	108	/	/		/	/
C) Proventil HFA	56	1.20 (1.25)	1.20 (0.18)	C-D	0.97 (0.25)	0.0001
Males	22	1.14 (1.63)	1.14 (0.29)		0.61 (0.38)	0.1081
Females	34	1.25 (0.96)	1.25 (0.22)		1.31 (0.32)	0.0001
D) Placebo	58	0.23 (0.92)	0.23 (0.17)			
Males	29	0.53 (0.99)	0.53 (0.25)	A-C	0.07 (0.25)	0.7732
Females	29	-0.06 (0.76)	-0.06 (0.24)	Males	0.82 (0.41)	
				Females	-0.33 (0.30)	
				B-C		
				Males	/	/
				Females	/	/
				A-B		
				Males	/	/
				Females	/	/

¹ Based on a one-way ANOVA model using the pre-specified assessment times, not actual assessment times.

Source: M5, v 1.17, Table 14.2.1.1, p 500307; Tables 14.2.1.10-11, p 500325-6

Table 31. BNP-301-4-167, AUEC₀₋₆ (L•Hr) of baseline-adjusted FEV₁ at Day 43/LOCF, by patients on inhaled corticosteroids, MITT

Treatment	N	Mean (SD)	LS Mean (STE)	Treatment Comparison	LS Mean Diff (SE) ¹	p-value ¹
A) Albuterol HFA-MDI	58	1.28 (1.69)	1.28 (0.17)	A-D	1.04 (0.25)	0.0000
On inhaled CS	33	1.37 (0.22)	1.37 (0.22)		1.07 (0.29)	0.0001
NOT on inhaled CS	25	1.15 (0.42)	1.15 (0.42)		1.00 (0.41)	0.0155
B) Albuterol HFA-BOI	173	/	/	B-D	/	/
On inhaled CS	89	/	/		/	/
NOT on inhaled CS	84	/	/		/	/
C) Proventil HFA	56	1.20 (1.25)	1.20 (0.18)	C-D	0.97 (0.25)	0.0001
On inhaled CS	32	1.35 (0.22)	1.35 (0.21)		1.05 (0.29)	0.0004
NOT on inhaled CS	24	1.00 (0.26)	1.00 (0.30)		0.84 (0.41)	0.0423
D) Placebo	58	0.23 (0.92)	0.23 (0.17)			
On inhaled CS	31	0.53 (0.99)	0.53 (0.25)	A-C	0.07 (0.25)	0.7732
NOT on inhaled CS	27	0.16 (0.19)	0.16 (0.28)	On ICS	0.02 (0.29)	
				NOT on ICS	0.15 (0.42)	
				B-C		
				On ICS	/	/
				NOT on ICS	/	/

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Treatment	N	Mean (SD)	LS Mean (STE)	Treatment Comparison	LS Mean Diff (SE) ¹	p-value ¹
				A-B On ICS NOT on ICS	/	

Source: Electronic submission of 1/30/03, ISE, SUBSTR1A.pdf, SUBSTR1B.pdf, SUBSTR2A.pdf, SUBSTR2B.pdf

11.1.2.2.2. Secondary efficacy measures

Secondary efficacy analyses included analyses of pulmonary function (spirometric and pharmacodynamic) parameters based on spirometric measurements performed during clinic visits at various timepoints throughout the study, ambulatory function parameters recorded on diary cards, and device performance as measured by an ease-of-use questionnaire at the end of the study.

The applicant performed multiple analyses on pulmonary function parameters, and presented them in the study report separately as pulmonary function and pharmacodynamic analyses. Pulmonary function analyses included AUEC₀₋₆ (L•Hr) of baseline-adjusted FEV₁, AUEC₀₋₆ (%•Hr) of percent change in FEV₁, AUEC₀₋₆ (%•Hr) of baseline-adjusted percent predicted FEV₁, hourly FEV₁ (L), hourly percent change from pre-dose baseline in FEV₁, and hourly percent predicted FEV₁. Some analyses, such as hourly percent change from pre-dose baseline in FEV₁, and hourly percent predicted FEV₁ were judged as noncontributory and are not included in this review. Pharmacodynamic analyses included baseline-adjusted maximum FEV₁, baseline-adjusted maximum percent predicted FEV₁ (%), time to maximum FEV₁ (H), response rate, time (in minutes) to response onset (defined as an increase from baseline in FEV₁ ≥15%), and duration of response (response duration for responders was defined as the number of minutes from the time of dosing to response offset: change from baseline <15%).

Comment: Not all of the pharmacodynamic parameters listed above had been declared as secondary analyses in the protocol. Undeclared secondary PD parameters included baseline-adjusted maximum FEV₁, baseline-adjusted maximum percent predicted FEV₁ (%), and response rate.

Ambulatory function analyses included weekly pre-dose AM PEF and weekly daytime asthma scores, worst daily asthma symptom score, number of nocturnal awakenings, number of puffs of rescue medication.

Device performance analyses included analyses of each measure from the device questionnaire for the MDI product (items A1-A4); and the distribution of device preference (BOI, MDI, or no preference) from the device questionnaire, item C.

11.1.2.2.2.1. AUEC₀₋₆ (L•Hr) of baseline-adjusted FEV₁, percent change in FEV₁, and percent predicted FEV₁

The AUEC₀₋₆ (L•Hr) of baseline-adjusted FEV₁ at Days 1, 22, and 43 was compared by study day and treatment group. Results are shown in Table 32 and graphically in Figure 2. There was a significant effect of treatment and study day (p = 0.0005), but their interaction was not significant (p = 0.3934), implying that while there was a trend toward decreasing AUEC₀₋₆ over time, differences between treatment groups did not change [M5, v 1.17, p

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500079-82]. This trend was likely due to the development of tolerance (tachyphylaxis) [M5, v 1.17, p 500096-7].

AUEC₀₋₆ of percent change in FEV₁ and AUEC₀₋₆ of baseline-adjusted percent predicted FEV₁ showed similar results and trends, and therefore the results are not shown in this review. [M5, v 1.17, p 500079-82]

Table 32. BNP-301-4-167, AUEC₀₋₆ (L•Hr) of baseline-adjusted FEV₁, Overall and by study day, MITT¹

Treatment	N	Mean (SD)	LS Mean (STE)	Treatment Comparison	LS Mean Diff (STE) ²	p-value ²
Overall (All study days)						
A) Albuterol HFA-MDI	58	1.43 (1.35)	1.41 (0.14)	A-D	1.10 (0.20)	0.0000
B) Albuterol HFA-BOI	173	 		B-D	 	
C) Proventil HFA	56	1.41 (0.99)	1.40 (0.14)	C-D	1.09 (0.20)	0.0000
D) Placebo	58	0.32 (0.63)	0.31 (0.14)	A-C	0.01 (0.20)	0.9745
				B-C	 	
				A-B	 	
				Treatment		0.0000
				Study Day		0.0005
				Treatment by Study Day		0.3934
Day 1						
A) Albuterol HFA-MDI	58	1.54 (1.23)	1.54 (0.17)	A-D	1.27 (0.23)	0.0000
B) Albuterol HFA-BOI	173	 		B-D	 	
C) Proventil HFA	56	1.65 (1.10)	1.65 (0.17)	C-D	1.39 (0.24)	0.0000
D) Placebo	58	0.26 (0.70)	0.26 (0.17)	A-C	-0.12 (0.24)	0.6231
				B-C	 	
				A-B	 	
Day 22						
A) Albuterol HFA-MDI	53	1.44 (1.51)	1.46 (0.17)	A-D	1.01 (0.24)	0.0000
B) Albuterol HFA-BOI	155	 		B-D	 	
C) Proventil HFA	53	1.33 (1.24)	1.33 (0.17)	C-D	0.89 (0.24)	0.0003
D) Placebo	54	0.44 (0.89)	0.45 (0.17)	A-C	0.12 (0.24)	0.6138
				B-C	 	
				A-B	 	
Day 43						
A) Albuterol HFA-MDI	52	1.21 (1.70)	1.23 (0.17)	A-D	1.01 (0.25)	0.0000
B) Albuterol HFA-BOI	141	 		B-D	 	
C) Proventil HFA	49	1.27 (1.16)	1.21 (0.18)	C-D	1.00 (0.25)	0.0001
D) Placebo	49	0.18 (0.94)	0.22 (0.18)	A-C	-0.01 (0.25)	0.9588
				B-C	 	
				A-B	 	

1 Observed cases, not LOCF.

2 Based on a mixed-effect ANOVA model with treatment, study day, and treatment-by-study-day interaction as fixed effects and patient as a random effect. The model used the pre-specified assessment times, not actual

Treatment	N	Mean (SD)	LS Mean (STE)	Treatment Comparison	LS Mean Diff (STE) ²	p-value ²
assessment times.						

Source: M5, v 1.17, Table 14.2.2.1, p 500327-8

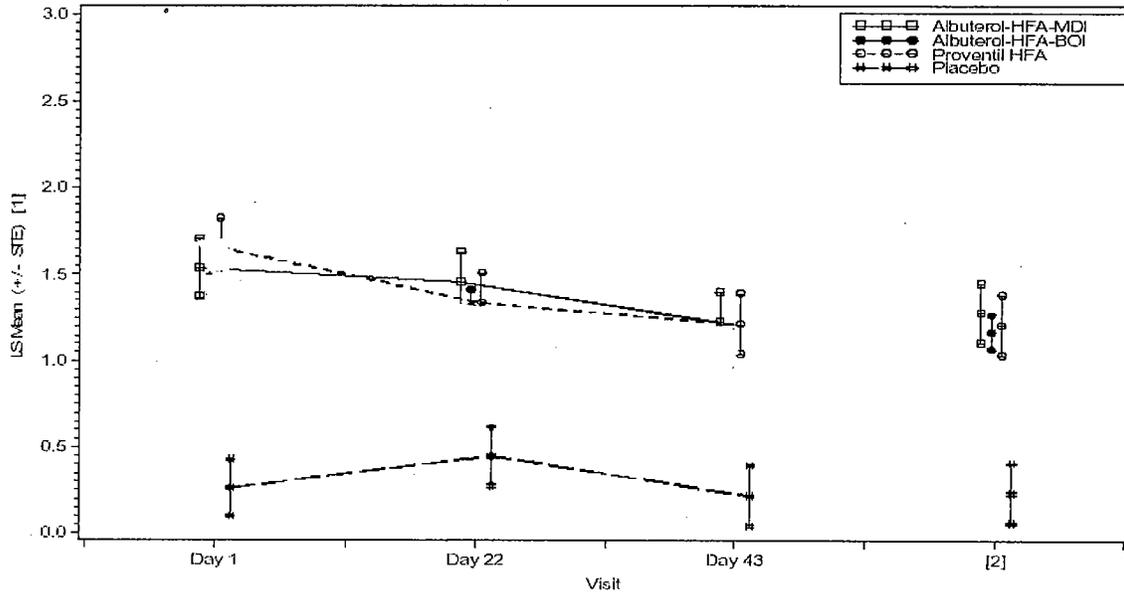


Figure 2. BNP-301-4-167, AUEC₀₋₆ of baseline-adjusted FEV₁, LS Means

Source: M5, v 1.17, Figure 11-1, p 500077, v 1.22, Figure 14.2.1.1, p 501956; Submission of 07/18/2003, Figure 11-1

11.1.2.2.2. Baseline-adjusted FEV₁, Maximum FEV₁, and Maximum Percent Predicted FEV₁, Time to maximum FEV₁

Change from pre-dose baseline in FEV₁ was comparable among all active treatment groups on Day 1, 22, and 43. Results are shown in Figure 3, Figure 4, and Figure 5. For all active treatments, differences between active and placebo were largest up to one hour, and steadily declined over the six-hour period. Whereas there was some visual separation of the active treatment groups from placebo throughout the 6-hour period on Day 1, on Days 22 and 43 the differences between active and placebo became quite small after 4 hours. On Day 43, Albuterol-HFA-MDI appeared to give a higher mean change from baseline than either Albuterol-HFA-BOI or Proventil HFA (Figure 5).

Baseline-adjusted maximum FEV₁ and baseline adjusted maximum percent predicted FEV₁ overall, and at Days 1, 22, 43 were evaluated in a mixed-effect ANOVA model with treatment, study day, and treatment-by-study-day interaction as fixed effects and patient as a random effect. Both sets of analyses showed similar results. The results for the baseline-adjusted maximum FEV₁ overall, and at Days 1, 22, 43 are shown in Table 33, but the results for percent predicted FEV₁ are not shown. The main effect of treatment was statistically significant (p≤0.0001 for both), with the effect of study day less so (p=0.0517 and p=0.0484, respectively). Treatment by study day interaction effect was not significant. Pairwise comparisons of each of the treatment group with placebo remained statistically significant (p≤0.0001) for all comparisons over time. [Note: Since the p-values were all

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secondary and not adjusted for multiple comparisons, the *p*-values are not shown in the table.] There was a marginal decrease in baseline-adjusted maximum FEV₁ and percent predicted FEV₁ over time for the _____ Proventil HFA groups, but not the Albuterol-HFA-MDI group. This decrease resulted in minor differences between treatment groups which emerged over time (seen visually in Figure 5), although the active treatment groups were not statistically different from each other on any study day ($p > 0.12$ and $p > 0.09$, respectively). [M5, v 1.17, p 500084-7, 500100]

Median time (in minutes) to baseline-adjusted maximum FEV₁ for the active treatment groups ranged from 46.8 to 54.0 minutes on Day 1, to 46.2 to 49.8 minutes on Day 22, to 31.2 to 49.2 minutes on Day 43. For the placebo group, median times were at least 2 hours on each study day. Differences among active treatment groups were not statistically significant ($p > 0.05$ for hazard ratios), but differences between active and placebo were statistically significant ($p < 0.05$). [M5, v 1.17, p 500087-8]

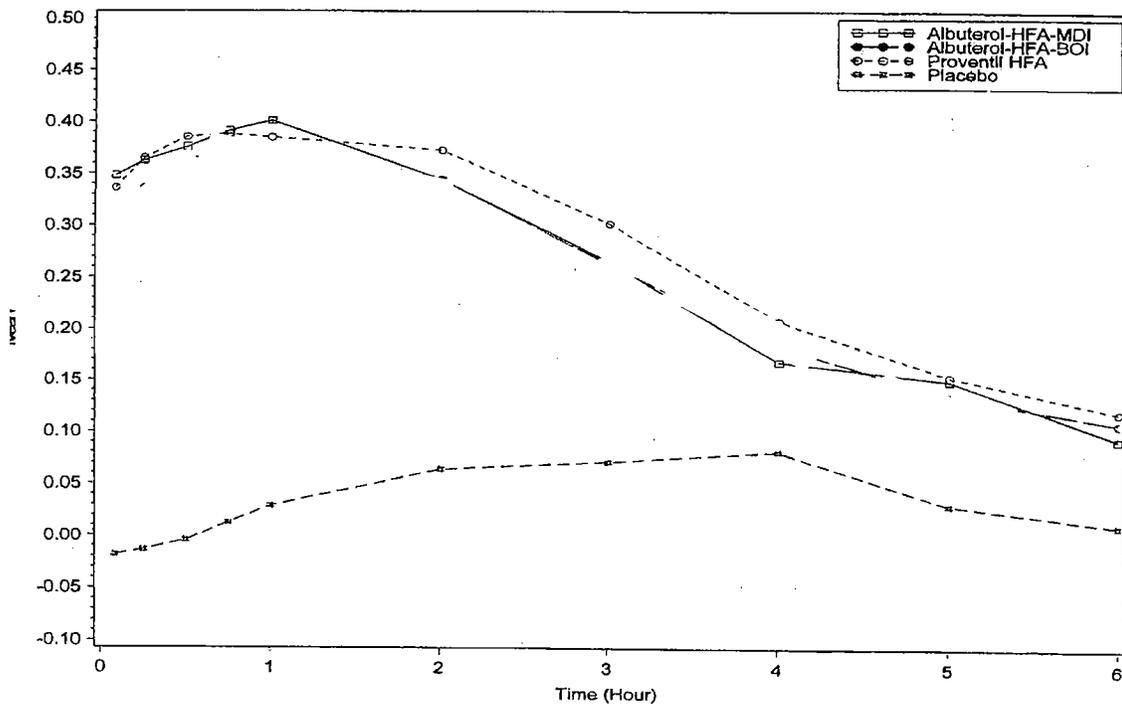


Figure 3. BNP-301-4-167, Change from baseline in FEV₁ (L), Day 1

Source: M5, v 1.22, Figure 14.2.5.1, p 501965

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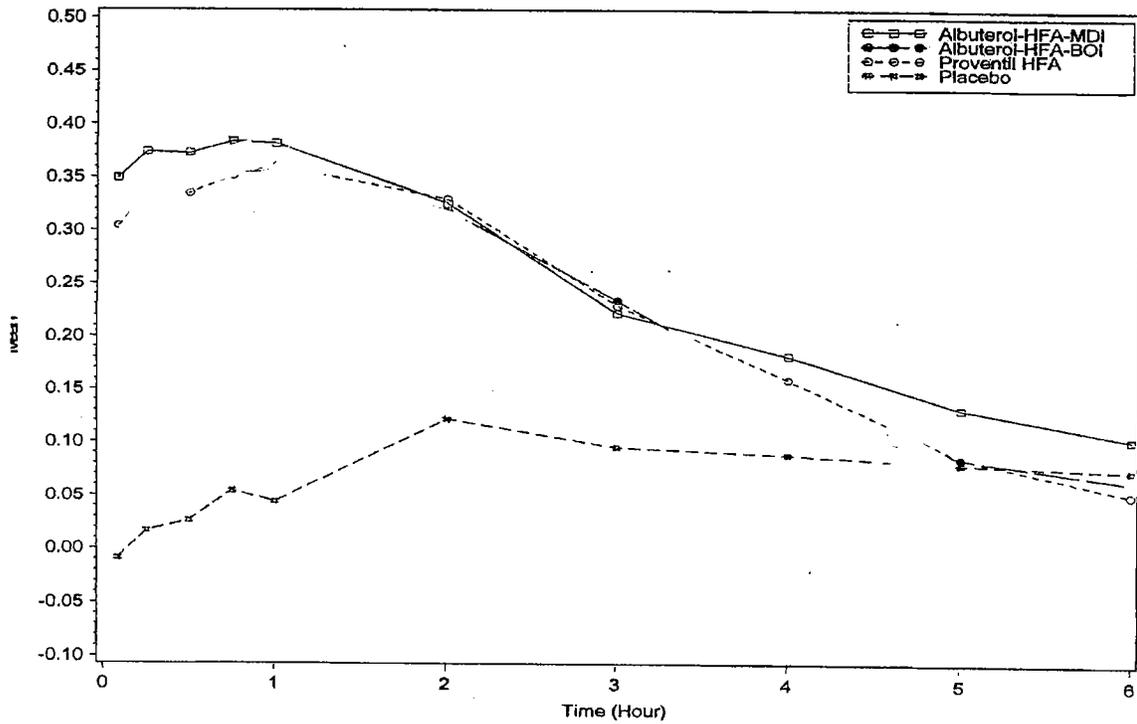


Figure 4. BNP-301-4-167, Change from baseline in FEV₁ (L), Day 22

Source: M5, v 1.22, Figure 14.2.5.2, p 501966

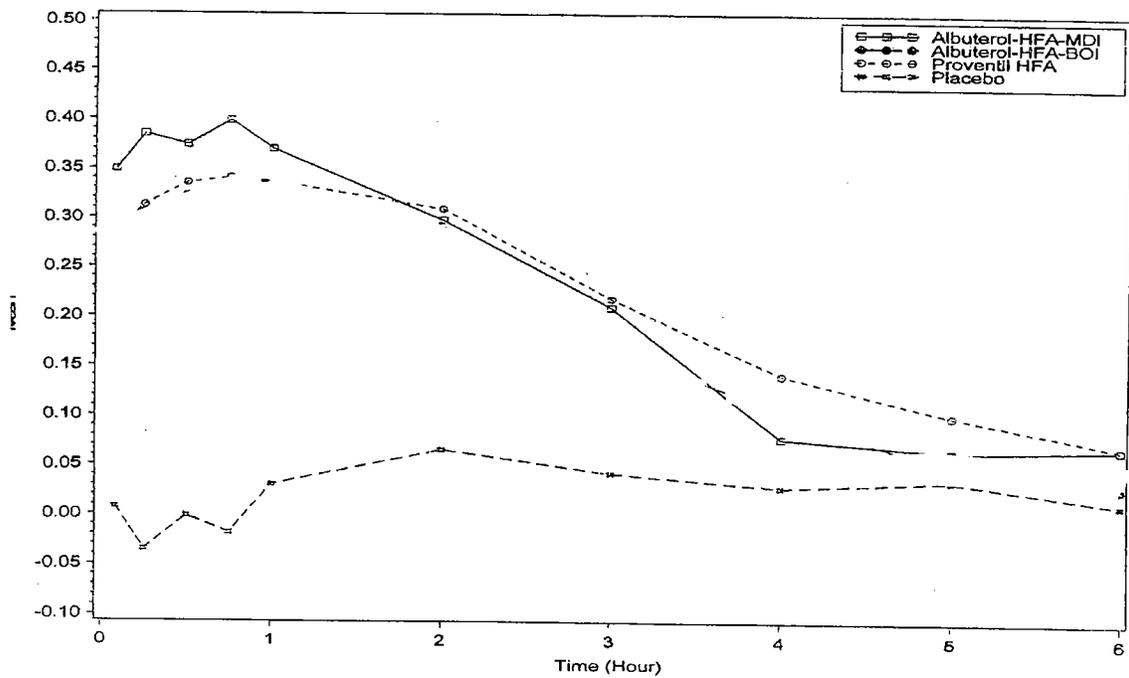


Figure 5. BNP-301-4-167, Change from baseline in FEV₁ (L), Day 43

Source: M5, v 1.22, Figure 14.2.5.3, p 501967

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Table 33. BNP-301-4-167, Baseline-adjusted maximum FEV₁ (L), MITT

Treatment	N	Mean (SD)	LS Mean (STE)	Treatment Comparison	LS Mean Diff (STE) ¹	Day 43-Day1
Overall (All study days)						
A) Albuterol HFA-MDI	58	0.46 (0.25)	0.46 (0.03)	A-D	0.27 (0.04)	A) 0.00
B) Albuterol HFA-BOI	173			B-D		
C) Proventil HFA	56	0.43 (0.20)	0.43 (0.03)	C-D	0.24 (0.04)	C) -0.07
D) Placebo	58	0.19 (0.13)	0.19 (0.03)	A-C	0.03 (0.04)	D) -0.01
				B-C		
				A-B		
Day 1						
A) Albuterol HFA-MDI	58	0.46 (0.23)	0.46 (0.03)	A-D	0.28 (0.05)	
B) Albuterol HFA-BOI	173			B-D		
C) Proventil HFA	56	0.46 (0.23)	0.46 (0.03)	C-D	0.28 (0.05)	
D) Placebo	58	0.18 (0.14)	0.18 (0.03)	A-C	-0.00 (0.05)	
				B-C		
				A-B		
Day 22						
A) Albuterol HFA-MDI	53	0.46 (0.27)	0.46 (0.03)	A-D	0.26 (0.05)	
B) Albuterol HFA-BOI	155			B-D		
C) Proventil HFA	53	0.42 (0.22)	0.42 (0.03)	C-D	0.22 (0.05)	
D) Placebo	54	0.20 (0.20)	0.21 (0.03)	A-C	0.04 (0.05)	
				B-C		
				A-B		
Day 43						
A) Albuterol HFA-MDI	52	0.45 (0.29)	0.46 (0.03)	A-D	0.28 (0.05)	
B) Albuterol HFA-BOI	141			B-D		
C) Proventil HFA	49	0.40 (0.23)	0.40 (0.03)	C-D	0.22 (0.05)	
D) Placebo	49	0.17 (0.16)	0.17 (0.03)	A-C	0.06 (0.05)	
				B-C		
				A-B		
¹ Based on a mixed-effect ANOVA model with treatment, study day, and treatment-by-study-day interaction as fixed effects and patient as a random effect. The model used the pre-specified assessment times, not actual assessment times.						

Source: M5, v 1.17, Table 11-11, p 500085 and v 1.18, Table 14.2.7.1, p 5000489-90

11.1.2.2.2.3. Non-baseline-adjusted Hourly FEV₁

Hourly non-baseline-adjusted FEV₁ is shown in Figure 6 and Figure 7 for Days 1 and 43, respectively. These figures differ from the previous baseline-adjusted figures, which more clearly defined the efficacy of the drug. In contrast, these figures point toward the tendency of albuterol to produce tachyphylaxis when used routinely over periods of time.

Tachyphylaxis, a partial drug tolerance, is a well-known phenomenon associated with chronic use of all β_2 -agonists. When used on a regular basis, tachyphylaxis may occur within days to weeks from the start of treatment, and this phenomenon continues without further reduction while routine treatment is continued. This presents as a limited reduction

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in efficacy, and is evidenced on PFTs more by a decrease in the duration rather than a decrease in the peak effect. However, prolonged therapy may lead to reduction in the control of asthma symptoms, and use in this manner is discouraged. PRN use of beta agonists, on the other hand, does not appear to be associated with clinically significant tolerance.

As expected, tachyphylaxis occurred during the course of this study. This phenomenon was noted for all active drugs, and may be seen by comparison of both the baseline-adjusted $FEV_{1\ 0-6}$ (Figure 3, Figure 4, and Figure 5) and the non-baseline-adjusted (raw) $FEV_{1\ 0-6}$ (Figure 6 and Figure 7 below) over the course of the study visits. On Day 1, non-baseline-adjusted FEV_1 increased by 200-300 ml and maintained a separation for up to 3-4 hours. By Day 43, non-baseline-adjusted FEV_1 increased by only 100-200 ml, and maintained separation for only 2-3 hours. Note that on Day 1, the Proventil HFA appeared to produce a higher FEV_1 with longer duration of response than either of the Albuterol-HFA-MDI which produced about the same FEV_1 response. On Day 43, the Proventil HFA produced a higher FEV_1 with longer duration of response than Albuterol-HFA-MDI.

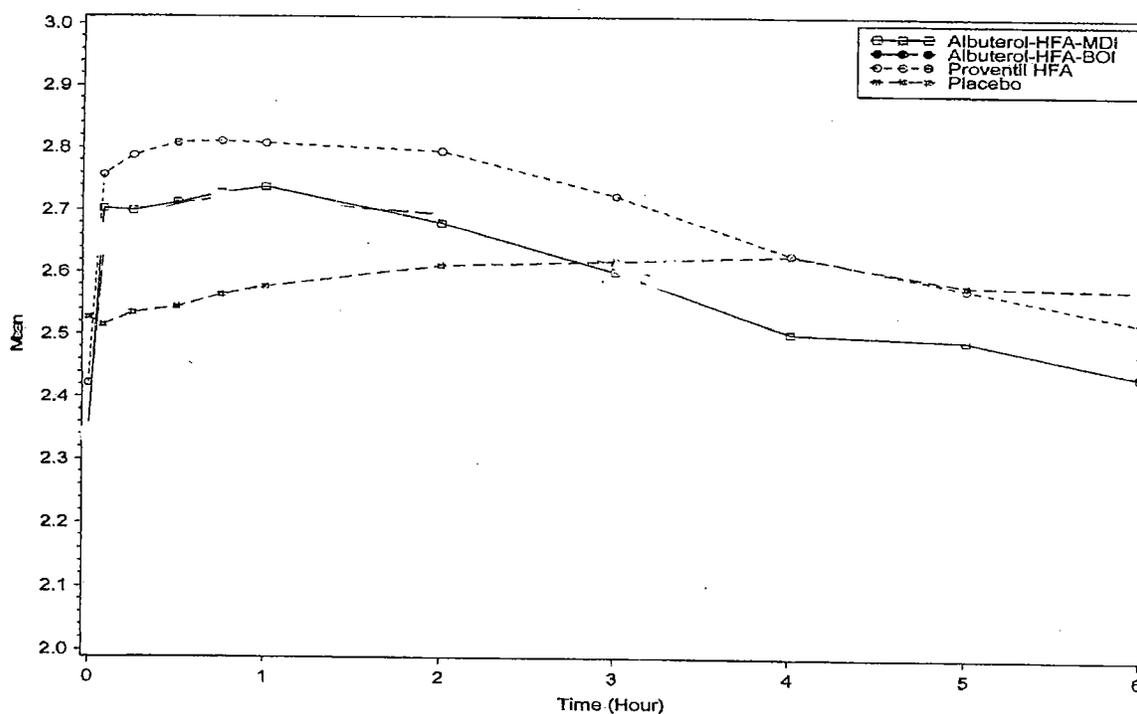


Figure 6. BNP-301-4-167, FEV_1 (L), Day 1

Source: Source: M5, v 1.22, Figure 14.2.4.1, p 501962

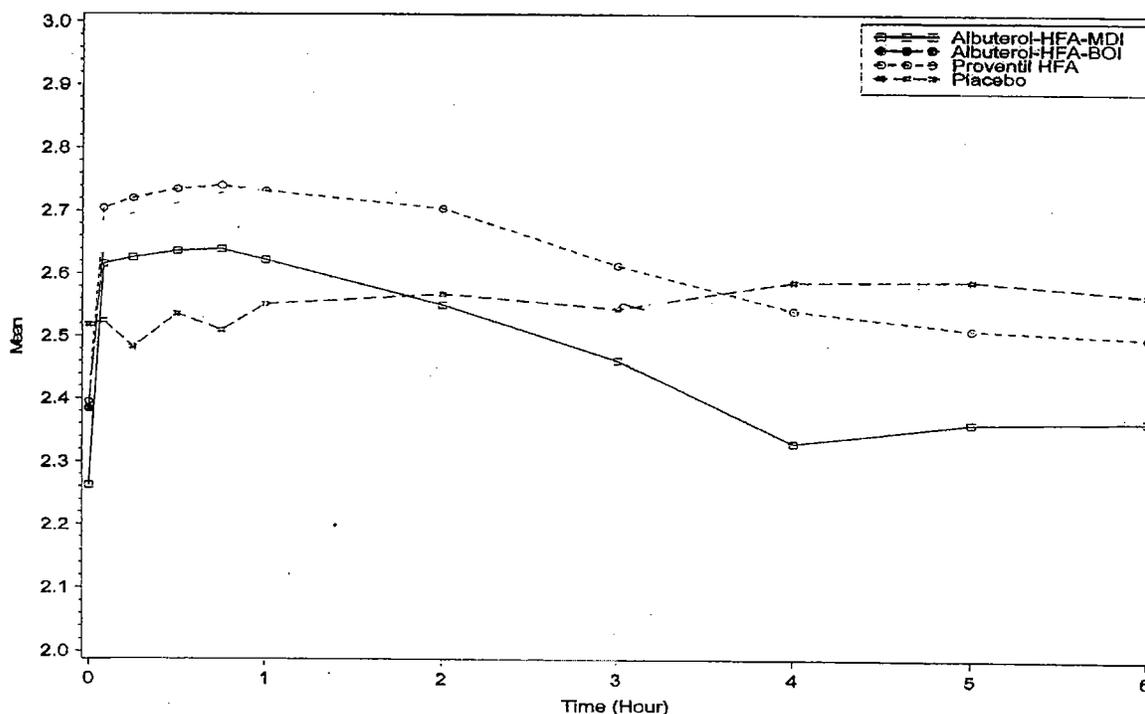


Figure 7. BNP-301-4-167, FEV₁ (L), Day 43

Source: Source: M5, v 1.22, Figure 14.2.4.3, p 501964

11.1.2.2.4. Time to response onset (15% and 12%) and duration of response

Time to response onset is shown in Table 34. Time to response onset was defined in the protocol as the time to an increase from baseline in FEV₁ ≥15%. All active treatment groups were significantly different than placebo. For each active treatment group, the number of patients who responded decreased from Day 1 to Day 43. The median time to a 15% response in FEV₁ increased from Day 1 to Day 43 for ~~the~~ the Proventil HFA groups, but not for the Albuterol-HFA-MDI group. Differences primarily were due to increases in the range of time to onset of response, i.e. fewer patients reached a 15% response in FEV₁, and more patients took longer to respond to this level. [M5, v 1.17, p 500090-2]

Since the response rate was lower than the applicant expected, a *post-hoc* analysis using a 12% response rate was added. This is also shown in Table 34. All active treatment groups were significantly different than placebo. ~~the~~

Table 34. BNP-301-4-167, Time (Hours) to response onset, MITT

	15% response ¹	12% response ²
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Treatment	N	Responders N (%)	Median time to response (95% CI)	Responders N (%)	Median time to response (95% CI)
Day 1					
Albuterol HFA-MDI	58	37 (63.8)	0.42 (0.19, 3.08)	45 (77.6)	0.18 (0.13, 0.31)
Albuterol HFA-BOI	173				
Proventil HFA	56	36 (64.3)	0.32 (0.13, 2.04)	42 (75.0)	0.13 (0.12, 0.32)
Placebo	58	4 (6.9)	>6.14 (>6.14,)	12 (20.7)	>6.14 (>6.14,)
Day 22					
Albuterol HFA-MDI	53	35 (66.0)	0.29 (0.18, 2.54)	43 (81.1)	0.15 (0.12, 0.28)
Albuterol HFA-BOI	155				
Proventil HFA	53	27 (50.9)	0.75 (0.12, >6.13)	37 (69.8)	0.26 (0.11, 0.57)
Placebo	54	14 (25.9)	>6.10 (>6.10,)	18 (33.3)	>6.10 (>6.10,)
Day 43					
Albuterol HFA-MDI	52	32 (61.5)	0.27 (0.13, 6.84)	39 (75.0)	0.13 (0.11, 0.50)
Albuterol HFA-BOI	141				, 2.11)
Proventil HFA	49	24 (49.0)	>6.09 (0.26, >6.09)	32 (65.3)	0.28 (0.12, 2.99)
Placebo	49	7 (14.3)	>6.18 (>6.18,)	11 (22.5)	>6.18 (>6.18,)

1 Defined in protocol as the first time that an increase from baseline in FEV₁ of at least 15% was noted.

2 *Post-hoc* analysis: first time that an increase from baseline in FEV₁ of at least 12% was noted.

Source: M5, v 1.17, Tables 11-16 and 11-17, p 500093-4

Duration of response, defined as the duration from the onset of a 15% response in FEV₁ to the time of offset of response was evaluated for responders only. Results are shown in Table 35. On Days 1 and 43, no difference between the active treatment groups was noted. On Day 22, the Albuterol-HFA-MDI group had duration times that were significantly shorter than the other two active treatment groups. While tachyphylaxis was not seen in the duration of response as measured by a 15% response, there was a trend noted when measured by the duration of a 12% response (Table 35). [M5, v 1.17, p 500095, 500099-100]

Table 35. BNP-301-4-167, Mean duration of response (Hours), MITT

Treatment	Day 1		Day 22		Day 43	
	N / Responders	Duration	N / Responders	Duration	N / Responders	Duration
15% response¹						
Albuterol HFA-MDI	37 / 34	2.66	35 / 32	1.27	32 / 27	2.88
Albuterol HFA-BOI						
Proventil HFA	36 / 29	3.18	27 / 22	3.93	24 / 21	2.94
Placebo	4 / 4	1.00	14 / 11	1.00	7 / 7	1.00
12% response²						
Albuterol HFA-MDI	45 / 40	3.71	4 / 34	2.90	39 / 33	2.95
Albuterol HFA-BOI						
Proventil HFA	42 / 35	3.95	37 / 27	3.87	32 / 28	2.34
Placebo	12 / 11	0.94	18 / 16	1.75	11 / 9	1.07

1 Defined in protocol as the first time that an increase from baseline in FEV₁ of at least 15% was noted.

2 *Post-hoc* analysis: first time that an increase from baseline in FEV₁ of at least 12% was noted.

Source: M5, v 1.17, Tables 11-19 and 11-20, p 500099-100; v 1.18, Tables 14.2.11.1 and 14.2.11.13, p 500608-10, 500669

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11.1.2.2.2.5. Diary parameters

Diary parameters included pre-dose AM PEF, daytime asthma scores, number of nocturnal awakenings, and number of puffs of rescue medication.

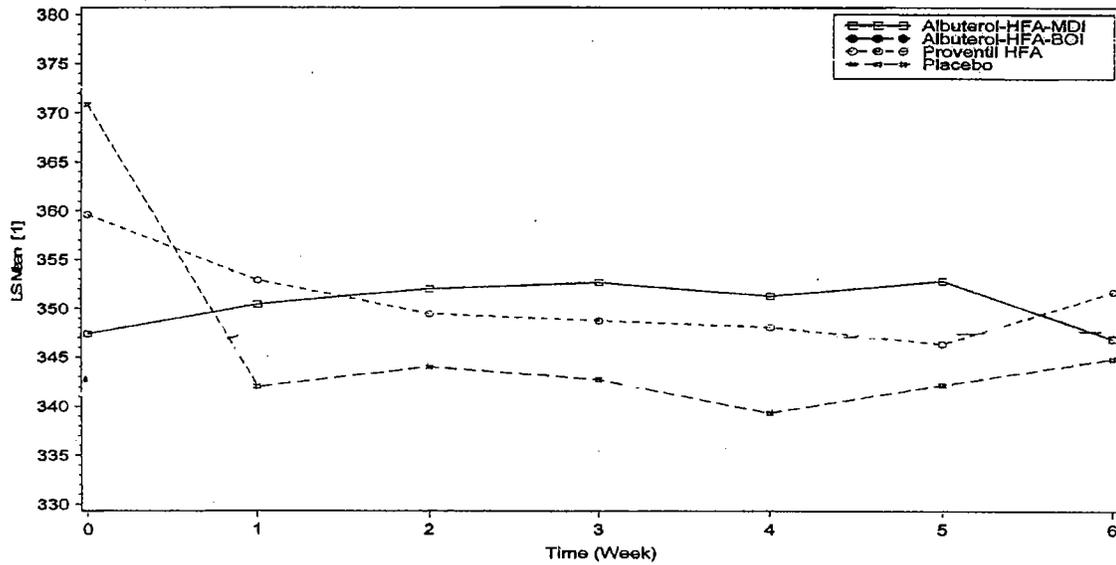
Mean daily PEF per week (Figure 8) showed no significant changes during treatment for any of the active treatment groups, and no significant differences from placebo. Curiously, the placebo group started with the highest PEF (LS mean 371), and dropped to the lowest of any of the groups (340-345) during each weekly treatment interval. [M5, v 1.17, p 500110-1]

Asthma symptom scores averaged by week showed a slight mean improvement for all treatment groups, with no statistically significant differences among the groups. In general, the group with the lowest symptom scores was the Albuterol-HFA-MDI group. Change from baseline for asthma symptom scores was largest for the Albuterol-HFA-MDI group (mean = -0.19), ~~Proventil HFA (mean = -0.12), and placebo (mean = -0.07).~~, Proventil HFA (mean = -0.12), and placebo (mean = -0.07). [M5, v 1.17, p 500103-5]

Nighttime awakenings due to asthma requiring rescue medication showed minimal changes over time and no clear trends. [M5, v 1.17, p 500106-7]

The number of puffs of rescue medication per day differed among treatment groups during the baseline run-in period (Albuterol-HFA-MDI 2.6, Albuterol-HFA-BOI ~~2.9~~, Proventil HFA 2.9, placebo 2.6). During the treatment period, use of rescue medication decreased for all active treatment groups, but not for placebo (Albuterol-HFA-MDI 1.5, Albuterol-HFA-BOI ~~2.5~~, Proventil HFA 1.5, placebo 2.5). When adjusted for baseline differences, the change from baseline compared to placebo was significant for Albuterol-HFA-MDI ($p = 0.003$) and Proventil HFA ($p = 0.001$), ~~Albuterol-HFA-BOI ($p = 0.001$).~~ [M5, v 1.17, p 500108-9]

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[1] Obtained from a mixed effect ANOVA model with treatment, week, their interaction, and baseline as fixed effects and patient as a random effect
 Note that: Week 0 is the mean over the run-in period, i.e., study baseline.

Figure 8. BNP-301-4-167, PEF (L/min) by week, LS means

Source: M5, v 1.22, Figure 14.2.10.1, p 501979

11.1.2.2.3. Other efficacy measures

At the End of Phase 2 meeting, the Division had discussed with the applicant evaluating device performance for each three week period during the trial. Specifically the Division requested evaluations of devices for clogging and spray pattern. The Division also requested information regarding frequency of jamming of the BOI device. To satisfy the Division's request, the applicant performed in vitro testing as well as inspection of the inhalers upon their return. In vitro testing included evaluation of the drug delivery profile and particle size distribution for a sampling of 24 inhalers used in this study. Information regarding these evaluations may be found in the safety section of this study review.

Device performance was also measured by a non-validated questionnaire developed by the applicant and completed by each patient at Day 43 or early termination. The two devices were compared for ease of use, ease of learning to use, ease of breathing, overall opinion, and preference for the device. Since the information regarding device performance obtained by patient questionnaires was considered to relate more to efficacy than safety, the information is presented below.

11.1.2.2.3.1. Device questionnaires

While most patients rated both products very easy to use, a comparison of ease of use

The overall opinion comparison also slightly favored the Albuterol-HFA-MDI device. However, among patients randomized to active treatment with the MDI device, the overall opinion was evenly split between the two devices, whereas

among those randomized to active treatment with the BOI device,

11.1.2.3. Safety Outcomes

11.1.2.3.1. Extent of exposure

The mean duration of exposure varied only slightly among treatment groups, from 39.4 to 41.0 days, with a median of 43 days for all groups. Mean exposure (mean ± SD) was 40.6 ± 7.0, 39.4 ± 10.0, 41.1 ± 7.6, and 40.0 ± 9.0 days for the Albuterol-HFA-MDI, Albuterol-HFA-BOI, Proventil HFA, and placebo groups, respectively. [M5, v 1.17, p 500128]

11.1.2.3.2. Clinical adverse events

Of the 345 patients enrolled, 136 (39.4%) reported 243 adverse events (AEs) during the treatment phase. The events were distributed almost equally among treatment groups: 23 patients (39.7%) in the Albuterol-HFA-MDI group, 71 patients (41.0%) in the Albuterol-HFA-BOI group, 20 patients (35.7%) in the Proventil HFA group, and 22 patients (37.9%) in the placebo group. Twenty-three patients (6.7%) experienced an adverse event that was considered severe in intensity. AEs that occurred in ≥3% of patients in at least one treatment group are listed in Table 36. The most frequent AEs were pharyngitis, asthma, and headache, of which headache was more prevalent in the active treatment groups than in the placebo group. Of note, the incidence of tachycardia was about equal among active treatment groups. While more patients in the White, and more patients in the 18 to 65 year age groups had Nervous System AEs as assessed by Body System, there were no significant differences in AEs by Preferred Term by gender, race, or age group. Overall, the severity of AEs was comparable among the treatment groups. [M5, v 1.17, p 500128-35; v 1.22, Table 14.3.1.1, p 501988]

Table 36. BNP-301-4-167, Treatment-emergent adverse events occurring in ≥3% of patients in at least one treatment group, MITT

	Albuterol-HFA-MDI n = 58 (%)	Albuterol-HFA-BOI n = 173 (%)	Proventil HFA n = 56 (%)	Placebo n = 58 (%)	Total n = 345 (%)
Total patients with an AE	23 (39.7)	71 (41.0)	20 (35.7)	22 (37.9)	136 (39.4)
Body as a Whole					
Abdominal pain	0	1 (0.6)	3 (5.4)	0	4 (1.2)
Back pain	2 (3.4)	0	2 (3.6)	3 (5.2)	7 (2.0)
Flu syndrome	0	0	1 (1.8)	2 (3.4)	3 (0.9)
Headache	4 (6.9)	11 (6.4)	3 (5.4)	1 (1.7)	19 (5.5)
Cardiovascular system					
Tachycardia	2 (3.4)	1 (0.6)	1 (1.8)	0	4 (1.2)
Musculo-skeletal system					
Pain	2 (3.4)	2 (1.2)	0	0	4 (1.2)
Nervous system					
Dizziness	2 (3.4)	0	0	0	2 (0.6)
Respiratory system					
Asthma	4 (6.9)	17 (9.8)	3 (5.4)	4 (6.9)	28 (8.1)

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	Albuterol-HFA-MDI n = 58 (%)	Albuterol-HFA-BOI n = 173 (%)	Proventil HFA n = 56 (%)	Placebo n = 58 (%)	Total n = 345 (%)
Bronchitis	0	5 (2.9)	1 (1.8)	2 (3.4)	8 (2.3)
Cough increased	2 (3.4)	1 (0.6)	0	2 (3.4)	5 (1.4)
Infection	2 (3.4)	4 (2.3)	2 (3.6)	2 (3.4)	10 (2.9)
Pharyngitis	8 (13.8)	22 (12.7)	4 (7.1)	5 (8.6)	39 (11.3)
Rhinitis	3 (5.2)	3 (1.7)	2 (3.6)	1 (1.7)	9 (2.6)

Source: M5, v 1.17, Table 12-2, p 500131

11.1.2.3.2.1. Clinical adverse events attributed to study drug treatment

Eleven patients (3.2%) experienced a total of 16 adverse events that was attributed to study drug by an investigator: 4 AEs in 3 patients (5.2%) in the Albuterol-HFA-MDI group, 7 AEs in 4 patients (2.3%) in the Albuterol-HFA-BOI group, 3 AEs in 2 patients (3.6%) in the Proventil HFA group, and 2 AEs in 2 patients (3.4%) in the placebo group. These are summarized in Table 37. There were no trends noted by treatment group, body system, race, or severity. There were no AEs judged drug-related in the 12 to <18 year old age group. In the age group >65 years (n = 19), one patient on Albuterol-HFA-BOI experienced three drug-related AEs of insomnia, asthma, and dyspnea. Analysis by gender did not reveal any trends, although the types of AEs were different. [M5, v 1.17, p 500129, 32-4; v 1.24, Table 14.3.11, p 502599]

Table 37. BNP-301-4-167, Treatment-emergent adverse events attributed to study drug, MITT

	Albuterol-HFA-MDI n = 58 (%)	Albuterol-HFA-BOI n = 173 (%)	Proventil HFA n = 56 (%)	Placebo n = 58 (%)	Total n = 345 (%)
Total patients with an AE	3 (5.2)	4 (2.3)	2 (3.6)	2 (3.4)	11 (3.2)
Total AEs	4	7	2	2	15
Headache	1 (1.7)	0	1 (1.8)	0	2 (0.6)
Hypertension	0	1 (0.6)	0	0	1 (0.3)
Palpitation	0	1 (0.6)	0	0	1 (0.3)
Tachycardia	2 (3.4)	0	1 (1.8)	0	3 (0.9)
Glossitis	1 (1.7)	0	0	0	1 (0.3)
Eosinophilia	0	0	0	1 (1.7)	1 (0.3)
Insomnia	0	1 (0.6)	0	0	1 (0.3)
Application site reaction	0	1 (0.6)	0	0	1 (0.3)
Asthma	0	1 (0.6)	0	1 (1.7)	2 (0.6)
Dyspnea	0	1 (0.6)	0	0	1 (0.3)
Acne	0	1 (0.6)	0	0	1 (0.3)

Source: M5, v 1.17, Table 12-3, p 500133

11.1.2.3.2.2. Serious adverse events, Deaths, and Discontinuations

There were no deaths reported. Two patients (one on Albuterol-HFA-BOI, and one on Proventil HFA) experienced three serious adverse events during the study [M5, v 1.17, p 500129, 500136-7]. Serious adverse events included:

- Patient 2006 (Site 3334), a 46 year old White female randomized to Albuterol-HFA-BOI, was hospitalized for acute exacerbation of asthma 5 weeks into the study.

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Concomitant medications included: fluticasone 200mcg QD for asthma, Privilil 10mg QD and hydrochlorothiazide 5mg QD for hypertension, Cephalexin 500mg BID, loratadine 10mg prn, clotrimazole plus betamethasone dipropionate for rash. The patient was considered an early termination, and PFTs were not performed on Day 43.

- Patient 2115 (Site 3330), a 31 year old White male randomized to Proventil HFA, was hospitalized for abdominal pain (severe) and diarrhea (mild) 5-6 weeks into the study. He patient was not discontinued.

Twenty-six patients (7.5%) discontinued the study due to an adverse event, of whom three patients completed 42 days of treatment but were considered early terminators because they did not complete pulmonary function testing on Day 43. The discontinued patients are detailed in Table 38, and include a higher number and percent of patients on each of the two active Albuterol-HFA products than on either the active comparator or placebo (4 {6.9%} Albuterol-HFA-MDI, 17 {9.8%} Albuterol-HFA-BOI, 2 {3.6%} Proventil HFA, and 3 {5.2%} placebo). Most patients were discontinued due to an asthma exacerbation or a combination of an upper respiratory infection (URI) and an asthma exacerbation. [M5, v 1.17, p 500129, 500136]

Table 38. BNP-301-4-167, Discontinuations due to an adverse event, MITT

Treatment	Site	ID#	Age	Race / Gender	Treatment Duration	SAE
Albuterol-HFA-MDI	3315	2346	19	White F	17	Asthma exacerbation
	3325	2371	32	White F	43	Viral URI
	3336	2331	27	White M	18	Asthma exacerbation
		2375	57	White F	17	URI/asthma exacerbation
Albuterol-HFA-BOI	3185	2322	38	White F	20	URI/worsening asthma
	3275	2067	14	Other F	42	Asthma exacerbation
		2070	37	White F	21	Asthma exacerbation
		2394	22	White F	29	Asthma exacerbation
	3303	2177	60	White F	10	Asthma exacerbation
		2178	40	White F	11	Headache
	3307	2219	29	White F	34	Allergic contact dermatitis
		2277	51	White M	34	Asthma exacerbation
	3311	2422	73	White M	18	Asthma exacerbation
	3314	2305	45	Black F	36	Asthma exacerbation
	3315	2343	57	White F	22	Asthma exacerbation/bronchitis
	3316	2366	53	White F	37	Asthma exacerbation
		3319	2213	29	White M	27
			2287	55	White F	23
	3320	2208	53	White F	14	Asthma exacerbation
3327	2092	68	White M	21	Wheezing/SOB	
3334	2006	47	White F	47	Asthma exacerbation	
Proventil HFA	3315	2086	61	White F	21	Asthma exacerbation
	3336	2334	31	White F	21	URI/Asthma exacerbation
Placebo	3185	2319	31	White M	22	Worsening asthma
	3281	2172	75	Other M	24	Asthma exacerbation
	3309	2039	63	White F	38	Asthma exacerbation

Source: M5, v 1.23, Table 14.3.3, p 502194-8

11.1.2.3.2.3. Adverse events requiring concomitant therapy

Ninety-nine (28.7%) of patients experienced an adverse event that required treatment with medication, and the incidence was comparable among treatment groups. Fifty-nine patients (17.1%) reported worsening asthma, with a breakdown as shown in Table 39. [M5, v 1.17, p 500149-50]

Note: The Albuterol-HFA-MDI and Albuterol-HFA-BOI columns in Table 39 do not reconcile with the number of patients D/C'd from the study, as shown in the Patient Disposition table (Table 22). Since not all patients who experienced worsening of their asthma were withdrawn from the study, no attempt was made to reconcile the differences between these two tables. It would have been helpful if 'Medication and D/C from study' had been a line item in the Disposition table.

Table 39. BNP-301-4-167, Number of patients with worsening asthma and treatments given, MITT

Treatment	Albuterol-HFA-MDI n = 58 (%)	Albuterol-HFA-BOI n = 173 (%)	Proventil HFA n = 56 (%)	Placebo n = 58 (%)	Total n = 345 (%)
Number of patients with worsening asthma	10 (17.2)	30 (17.3)	9 (16.0)	10 (17.2)	59 (17.1)
None	1 (1.7)	1 (0.6)	0	0	2 (0.6)
Medication only	1 (1.7)	2 (1.2)	1 (1.8)	1 (1.7)	5 (1.4)
D/C from study	0	3 (1.7)	1 (1.8)	2 (3.4)	6 (1.7)
Medication and D/C from study	3 (5.2)	9 (5.2)	1 (1.8)	1 (1.7)	14 (4.1)
Medication and other	0	1 (0.6)	0	0	1 (0.3)
Hospitalized, medication, and D/C from study	0	1 (0.6)	0	0	1 (0.3)
Unspecified	5 (8.6)	13 (7.5)	6 (10.7)	6 (10.3)	30 (8.7)

Source: M5, v 1.17, Table 12-5, p 500150

11.1.2.3.3. Vital signs and Physical examinations

There were no significant differences among treatment groups for mean changes in vital signs throughout the study [M5, v 1.17, p 500163-71]. None of the changes in respiratory rate that were found appeared to be clinically relevant [M5, v 1.17, p 500168]. No clinically significant abnormal changes in electrocardiograms were described [M5, v 1.17, p 500171]. Since changes in heart rate and blood pressure might be expected with albuterol treatment, these results are discussed separately in sections below.

Most patients had normal physical findings at screening that remained normal at Day 43. Changes in physical findings from normal to abnormal generally related to examination of the chest and lungs. On Day 43, the Albuterol-HFA-MDI (2/58, 3.4%) and Albuterol HFA-BOI (11/166, 6.6%) groups had fewer physical examination abnormalities of the chest and lungs than Proventil (5/55, 9.0%) or placebo (7/57, 12.2%) [M5, v 1.17, p 500168-9].

11.1.2.3.3.1. Blood pressure

With minor exceptions, there were no statistically significant differences between treatment groups for mean systolic or diastolic blood pressures (BP) from pre-dose to post-dose

measurements. The highest mean increase in systolic BP was 2.17 mmHg in the placebo group on Day 43 at 6 hours after dosing.

However, 13/345 patients (3.8%) had individual increases in systolic BP of at least 30 mmHg and 53 (15.4%) had increases in diastolic BP of at least 15 mmHg during the 6-hour post-drug observations period. Systolic BP increases of ≥ 30 mmHg occurred more frequently in the two Albuterol treatment groups than in the active comparator or placebo: 3 (5.2%) of patients on Albuterol-HFA-MDI, 8 (4.6%) on Albuterol-HFA-BOI, 1 (1.8%) on Proventil HFA, and 1 (1.7%) on placebo. Diastolic BP increases of ≥ 15 mmHg also occurred more frequently in the two Albuterol treatment groups than in the active comparator or placebo: 8 (13.8%) of patients on Albuterol-HFA-MDI, 29 (16.2%) on Albuterol-HFA-BOI, 5 (8.9%) on Proventil HFA, and 11 (9.0%) on placebo. A maximum increase in systolic BP of 39 mmHg was noted in a patient on Albuterol-HFA-MDI. A maximum increase in diastolic BP of 31 mmHg was noted in a patient (2087) on placebo. Only one patient had a systolic BP increase on more than one treatment day, and many of the increases were more or less sporadic. The study report states that two patients (2037) on Albuterol-HFA-MDI and (2038) on Albuterol-HFA-BOI had sustained increases in systolic BP [M5, v 1.17, p 500164]. However review of the line listings reveals that five patients had 2 consecutive systolic BP increases of ≥ 30 mmHg (1 on Albuterol-HFA-MDI, 3 on Albuterol-HFA-BOI, 1 on Proventil HFA), of whom one had a baseline systolic BP of 90 and a peak of 120 mmHg. Three patients (2 on Albuterol-HFA-BOI, 1 on Proventil HFA) had increases in systolic BP accompanied by increases in diastolic BP ≥ 15 mmHg. [M5, v 1.17, p 500163-5]

Twenty-one patients (6.1%) had decreases in systolic BP of at least 30 mmHg and 96 (27.8%) had decreases in diastolic BP of at least 15 mmHg during the 6-hour post-drug observations period. Blood pressure decreases were comparable among treatment groups. Systolic BP decreases of ≥ 30 mmHg occurred in 3 (5.2%) of patients on Albuterol-HFA-MDI, 12 (7.0%) on Albuterol-HFA-BOI, 4 (7.1%) on Proventil HFA, and 2 (3.4%) on placebo. Diastolic BP decreases of ≥ 15 mmHg occurred in 12 (20.7%) of patients on Albuterol-HFA-MDI, 51 (29.5%) on Albuterol-HFA-BOI, 16 (28.6%) on Proventil HFA, and 17 (29.3%) on placebo. [M5, v 1.17, p 500163-5]

11.1.2.3.3.2. Heart rate

When adjusted for baseline, no clear trends in mean heart rate from pre- to post-dose were seen. On Day 1, for example, the differences among treatment groups at baseline were larger than the differences with treatment. AUEC₀₋₆ of change from pre-dose baseline in mean heart rate is shown in Table 40. Albuterol-HFA-MDI and Proventil both showed an overall decrease in heart rate compared to baseline, whereas Albuterol-HFA-BOI and placebo showed an overall increase in heart rate, with placebo showing the highest change in heart rate from baseline. [M5, v 1.17, p 500166-7]

Comment: These results are hard to interpret, since it would typically be expected for albuterol to exhibit some inotropic effects compared with placebo, and this is the opposite of what was found.

Table 40. BNP-301-4-167, AUEC₀₋₆ of change from pre-dose heart rate, MITT

Treatment	N	LS Mean (STE) BPM	Treatment Comparison	LS Mean Diff (STE) ¹
Overall (All study days)				
A) Albuterol HFA-MDI	58	-6.84 (3.66)	A-D	-13.73 (5.19)
B) Albuterol HFA-BOI	173	2.42 (2.16)	B-D	-4.47 (4.27)
C) Proventil HFA	56	-1.14 (3.72)	C-D	-8.04 (5.23)
D) Placebo	58	6.90 (3.68)		
			A-C	-5.70 (5.22)
			B-C	3.56 (4.30)
			A-B	-9.26 (4.25)

Source: M5, v 1.17, Table 12-11, p 500167

11.1.2.3.4. Laboratory Adverse Events

Clinical laboratory tests were analyzed at screening and at the end of therapy. There were no trends for laboratory AEs. There were no pregnancies. Clinically significant laboratory values outside the range defined in the protocol occurred in five patients (4 Albuterol-HFA-BOI, 1 Proventil HFA). In addition, two patients had mild laboratory abnormalities considered clinically significant by the investigator. [Source: M5, v 1.17, p 500157-63]

The seven patients included:

- Patient 2089 (Site 3115), a 74 year old White male randomized to Albuterol-HFA-BOI, had elevated potassium levels of 5.8, 5.4, and 6.3 mEq/L. The patient had a history of hypertension and pedal edema treated with lisinopril, diltiazam, spiro lactone, and potassium supplements of 8mg/day. He had previous elevations in his potassium levels, and reported taking a double dose of potassium on his own.
- Patient 2117 (Site 3330), a 57 year old Black female randomized to Albuterol-HFA-BOI, had an elevated serum glucose of 220 mg/dL. The patient had a history of non-insulin-dependent diabetes treated with Amaryl 8mg QD. Her screening glucose was 183 mg/dL.
- Patient 2171 (Site 3281), a 37 year old Black female randomized to Albuterol-HFA-BOI, had a low hemoglobin of 10.3 g/dL at screening and a low hemoglobin of 9.8 g/dL and elevated serum potassium of 6.2 mEq/L at the end of the study. The patient had a history of obesity, two eye surgeries, herniated cervical disk, urticaria, seasonal and perennial allergic rhinitis, chronic sinusitis, and allergies to multiple drugs. During the study, the patient's asthma worsened, for which no action was taken, and it resolved. She was treated for bronchitis during the study. Her end of study labs were reported to show hemolysis.
- Patient 2445 (Site 3303), a 30 year old White male randomized to Albuterol-HFA-BOI, had a high WBC of $17.36 \times 10^3/\text{mm}^3$. The patient had history of ulcerative colitis, bronchitis, laryngitis, cervical myositis, pneumonia, and allergies to drugs. He had no AEs, but did require 8 puffs of rescue medication per day. At Day 43, his temperature was 36.6°C, maximum BP 148/100 mmHg, maximum HR 81 bpm. The reason for the elevated WBC was unexplained.
- Patient 2249 (Site 3322), a 34 year old White female randomized to Proventil HFA, had elevated serum glucoses of 220 mg/dL at screening, and 525 and 294 mg/dL on

Day 43. The patient had history of diabetes treated with Glucophage 500mg BID. On Day 43, she had evidence of a viral upper respiratory infection.

- Patient 2373 (Site 3336), a 39 year old White female randomized to Proventil HFA, had elevated SGOT of 64, 57, 63 IU/L, SGPT of 97, 142, and 113 IU/L, and eosinophils of 11.3%. The patient had history of headaches, sinus problems, and perennial allergic rhinitis. Screening SGOT 32, SGPT 30. The patient was on Nikken vitamins, Flovent, and Rhinocort aqua, and received Zithromax for URI and chlorzoxazone for stiff neck during the study. Labs: Day: 43 SGOT 64, SGPT 97, Eos 11.3%; Day 54: SGOT 57, SGPT 142; Day 78: SGOT 63, SGPT 1137; and Day 95: SGOT 41, SGPT 52.
- Patient 2218 (Site 3307), a 38 year old White female randomized to placebo, had low serum potassium of 3.4 mEq/L on Day 43. The patient had history of hiatal hernia, perennial and seasonal allergic rhinitis, allergic headache, degenerated C5 disk with neck pain, premenstrual dysphoric disorder, and food allergies. The patient was on fluticasone inhaler and nasal spray, immunotherapy, loratadine, omeprazole, fluoxetine, and acetaminophen. On Day 45 the potassium was 4.0 mEq/L.

While the study report discusses changes from baseline in hematology values that were statistically significant for treatment groups and sub-groups, there were no clinically relevant changes in hematological or clinical chemistry values [Source: M5, v 1.17, p 500152-6]. Laboratory shift tables showed no trends for changes from normal to abnormal values from before to after treatment. Results for shifts in blood glucose, phosphorous, and SGPT are noted here. Change from normal to abnormal in blood glucose occurred in 5/58 (8.6%), 13/173 (7.8%), 2/56 (3.7%), and 4/58 (7.0%) of patients on Albuterol-HFA-MDI, Albuterol-HFA-BOI, Proventil, and placebo, respectively. Change from normal to abnormal in blood phosphorous occurred in 3/58 (5.2%), 13/173 (7.8%), 3/56 (5.6%), and 4/58 (7.0%) of patients on Albuterol-HFA-MDI, Albuterol-HFA-BOI, Proventil, and placebo, respectively. Change from normal to abnormal in SGPT occurred in 4/58 (6.9%), 5/173 (3.0%), 2/56 (3.7%), and 1/58 (1.8%) of patients on Albuterol-HFA-MDI, Albuterol-HFA-BOI, Proventil, and placebo, respectively. [M5, v 1.23, 14.3.6.2.1, p 502418-24]

11.1.2.3.5. Device performance: Study medication return, Inspection of devices, In vitro testing, and Medical device incidents or malfunctions

At the End of Phase 2 meeting, the Division had discussed with the applicant evaluating device performance for each three week period during the trial. Specifically the Division requested evaluations of devices for clogging and spray pattern. The Division also requested information regarding frequency of jamming of the BOI device. To satisfy the Division's request, the applicant performed *in vitro* testing as well as inspection of the inhalers upon their return. Device performance was also measured by a non-validated questionnaire developed by the applicant and completed by each patient at Day 43 or early termination. The two devices were compared for ease of use, ease of learning to use, ease of breathing, overall opinion, and preference for the device. Since the information regarding device performance obtained by patient questionnaires was considered to relate more to efficacy than safety, the information is presented in the Efficacy section of this study review. Information regarding device inspection and *in vitro* testing relates to safety, and is therefore in this section.

11.1.2.3.5.1. Study medication return and inspection of devices

Greater than 98.5% of the inhalers were returned at each visit. Patients had been instructed to clean the inhalers weekly. At each of Days 22 and 43, site personnel recorded whether any deposits were noted in the inhaler mouthpiece. For the MDI device, deposits were observed in 9.9% and 14.6% of inhalers on Days 22 and 43, respectively. For the BOI device, deposits were observed in 8.7% and 7.5% of inhalers on Days 22 and 43, respectively. None of the deposits were associated with any reported device malfunctions. [M5, v 1.17, p 500118]

11.1.2.3.5.2. In vitro device testing

In vitro testing included evaluation of the drug delivery profile and particle size distribution for a sampling of 24 inhalers used in this study. The sampling planned for collection of the two active inhalers used by one patient from each of the 12 sites in the study. The patient must have completed all six weeks of study treatment. The sample was equally divided between testing for drug delivery and particle size distribution, such that six MDI and six BOI inhalers were tested for drug delivery, and six MDI and six BOI inhalers were tested for particle size distribution. Table 41 shows the drug product lot returns for *in vivo* testing. Note that the drug product tested was two months prior to the expiry date. The report does not mention whether the canisters were weighed to confirm use. Instead, it appears that the applicant assumed that 177 actuations had been consumed during the study. [Submission of 8/7/03, p 2-4]

It was noted during testing of the MDI product for dose content uniformity that one of the canisters returned did not contain active drug. The MDI canister contained placebo, and subsequently active drug was found in the BOI inhaler canister used by the same patient. It does not appear that the active canister was tested, and therefore only 5 MDI canisters underwent *in vitro* testing for dose content uniformity. Please see the Protocol Violations section of this study review for further details.

The applicant reports that all test results were within finished product specifications and no specific trends were noted in the testing. The conclusion was that the post-study testing showed that the Albuterol-HFA inhalers met the current product specifications. Please refer to the CMC Review for more details regarding drug product specifications and an evaluation of the adequacy of the post-study testing program. [Submission of 8/7/03, p 2-4]

Table 41. BNP-301-4-167, Drug Product Lot Returns for *In Vitro* Testing

Product	Product Batch No	Actuator Batch No	Date of Manufacture	Date Returned	Product Expiry Date
Albuterol-HFA-MDI	AAW13A	01R0010	June 2000	April 2002	June 2002
Albuterol-HFA-BOI	AAW13A	00R0159 / 00R0156	June 2000	April 2002	June 2002

Source: Submission of 8/7/03, p 2

11.1.2.3.5.3. Medical device incidents or malfunctions

The study report listed 8 device malfunctions in the patient disposition table but did not discuss the nature of the malfunctions in the text. Six of the patients experienced a BOI malfunction and 2 experienced an MDI malfunction. Table 22 is misleading in that the

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withdrawal is attributed to the study drug to which the patient was randomized. However, not all of the devices that malfunctioned were those that contained active drug (i.e. some were placebo inhalers given to patients randomized to other treatments). As shown in Table 42, only three of the malfunctioning inhalers contained active drug (2 BOI and 1 MDI, shown in **bold** in the table). In the clinical modules, no explanation was provided for what happened to these patients i.e. why they were discontinued as opposed to dispensing new inhalers and allowing continuation in the study. The submitted Case Report Forms for patients withdrawn due to an adverse event did not include any of the patients withdrawn for an inhaler malfunction [M5, Attachment 5, v 1.86, p 500966-73; Attachment 8, v 1.88-1.91]. Review of the listing of inhalers sent for in vitro testing reveals that non of these were part of the 24 inhalers sent for evaluation of the drug delivery profile and particle size distribution. However, Module 3 provided information for the two HFA-MDI inhalers that were returned due to a malfunction. The defect analysis (Table 43) revealed that one (placebo) inhaler had malfunctioned due to a deformed actuator orifice, in turn due to excessive pressure that had been used to actuate canister. When the canister was tested with a new actuator, no problem was noted. No problem could be found with the second (active) returned device. [M5, v 1.17, Table 10-2, p 500062; M2, v1.3, Table 2.4.2, p 2000118; Submission of August 7, 2003, Tab 3, p 301220-1; M3, v 1.6, p 301239-44]

Table 42. BNP-301-4-167, Patients withdrawn for inhaler malfunction

Treatment Group	Site	ID#	Device Malfunction	Timing and Cause of Malfunction
Placebo HFA	3335	2265	BOI	Not provided
Albuterol-HFA-BOI	3330	2429	BOI	Not provided
		2431	BOI	Not provided
Albuterol-HFA-MDI	3336	2333	MDI	Not provided
	3319	2215	MDI	Not provided
Proventil HFA	3303	2176	BOI	Not provided
	3314	2303	BOI	After Day 22 visit
	3330	2430	BOI	Not provided

Source: M2, v 1.3, Table 2.4.2, p 200118; Submission of 8/5/03, Tab 3, p 8

Table 43. BNP-301-4-167, MDI defect analysis

Inhaler Type	Dosing Period	ID#	Complaint	Investigation	Conclusion
Placebo-HFA-MDI	Days 22-43 Inhaler #1	2333	Inhaler would not fire on depressing the canister, but would fire on release of the canister	Actuator orifice deformed due to excessive pressure used to actuate canister	Post-packing fault
Albuterol-HFA-MDI	Days 1-22 Inhaler #1	2215	Not working right	Orifice not blocked. Complaint can & placebo both actuate through the device	No fault found

Source: M3, v 1.6, p 301244

11.1.3. Discussion

This was a six-week, multi-center, randomized, evaluator-blind, (double-blind, double-dummy vs placebo for the IVAX products), placebo-controlled, parallel group study comparing the efficacy and safety of Albuterol-HFA-MDI and Albuterol-HFA-BOI with that of placebo and Proventil HFA administered to at 345 mild-to-moderate asthmatics ≥ 12 years of age. Eligibility requirements included an FEV₁ 50-85% predicted and demonstration of reversible bronchoconstriction as evidenced by a $\geq 12\%$ increase in FEV₁ within 30 minutes following inhalation of albuterol 180 mcg (2 actuations). Eligible patients were randomized to receive Placebo HFA-BOI/MDI, Albuterol HFA-MDI, Albuterol-HFA-BOI, or Proventil HFA administered as 2 puffs (180 mcg) four times daily for 42 days. A double-dummy technique for the MDI and BOI inhalers allowed maintenance of a double-blind for the Placebo-HFA-BOI/MDI, Albuterol-HFA-MDI, and Albuterol-HFA-BOI arms. Because a Proventil HFA placebo was not available, the Proventil HFA arm could not be visually blinded, and therefore was only evaluator blinded.

A total of 345 patients were randomized, of whom 290 completed study treatment, and 259 (89% of the patients completing six weeks of treatment) completed evaluations on the final day of the study. Randomization was not equal, but was 1:3:1:1 for the Albuterol-HFA-MDI : Albuterol-HFA-BOI : Proventil HFA : Placebo groups. The unbalanced randomization was designed to provide greater information to support the application for the Albuterol-HFA-BOI drug product. The ITT population included 58, 173, 56, and 58 patients in the Albuterol-HFA-MDI, Albuterol-HFA-BOI, Proventil HFA, and placebo groups, respectively. Because of the unbalanced randomization, the number of patients who completed the study Albuterol-HFA-MDI and placebo groups was quite small: 52 and 47 patients, respectively. Treatment groups were relatively well balanced at randomization, except that there was a higher percent of males in the placebo group than the other groups. Overall there were more females (61%) than males (39%) enrolled, and Whites were in the large majority (81%), with Asians and 'Other' races poorly represented.

The primary efficacy analysis was a comparison of the mean difference between Albuterol-HFA-MDI and placebo for the AUEC₀₋₆ of baseline-adjusted FEV₁ at Day 43 or last observation was statistically significant (LS mean difference = 1.04 L•Hr, $p = <0.0001$). Other comparisons of interest between Albuterol-HFA-MDI vs Proventil-HFA vs placebo were also significant (Albuterol-HFA-MDI vs Proventil-HFA $p = <0.0001$; Proventil vs placebo LS mean difference = 0.97, $p = 0.0001$). There were minor and not statistically significant differences among active treatments, with the largest numerical difference between the Albuterol-HFA-MDI and Albuterol-HFA-BOI products. Analysis by subgroups of age, race, and gender did not reveal any trends. Note that the devices used on Day 1 were new, whereas devices used on Days 22 and 43 were not cleaned prior to use and had been used for about 3 weeks with weekly cleaning at home.

Secondary efficacy analyses included analyses of pulmonary function (spirometric and pharmacodynamic) parameters based on spirometric measurements performed during clinic visits at various timepoints throughout the study, ambulatory function parameters recorded on diary cards, and device performance as measured by an ease-of-use questionnaire at the end of the study. Pulmonary function analyses included AUEC₀₋₆ (L•Hr) of baseline-adjusted FEV₁, AUEC₀₋₆ (%•Hr) of percent change in FEV₁, AUEC₀₋₆ (%•Hr) of baseline-

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adjusted percent predicted FEV₁, hourly FEV₁ (L), hourly percent change from pre-dose baseline in FEV₁, and hourly percent predicted FEV₁. Pharmacodynamic analyses included baseline-adjusted maximum FEV₁, baseline-adjusted maximum percent predicted FEV₁ (%), time to maximum FEV₁ (H), response rate, time (in minutes) to response onset (defined as an increase from baseline in FEV₁ ≥15%), and duration of response (response duration for responders was defined as the number of minutes from the time of dosing to response offset: change from baseline <15%). All secondary and pharmacodynamic parameters were supportive of efficacy of Albuterol-HFA-MDI, and the comparability of Albuterol-HFA-MDI with Proventil HFA.

As expected, tachyphylaxis occurred during the course of this study. This phenomenon was noted for all active drugs, and may be seen by comparison of both the baseline-adjusted FEV_{1 0-6} and the non-baseline-adjusted (raw) FEV_{1 0-6} over the course of the study visits. For the non-baseline-adjusted FEV_{1 0-6} on Day 1, the Proventil HFA appeared to produce a higher FEV₁ with longer duration of response than the Albuterol-HFA-MDI

While most patients rated both products very easy to use,

however, among patients randomized to active treatment with the MDI device, the overall opinion was evenly split between the two devices, whereas among those randomized to active treatment with the BOI device,

There were no specific safety concerns raised in the review of this study.

The mean duration of exposure varied only slightly among treatment groups. Of the 345 patients enrolled, 136 (39.4%) reported 243 adverse events, which were distributed almost equally among treatment groups: 23 patients (39.7%) in the Albuterol-HFA-MDI group, 71 patients (41.0%) in the Albuterol-HFA-BOI group, 20 patients (35.7%) in the Proventil HFA group, and 22 patients (37.9%) in the placebo group. Twenty-three patients (6.7%) experienced an adverse event that was considered severe in intensity. The most frequent AEs were pharyngitis, asthma, and headache, of which headache was more prevalent in the active treatment groups than in the placebo group. Of note, the incidence of tachycardia was about equal among active treatment groups. While more patients in the White, and more patients in the 18 to 65 year age groups had Nervous System AEs as assessed by Body System, there were no significant differences in AEs by Preferred Term by gender, race, or age group. Overall, the severity of AEs was comparable among the treatment groups.

Eleven patients (3.2%) experienced a total of 16 adverse events that was attributed to study drug by an investigator: 4 AEs in 3 patients (5.2%) in the Albuterol-HFA-MDI group, 7 AEs in 4 patients (2.3%) in the Albuterol-HFA-BOI group, 3 AEs in 2 patients (3.6%) in the Proventil HFA group, and 2 AEs in 2 patients (3.4%) in the placebo group. There were no trends noted by treatment group, body system, race, or severity. There were no AEs judged drug-related in the 12 to <18 year old age group. In the age group >65 years (n = 19), one patient on Albuterol-HFA-BOI experienced three drug-related AEs of insomnia, asthma, and

dyspnea. Analysis by gender did not reveal any trends, although the types of AEs were different.

There were no deaths, and there were no pregnancies. Two patients experienced three serious adverse events during the study. Serious adverse events included one patient on Albuterol-HFA-BOI hospitalized for acute exacerbation of asthma 5 weeks into the study, and one patient on Proventil HFA hospitalized for abdominal pain (severe) and diarrhea (mild) 5-6 weeks into the study.

Of the twenty-six patients (7.5%) who discontinued the study due to an adverse event, there were a higher number and percent of patients on each of the two Albuterol-HFA products (MDI and BOI) than on either Proventil HFA or placebo (Albuterol-HFA-MDI 4 {6.9%}, Albuterol-HFA-BOI 17 {9.8%}, Proventil HFA 2 {3.6%}, and placebo 3 {5.2%}). Most discontinuations were due to an asthma exacerbation or a combination of an upper respiratory infection (URI) and an asthma exacerbation.

There were no significant differences among treatment groups for mean changes in vital signs, laboratory parameters throughout the study.

Device performance evaluations included inspection of the inhaler mouthpiece was inspected when devices were returned at Days 22 and 43, and *in vitro* testing of selected canisters. Greater than 98.5% of the inhalers were returned at each visit. For the MDI device, deposits were observed in 9.9% and 14.6% of inhalers on Days 22 and 43, respectively. For the BOI device, deposits were observed in 8.7% and 7.5% of inhalers on Days 22 and 43, respectively. None of the deposits were associated with any reported device malfunctions. The *in vitro* testing included evaluation of the drug delivery profile and particle size distribution for a sampling of 24 inhalers used in this study: the two active inhalers used by one patient from each of the 12 sites in the study. The patient must have completed all six weeks of study treatment. The sample was equally divided between testing for drug delivery and particle size distribution, such that six MDI and six BOI inhalers were tested for drug delivery, and six MDI and six BOI inhalers were tested for particle size distribution. The drug product tested was two months prior to the expiry date. The applicant assumed that 177 actuations had been consumed during the study, and the canisters were not weighed to confirm use. All test results were stated to be within finished product specifications and no specific trends were reported. The concluded that the Albuterol-HFA inhalers met the current product specifications.

While the applicant specifically stated that there were no device malfunctions reported for this study, the line listings show one patient (2303 at site 3314) who was withdrawn from the study due to a BOI device malfunction. This patient had been randomized to Proventil HFA. No further information was given regarding the nature of the malfunction.

11.1.4. Conclusions

This six-week, multi-center, randomized, double-blind (evaluator-blind for the Proventil comparator), placebo-controlled, parallel group study supports both the efficacy and safety of Albuterol-HFA-MDI. Efficacy compared to placebo is clearly demonstrated. In addition, the Albuterol-HFA-MDI is substantially comparable to the active comparator, Proventil HFA MDI.

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11.2. Study BNP-301-4-105: Seven-period crossover bronchodilation equivalence study of Albuterol-HFA-MDI and Proventil HFA

Protocol #: BNP-301-4-105
Title: Bronchodilation therapeutic equivalence study of Albuterol-HFA-MDI and Proventil® HFA
Study Dates: November 3, 2000 to September 4, 2001
Sites: _____

William Lumry, MD Dallas, TX
S. David Miller, MD North Dartmouth, MA

IRB: New England Institutional Review Board
40 Washington Street, Suite 130
Wellesley, MA 02481

Source: M5, v 1.10, p 500002-3, 14

11.2.1. Protocol**11.2.1.1. Objective/Rationale**

The primary objectives of this study were (1) to evaluate the efficacy of Albuterol-HFA-MDI relative to placebo, and (2) to compare responses to Albuterol-HFA-MDI and Proventil HFA at each of three dose levels. A secondary objective was to show bioequivalence between the two active products. [M5, v 1.10, p 500021, v 1.11, p 500602]

11.2.1.2. Summary of the Study Design

This was a multi-center, randomized, evaluator blind, placebo-controlled, seven-treatment-seven-period, seven-sequence, single-dose crossover comparison study of the ability of Albuterol-HFA-MDI and Proventil HFA to produce bronchodilation in 47 moderate to moderately severe asthmatics (FEV₁ 50-75% predicted). Eligible patients were randomized to receive placebo HFA-MDI (3 actuations), Albuterol HFA-MDI (1, 2, or 3 actuations), or Proventil HFA (1, 2, or 3 actuations) administered at 2-7 day intervals. The dose of albuterol in the active treatment arms was 90, 180, or 270 mcg. [M5, v 1.10, p 500022, v 1.11, p 500602]

11.2.1.3. Population*11.2.1.3.1. Inclusion criteria [M5, v 1.10, p 500023-4; v 1.11, p 500606-8]*

Patients were included in the study if they met each of the following criteria:

1. Male, or non-pregnant, non-nursing females, 18 to 50 years of age at screening. Females of childbearing potential were included if practicing an acceptable method of birth control (barrier methods, oral birth control pills, progesterone implanted rods, IUDs, or Depo-Provera) and have a negative serum pregnancy test at screening.

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2. Had asthma for a minimum of six months duration that was stable for at least four weeks prior to the screening visit as defined by clinical history, and which was moderate to moderately severe (FEV₁ 50-75% predicted for age, height, gender, and race) at the screening visit. The diagnosis of asthma was made in accordance with the American Thoracic Society (ATS) definition. Study-qualifying FEV₁ values were obtained between 6AM and 10AM, of which the two highest FEV₁ values out of a maximum of eight could not differ by more than 5% or 0.1 L. For all other spirometric procedures, the highest of three measurements was used. [M5, v 1.11, p 500615]
3. Had the ability to perform spirometry reproducibly.
4. Had the ability to perform peak expiratory flow (PEF) determinations.
5. Had reversible bronchoconstriction as verified by a $\geq 15\%$ increase in FEV₁ within 30 minutes following inhalation of albuterol 180 mcg (2 actuations).
6. Could tolerate withdrawal of applicable medications including methyl xanthines, antileukotrienes, and oral or long-acting β_2 -agonists, for qualification at screening. Use of these medications was not permitted throughout the study.
7. Chest x-ray within 52 weeks prior to screening consistent with asthma and showing no evidence of other active disease.
8. Otherwise healthy individuals with a clinically acceptable medical history, physical examination, vital signs, 12-lead ECG, and clinical laboratory parameters.
9. Non-smokers for at least 6 months prior to the screening visit, with maximum smoking histories of five pack-years.

11.2.1.3.2. Exclusion criteria [M5, v 1.10, p 500024-5; v 1.11, p 500608-10]

Patients were not eligible for enrollment if they met any of the following criteria:

1. Allergy or sensitivity to albuterol, or to other components of the formulation used in the clinical trial materials.
2. Exposure to investigational drugs within 30 days prior to the screening visit.
3. Required continuous treatment with β -blockers (administered by any route), MAO inhibitors, tricyclic antidepressants, and or systemic corticosteroids flowing study admission.
4. Treated with oral or injectable corticosteroids within the previous six weeks.
5. Dosage of any required (1) inhaled corticosteroids, cromolyn and/or nedocromil, and (2) intranasal corticosteroids and/or cromolyns had not been stable for at least four weeks prior to the screening visit. Patients requiring subsequent dosage adjustment of these drug products were to be discontinued from the study.
6. Inability to tolerate or unwillingness to comply with required washout periods for all applicable medications and xanthine-containing foods and beverages prior to the screening visit.
7. Hospitalization for acute exacerbation of asthma more than two times in the past year.
8. Treatment in an emergency room for asthmatic symptoms or hospitalization for asthmatic symptoms within three months prior to the screening visit.
9. Treatment in an emergency room or hospitalization for asthmatic symptoms within six weeks prior to the screening visit.

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10. An upper respiratory tract infection and/or sinusitis associated with exacerbation of asthmatic symptoms and occurring within six weeks prior to the screening visit.
11. History and/or presence of any non-asthmatic acute or chronic disease, including but not limited to bronchitis, emphysema, active tuberculosis, bronchiectasis, cystic fibrosis, clinically-significant cardiovascular disease (including cardiac arrhythmias and uncontrolled hypertension), clinically-significant hepatic, renal, or endocrine dysfunction, stroke, uncontrolled diabetes, hyperthyroidism, convulsive disorders, and neoplastic disease other than basal cell carcinoma of the skin.
12. Known or suspected substance abuse (e.g. alcohol, marijuana, etc.) and/or any other medical or psychological conditions that in the investigator's opinion precluded study enrollment.
13. Lactating or pregnant female.
14. Failure to provide written informed consent.

11.2.1.3.3. Concomitant, Excluded, and Rescue Medications, Washout Periods, Other Restrictions

Patients were allowed inhaled/intranasal corticosteroids and/or cromones during the study, as long as the dosage was not modified. Acetaminophen, antacids, antidiarrheals, and birth control pills were allowed. Medications not allowed, and washout period for medications allowed and disallowed prior to screening and/or each treatment are shown in Table 44. Rescue medication was Albuterol-CFC-MDI from Zenith Goldline. Patients were allowed use of this medication between visits with a dose of up to 180 mcg (2 actuations) at any one time. Other restrictions included prohibition from strenuous exercise 12 hours prior to all clinic visits, change in exercise routine during the study, exposure to cold air within one hour of dosing, and consumption of alcohol-, xanthine-, and/or grapefruit-containing beverages within 24 hours prior to each clinic visit. [M5, v 1.10, p 500030-2; v 1.11, p 500613, 22-4, 40]

Table 44. BNP-301-4-105, Excluded drugs, Minimum drug washout periods

Medication	Excluded during study	Washout prior to screening and each treatment
Inhaled β_2 -agonists		
Short-acting (albuterol, pirbuterol, terbutaline)		6 hours
Long-acting (e.g. salmeterol)*	✓	2 weeks
Oral β_2 -agonists *	✓	2 weeks
Oral or injectable corticosteroids	✓	6 weeks
Oral theophyllines and methyl xanthines	✓	1 week
Antileukotrienes	✓	1 week
Oral and intranasal decongestants		1 day
Anticholinergics		
Inhaled (e.g. ipratropium)		12 hours
Oral		1 week
Antihistamines		
Hydroxyzine		4 days
Loratadine	✓	4 days
All others		2 days

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Medication	Excluded during study	Washout prior to screening and each treatment
Aspirin & other nonsteroidal anti-inflammatory drugs		1 week
Beta-blockers by any route	✓	
MAO inhibitors	✓	
Tricyclic antidepressants	✓	
* Patients receiving oral and long-acting β_2 -agonists could be switched to short-acting β_2 -agonists during the pre-study washout period.		

Source: M5, v 1.10, p 500030-2, v1.11, p 500622-4, 500640

11.2.1.3.4. Subject withdrawal [M5, v 1.10, p 500025-6; v 1.11, p 500628]

The following criteria were the basis for patient discontinuation from the study:

1. Occurrence of an adverse event sufficiently severe to warrant withdrawal as judged by the Principal Investigator and/or Sponsor.
2. Onset of any serious condition (including exacerbation of asthma) or the need to administer any medication that might pose a hazard to the patient or affect validity of the efficacy data.
3. Failure of patient to meet the criteria required at each treatment period to continue the study.
4. Desire by the patient to withdraw from the study at any time for any reason.
5. Non-compliance with the protocol and/or lack of willingness or commitment to cooperate in all phases of the study.

Patients who did not complete all study-related procedures were considered to have discontinued prematurely from the study.

11.2.1.3.5. Protocol amendments

The protocol was amended three times, all prior to initiation of the study. Amendments were dated November 24, 1999, July 12, 2000, and August 16, 2000. The original protocol was a bronchodilator bioequivalence study to support a 505(j) application. The first amendment was made with feedback from the Office of Generic Drugs. Amendment 2 was submitted to the Division of Pulmonary and Allergy Drug Products when the IND was switched to the Office of New Drugs, changing the primary comparison away from bioequivalence to a comparison with placebo. Amendment 3 incorporated minor changes based on feedback from the Division of Pulmonary and Allergy Drug Products. [M5, v 1.10, p 500043-6]

11.2.1.4. Conduct/Study Procedures

Eligible patients were randomized to receive seven treatments as shown below at 2-7 days intervals, with the treatment sequence defined by a seven-sequence randomization code. [M5, v 1.10, p 500026-7]

Treatment	Number of actuations	Dose of Albuterol (mcg)
Placebo-HFA-MDI	3	0
Albuterol-HFA-MDI	1	90

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Treatment	Number of actuations	Dose of Albuterol (mcg)
Albuterol-HFA-MDI	2	180
Albuterol-HFA-MDI	3	270
Proventil [®] -HFA-MDI	1	90
Proventil [®] -HFA-MDI	2	180
Proventil [®] -HFA-MDI	3	270

Because of the difference in appearance and the lack of a Proventil-HFA-MDI placebo, the study could only be evaluator blinded. Because of the study design, patients were blindfolded for the treatment administration procedure, necessitating a complex training regimen outlined in detail in the protocol. To maintain blinding of the individuals who conducted the evaluations or monitored patients the study, separate unblinded individuals called dosing administrators were used to dose the patient. Monitoring of drug accountability required an independent monitor not otherwise connected with the study. Likewise, the Principal Investigator was not allowed to review and sign off on the drug accountability documentation until the study database was locked. [M5, v 1.10, p 500029-30, v 1.11, p 500610-11]

Patients were asked to fast overnight prior to each study visit. Priming of canisters was performed five times by a routine of shaking for five seconds in an upright position, followed by actuating to waste, then a two-second pause. Administration of dosing was without a spacer device and with the patient blindfolded. For this reason, patients were required to practice inhalation technique during the screening phase. The time of day for each treatment was between 6:00 AM and 10:00 AM and was required to be ± 2 hours of the time of day that the study-qualifying value during screening was determined.

As per Amendment 2, FEV₁ measurements were performed 0.083 (5 minutes), 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, and 6 hours following each dosing. Spirometry was performed using a spirometer, and data was transmitted electronically to a centralized study database. Each FEV₁ determination was the highest of three spirometric maneuvers. FEV₁ was measured 0.5 hours and immediately prior to dosing with the average taken as the pre-dose FEV₁. The average pre-dose FEV₁ was required to be within $\pm 15\%$ of the study-qualifying, screening FEV₁, and could exceed 85% predicted for patients to continue in the study. If not within the 15%, patients returned the next day for re-testing and qualify within the study specified study time periods to remain in the study. [M5, v 1.10, p 500034, v 1.11, p 500611-13]

The study protocol schedule of events and product lots used are summarized in the Table 45 and in Table 46, respectively.

Table 45. BNP-301-4-105, Study Protocol Event Schedule

Events	Screening (-14 days)	Treatment Periods 1-6	Treatment Period 7
Informed consent	✓		
Qualifying spirometry (FEV ₁)	✓		
Reversible bronchoconstriction (15%) using Albuterol-CFC-MDI	✓		
Medical/medication history	✓		

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Events	Screening (-14 days)	Treatment Periods 1-6	Treatment Period 7
Physical examination	✓		✓
Vital signs	✓	✓ ¹	✓ ¹
Safety laboratory tests (fasting)	✓ ³		
12-lead ECG	✓		
Serum pregnancy test	✓		✓ ⁴
Chest X-ray (if applicable)	✓		
PEF, inhalation flow rate, & third-party dosing training	✓		
Inhalation technique training	✓		
Review of inclusion/exclusion criteria	✓		
Dispense peak flow, rescue medication, PEF diary	✓		
PFTs (6-hour serial FEV ₁)		✓ ²	✓ ²
Clinical trial material dosing		✓	✓
PEF (off-site AM and PM) measurements	✓ ⇒	⇔	⇐ ✓
Concomitant medications	✓	✓	✓
Adverse events		✓	✓

¹ Vital sign assessments at 0.5 hours prior to, and 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, and 6 hours after completion of dosing. RR and oral temp omitted after dosing.
² Spirometry assessments 0.5 hours and immediately prior to, and at 0.083 (5 minutes), 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, and 6 hours after completing of dosing.
³ CBC, Differential, Glucose, Sodium, Potassium, Chloride, Creatinine, Total protein, Albumin, Total bilirubin, Calcium, Phosphorus, Alkaline phosphatase, ALAT (SGPT), and ASAT (SGOT).
⁴ At Treatment 7 or at the time of discontinuation.

Source: M5, v 1.10, p 500031, 36, v 1.11, p 500617

Table 46. BNP-301-4-105, Investigational Product Lots

Product	Strength / Actuation	Manufacturer	Lot/Batch Number	Expiry Date
Placebo-HFA-MDI	0	IVAX Pharmaceuticals, Ireland	AA028A	NA
Albuterol-HFA-MDI	90 mcg	IVAX Pharmaceuticals, Ireland	AAN88A	9/01
Proventil HFA	90 mcg	Obtained from commercial sources. 3M Pharmaceuticals (Distributed by Key Pharmaceuticals, Inc., Kenilworth, NJ)	T99F02A & GBD002A	6/01 4/02
MDI Actuators			00E20953	NA

Source: M5, v 1.10, p 500026

11.2.1.5. Safety Evaluations

Safety variables at screening included physical examination, chest X-ray (if applicable), clinical labs including pregnancy tests, 12-lead ECG, and vital signs. During the study, patients were monitored with home AM and PM PEF measurements, on-site pre- and post-dose PFTs and vital signs, a post-study physical examination and serum pregnancy test, and adverse events. Screening laboratory studies included: CBC, differential, glucose, sodium, potassium, chloride, creatinine, total protein, albumin, total bilirubin, calcium, phosphorus, alkaline phosphatase, ALAT (SGPT), and ASAT (SGOT). Adverse events were evaluated for intensity and causality. Premature discontinuations were documented. [M5, v 1.10, p 500026; v1.10, p 500624-5]

11.2.1.6. Pharmacokinetic Evaluations

No pharmacokinetic evaluations were performed in this study.

11.2.1.7. Statistical Plan

11.2.1.7.1. Primary endpoint and analysis

The primary variable was the dose-related change in FEV₁ expressed as the baseline-adjusted average area-under-the-effect curve over 0-6 hours following dosing (AUEC₀₋₆). The AUEC₀₋₆ value was calculated using the linear trapezoidal rule. Baseline adjustments were made by subtracting the average of the two pre-dose FEV₁ measurements from each post-dose FEV₁ measurement. [M5, v 1.10, p 500039; v 1.11, p 500629]

The primary analysis was declared as comparisons of the mean difference between each active group and placebo at each dose level, the mean difference between active groups at each dose level, and the within-product difference of 1 versus 2, 1 versus 3, and 2 versus 3 actuations (i.e. dose response). In addition, the dose-response of Albuterol-HFA-MDI was compared to Proventil HFA. The analyses were performed using a mixed-effect ANOVA with fixed effects of sequence, treatment group, and period, and random effect for the patient within-sequence, each with a two-sided significance of 0.05. [M5, v 1.10, p 500042; v 1.11, p 500630]

Comment: There was no adjustment made for multiple comparisons.

11.2.1.7.2. Secondary endpoints and analyses

The secondary variable was the baseline-adjusted maximum FEV₁ value observed post-dose (FEV₁max). Secondary analyses were similar to those performed for the primary set of analyses. In addition, the protocol declared a secondary research hypothesis of bioequivalence using an Emax model to evaluate the relationship of AUEC₀₋₆ to dose. [M5, v 1.10, p 500039, 41-3; v 1.11, p 500629, 31-2]

11.2.1.7.3. Sample size considerations and data analysis methodology

All efficacy analyses were carried out on the per-protocol population of patients who completed all seven days of study drug treatment. The study design was similar another bronchodilator aerosol study (IX-101-071), in which the primary endpoint was the FEV₁ AUEC₀₋₆. The sponsor determined from that study that the within-patient standard deviation of the FEV₁ AUEC₀₋₆ was 1.23 L/hr, and mean differences between active and placebo were all greater than 1.25 L/hr. Differences between active treatments were small (0.08 L/hr), and within product comparisons of responses at different doses ranged from 0.34 to 0.82 L/hr. Therefore, a clinically relevant mean response was considered to be 0.50 L/hr. This study was powered to detect a mean response difference of 0.50 L/hr assuming a within-patient standard deviation of 1.23 L/hr. A sample size of 56 completed patients was required to obtain between-product differences in dose-response of at least 0.66 L/hr with an 80% power at the two-sided significance level. [M5, v 1.10, p 500041, 43; v 1.11, p 500629-30]

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The sponsor states that at the time of study termination, 47 patients had completed the study. While this was smaller than the originally planned population size, the overall (unadjusted) standard deviation in this study was 1.29 L•Hr. Because the baseline-adjusted standard deviation was smaller than that in the previous study, recruitment and enrollment was stopped. The sponsor states that the post-unblinding standard deviation of within-patient differences from the statistical analyses was 1.12 L•Hr, small enough to provide >80% statistical powering. [M5, v 1.10, p 500047]

11.2.2. Results

11.2.2.1. Description of Study Population

11.2.2.1.1. Disposition

A total of 121 patients were screened, of whom 58 were randomized, and 47 completed all seven treatments. Eleven patients failed to complete the study. Patient disposition is shown in Table 47, with reasons for discontinuation shown in descending order of frequency. Only four of the five sites enrolled patients. [M5, v 1.10, p 500049-50]

Table 47. BNP-301-4-105, Patient disposition

Disposition	Site/Investigator					Total
	1/3272	2/3282*	3/3281	4/3275	5/3280	
Screened	30	5	36	38	12	121
Randomized	13	0	11	28	6	58
Completed study	12	0	9	20	6	47
Discontinued	1	0	2	8	0	11
Failed to re-qualify	1	0	1	3	0	5
Lost to follow-up	0	0	0	2	0	2
Adverse event (s)	0	0	0	2	0	2
Restricted medication	0	0	0	1	0	1
Consent withdrawn	0	0	1	0	0	1
Protocol non-compliant	0	0	0	0	0	0

* Site number 2 was discontinued for inability to randomize patients, and was not included in any investigator-specific listings..

Source: M5, v 1.10, Table 10-1, p 500049

11.2.2.1.2. Protocol violations, Analysis populations, and Period discontinuations

As shown in Table 47 above, 11 of the randomized patients were discontinued from the study due to protocol deviations, reducing the number of patients who completed the study to 47. However, the Per-Protocol population included only 46 patients; one patient (065) was excluded due to having received treatments out of sequence because of an error in the treatment assignment instructions. In addition, one patient (044) had used Extra-strength Excedrin within a washout period. However, this was considered a minor deviation and the patient was not excluded from the analysis. Finally, due to a misunderstanding, two of the Principal Investigators (3275, 3280) [accounting for 26 patients] signed off on the supplies documentation prior to database lock. The sponsor states that this would not be expected to impact efficacy data, since the data was archived separately by a third party. There were 10

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protocol deviations that were not considered significant and did not result in excluded data were reviewed. Reasons included: visits outside protocol-specified window for date (5) or time (1), re-screening (2), serial PFTs shortened to 3 hours because of approaching snowstorm (1), and chest x-ray performed before pregnancy test (1). [M5, v 1.10, p 500050-1]

Sixteen patients completed the study, but had incomplete data for at least one period. Of these patients, 14 (88%) had incomplete data due to bronchoconstriction. Comparable numbers of patients discontinued during a period for all study drugs, and no period effect was noted. For most patients in active treatment, period discontinuation occurred between 4-5 hours post-dose, where as for patients on placebo the time was shorter (about 3 hours). For patients with period discontinuations for whom there was incomplete data, the area under the curve and other derived variables were calculated using whatever data was available until the time of discontinuation. [M5, v 1.10, p 500065-6]

11.2.2.1.3. Demographics and baseline characteristics

The demographics and baseline characteristics by site, intent-to-treat (ITT) population, and the per-protocol populations are shown in Table 48. The applicant's tables define a modified intent-to-treat (MITT) population of patients who were randomized received at least one treatment. However, in this study the ITT population = MITT population. There were minor differences in treatment sequence groups at baseline, as shown in Table 49.

Table 48. BNP-301-4-105, Patient demographics and baseline characteristics

	Site				ITT* n = 58	PP n = 46
	1/3272	3/3281	4/3275	5/3280		
Age, years:						
Mean (SD)	36.5 (5.4)	35.6 (7.9)	33.4 (8.8)	37.2 (10.7)	34.3 (8.4)	34.3 (8.0)
Range	27 - 48	24 - 49	20 - 47	19 - 48	19 - 49	19 - 49
Gender:						
Males, N (%)	3	6	7	0	19 (32.8)	16 (34.8)
Females, N (%)	9	3	12	6	39 (67.2)	30 (65.2)
Race:						
White, N (%)	9	5	17	6	47 (81.0)	37 (80.4)
Black, N (%)	3	3	1	0	8 (13.8)	7 (15.2)
Other, N (%)	0	1	1	0	3 (5.2)	2 (4.3)
Height, cm						
Mean (SD)	163 (9.2)	172 (14.2)	165 (10.1)	167 (10.5)	167 (10.8)	166 (10.9)
Range					147 - 198	147 - 198
Weight, Kg						
Mean (SD)	87.8 (23.8)	83.7 (17.9)	77.7 (23.1)	80.2 (21.2)	85.0 (22.0)	81.8 (21.8)
Range					45 - 140	45 - 140
FEV ₁ (L)	1.90 (0.44)	2.41 (0.59)	2.29 (0.44)	1.80 (0.21)	See Table 49	2.15 (0.50)
% Predicted FEV ₁	60.8 (8.1)	64.9 (5.0)	67.1 (5.8)	56.7 (3.6)		63.6 (7.0)
Reversibility, %	26.8 (15.5)	27.1 (10.4)	25.6 (10.1)	37.6 (7.5)		27.8 (11.8)

* Listed in the tables as the MITT population (modified Intent-to-treat population of patients who were randomized received at least one treatment). However, the ITT population = MITT population in this study.

Source: M5, v 1.10, Table 11.2(1), p 500052; Table 11.2(2), p 500053; Table 14B.1.1.1, p 500220

Table 49. BNP-301-4-105, Qualifying FEV₁, % predicted FEV₁, and % reversibility by treatment sequence, ITT population

Sequence No	N	Qualifying value		
		FEV ₁	% predicted	% reversibility
Overall	58	2.16 (0.46)	63.4 (7.4)	27.4 (11.5)
1	8	2.21 (0.47)	66.6 (8.2)	29.1 (13.5)
2	9	2.32 (0.58)	62.7 (7.2)	27.8 (11.5)
3	7	2.08 (0.52)	62.6 (8.5)	21.3 (6.3)
4	9	2.17 (0.36)	60.0 (6.1)	28.0 (11.4)
5	9	2.23 (0.42)	66.1 (7.5)	24.4 (6.9)
6	8	1.90 (0.24)	59.6 (5.5)	28.4 (10.5)
7	8	2.16 (0.57)	66.2 (7.5)	32.4 (17.6)

Source: M5, v 1.10, Table 14B.1.1.2, p 500221

11.2.2.1.4. Compliance

There were no compliance evaluations performed in this study. All patients received study drug under supervision on-site.

11.2.2.2. Efficacy Endpoint Outcomes

11.2.2.2.1. Primary efficacy measure

The primary efficacy analyses and treatment comparisons for the baseline-adjusted FEV₁ AUEC₀₋₆ for the per-protocol population are shown in Table 50. The differences in mean FEV₁ AUEC₀₋₆ for Albuterol-HFA-MDI and Proventil HFA compared to placebo were statistically significant for all dose comparisons (p < 0.0001). Comparison between similar doses of active drugs showed only small differences which were not statistically significant. Comparison of doses within each drug product showed a trend to more effect with higher doses. For Albuterol-HFA-MDI there was no statistically significant differences between doses, but for the Proventil HFA, there was a statistically significant difference between the 270 mg dose compared to both the 90 mg (p = 0.0006) and 180 mg (p = 0.0290) doses.

Baseline-adjusted mean FEV₁ AUEC₀₋₆ for the per-protocol population relative to dose level for both active drugs is shown in Figure 9. For the typical dose of 180 mg, the percent change from baseline in FEV₁ over the 6 hour treatment time period for the per-protocol population is shown in Figure 10. Although the Albuterol-HFA-MDI reaches a higher peak percent change in FEV₁, it may be seen that the curves substantially overlap.

For the MITT population, the findings were comparable, although the comparison of the Proventil HFA 180 mg and 270 mg doses were not significantly different for the MITT population [M5, v 1.10, Table 14B.2.1.1-3, p 500225-7]. Primary results for gender subgroups for the per-protocol population are shown in Table 51. The trend toward increasing effect with higher dose was seen for both active drugs in both genders except for the Albuterol-HFA-MDI 270 mg dose in males. As expected, all treatment comparisons with placebo were statistically significant.

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Table 50. BNP-301-4-105, Primary Efficacy, Baseline-adjusted FEV₁ AUEC₀₋₆ (L•Hr) and treatment comparisons, PP population

Treatment / Comparison group	Dose / Comparison	LS mean (SE)	LS mean difference (SE)	p-value
Dose vs dose between actives and placebo				
Placebo	0	0.45 (0.20)		
Albuterol-HFA-MDI	90	1.45 (0.20)	1.00 (0.17)	<0.0001
	180	1.59 (0.20)	1.14 (0.17)	<0.0001
	270	1.70 (0.20)	1.25 (0.17)	<0.0001
Proventil HFA	90	1.29 (0.20)	0.84 (0.17)	<0.0001
	180	1.50 (0.20)	1.05 (0.17)	<0.0001
	270	1.87 (0.20)	1.41 (0.17)	<0.0001
Dose vs dose between actives				
Albuterol-HFA-MDI vs Proventil HFA	90		0.16 (0.17)	0.3446
	180		0.09 (0.17)	0.5932
	270		-0.17 (0.17)	0.3196
Dose vs dose within actives				
Albuterol-HFA-MDI	90 vs 180		0.14 (0.17)	0.3926
	90 vs 270		0.25 (0.17)	0.1296
	180 vs 270		0.11 (0.17)	0.5061
Proventil HFA	90 vs 180		0.21 (0.17)	0.2060
	90 vs 270		0.58 (0.17)	0.0006
	180 vs 270		0.36 (0.17)	0.0290
1 Baseline-adjustment = each post-dose FEV ₁ minus the average of the two baseline FEV ₁ s. 2 LS means and p-values derived from a mixed effects model with fixed effects of sequence, period, and treatment group and random effect of subject within sequence.				

Source: M5, v 1.10, Table 11.4.1.2(1), p 500060; Table 14A.2.2.1-3, p 500097-9

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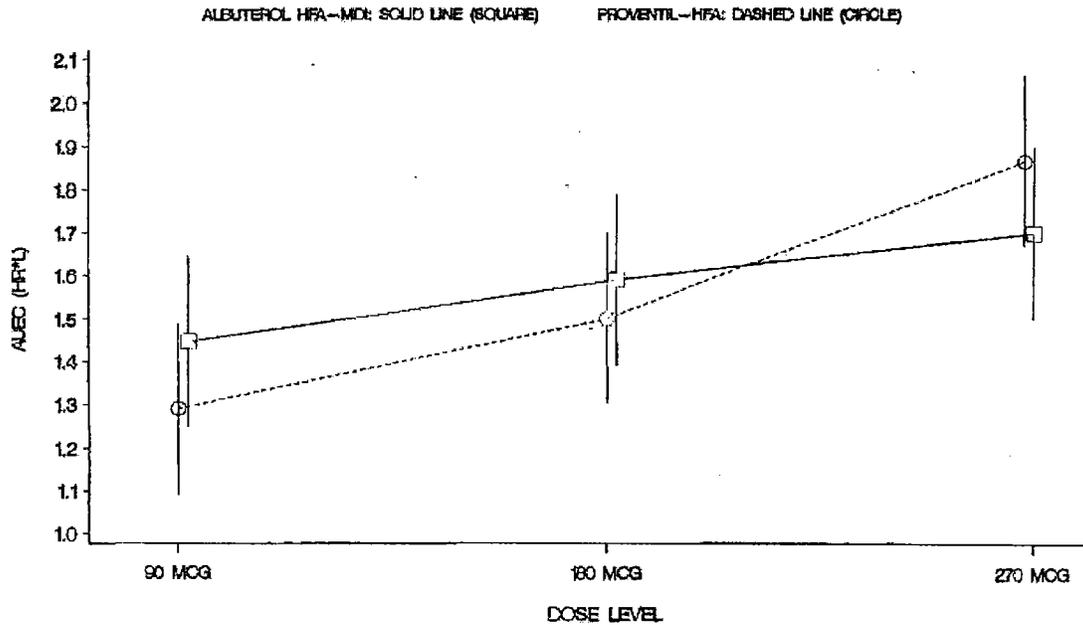


Figure 9. BNP-301-4-105, Primary Efficacy, Baseline-adjusted mean FEV₁ AUEC₀₋₆ (L·Hr±SEM) relative to dose level, PP population

Source: M5, v 1.10, Figure 11.4.1.2(1), p 500056; Figure 14A.5.1.1, p 500141

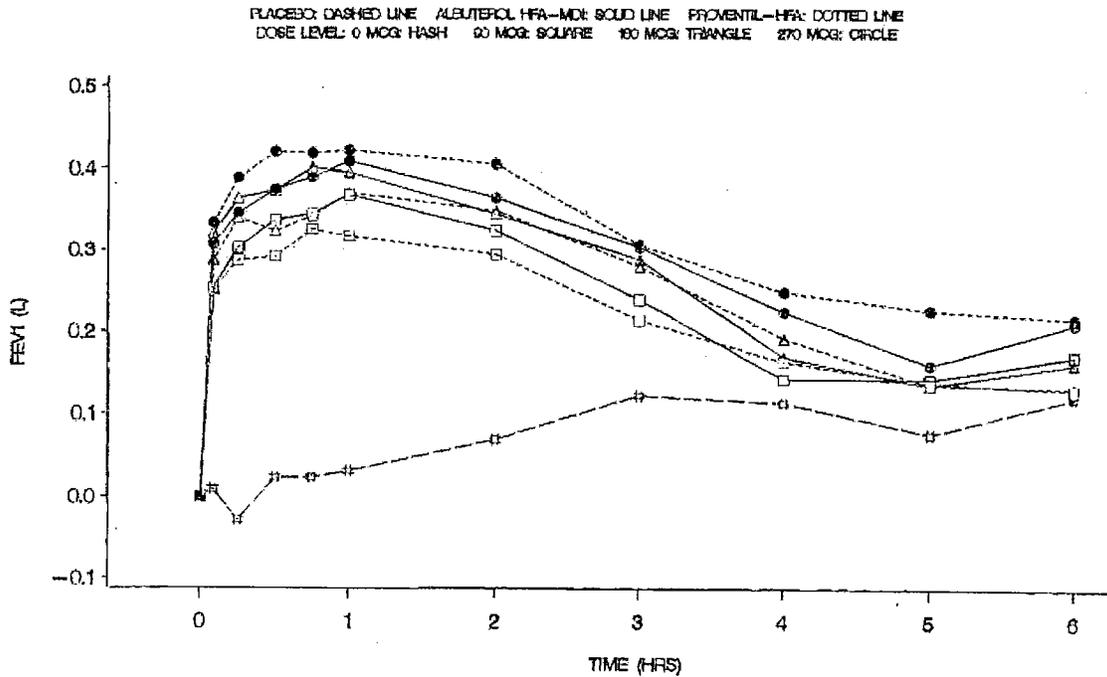


Figure 10. BNP-301-4-105, Primary Efficacy, Baseline-adjusted FEV₁ over 6 hours for all treatments, PP population

Source: M5, v 1.10, Figure 14A.5.3.1, p 500146

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Table 51. BNP-301-4-105, Primary Efficacy by Gender, Baseline-adjusted AUEC₀₋₆ FEV₁ (L•Hr), PP population

Treatment group / Treatment	Dose	LS mean (SE)	LS mean difference (SE)	p-value
Males				
Placebo	0	0.58 (0.43)		
Albuterol-HFA-MDI	90	1.93 (0.43)	1.35 (0.31)	<0.0001
	180	2.05 (0.43)	1.47 (0.31)	<0.0001
	270	1.88 (0.43)	1.29 (0.31)	<0.0001
Proventil HFA	90	1.67 (0.43)	1.09 (0.31)	0.0007
	180	1.94 (0.43)	1.36 (0.31)	<0.0001
	270	2.22 (0.43)	1.64 (0.31)	<0.0001
Females				
Placebo	0	0.48 (0.24)		
Albuterol-HFA-MDI	90	1.27 (0.24)	0.78 (0.20)	0.0001
	180	1.39 (0.24)	0.91 (0.20)	<0.0001
	270	1.71 (0.24)	1.22 (0.20)	<0.0001
Proventil HFA	90	1.14 (0.24)	0.65 (0.20)	0.0011
	180	1.33 (0.24)	0.84 (0.20)	<0.0001
	270	1.76 (0.24)	1.28 (0.20)	<0.0001
1 Baseline-adjustment = each post-dose FEV ₁ minus the average of the two baseline FEV ₁ s.				
2 LS means and p-values derived from a mixed effects model with fixed effects of sequence, period, and treatment group and random effect of subject within sequence.				

Source: M5, v 1.10, Table 14A.2.10.1, p 500125; Table 14A.2.11.1, p 500128

11.2.2.2.2. Secondary efficacy measures

The secondary efficacy analyses and treatment comparisons for the baseline-adjusted maximum FEV₁ (L) for the per-protocol population are shown in Table 52. Baseline-adjusted maximum FEV₁ (L) for the per-protocol population relative to dose level for both active drugs is shown in Figure 11. The differences in maximum FEV₁ for Albuterol-HFA-MDI and Proventil HFA compared to placebo were statistically significant for all dose comparisons (p < 0.0001). Comparison between similar doses of active drugs showed only small differences which were not statistically significant. Comparison of doses within each drug product showed a trend to higher maximum FEV₁ with increasing doses. For Albuterol-HFA-MDI there was no statistically significant differences between doses, but for the Proventil HFA, there was a statistically significant difference between the 90 mg and the 270 mg dose (p = 0.0052).

Table 52. BNP-301-4-105, Baseline-adjusted¹ maximum FEV₁ (L) and treatment comparisons, PP population

Treatment / Comparison group	Dose / Comparison	LS mean ² (SE)	LS mean difference (SE)	p-value
Placebo	0	0.23 (0.04)		
Albuterol-HFA-MDI	90	0.44 (0.04)	0.21 (0.03)	<0.0001
	180	0.48 (0.04)	0.24 (0.03)	<0.0001
	270	0.51 (0.04)	0.27 (0.03)	<0.0001
Proventil HFA	90	0.43 (0.04)	0.19 (0.03)	<0.0001
	180	0.46 (0.04)	0.22 (0.03)	<0.0001

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Treatment / Comparison group	Dose / Comparison	LS mean ² (SE)	LS mean difference (SE)	p-value
	270	0.52 (0.04)	0.29 (0.03)	<0.0001
Dose vs dose between actives				
Albuterol-HFA-MDI vs Proventil HFA	90		0.02 (0.03)	0.6455
	180		0.02 (0.03)	0.5926
	270		-0.02 (0.03)	0.6412
Dose vs dose within actives				
Albuterol-HFA-MDI	90 vs 180		0.03 (0.03)	0.3197
	90 vs 270		0.06 (0.03)	0.0609
	180 vs 270		0.03 (0.03)	0.3754
Proventil HFA	90 vs 180		0.03 (0.03)	0.3573
	90 vs 270		0.09 (0.03)	0.0052
	180 vs 270		0.06 (0.03)	0.0603

1 Baseline-adjusted maximum FEV₁ = maximum FEV₁ minus average of the two baseline FEV₁s.
 2 LS means and p-values derived from a mixed effects model with fixed effects of sequence, period, and treatment group and random effect of subject within sequence.

Source: M5, v 1.10, Table 14A.2.3.1-3, p 500103-5

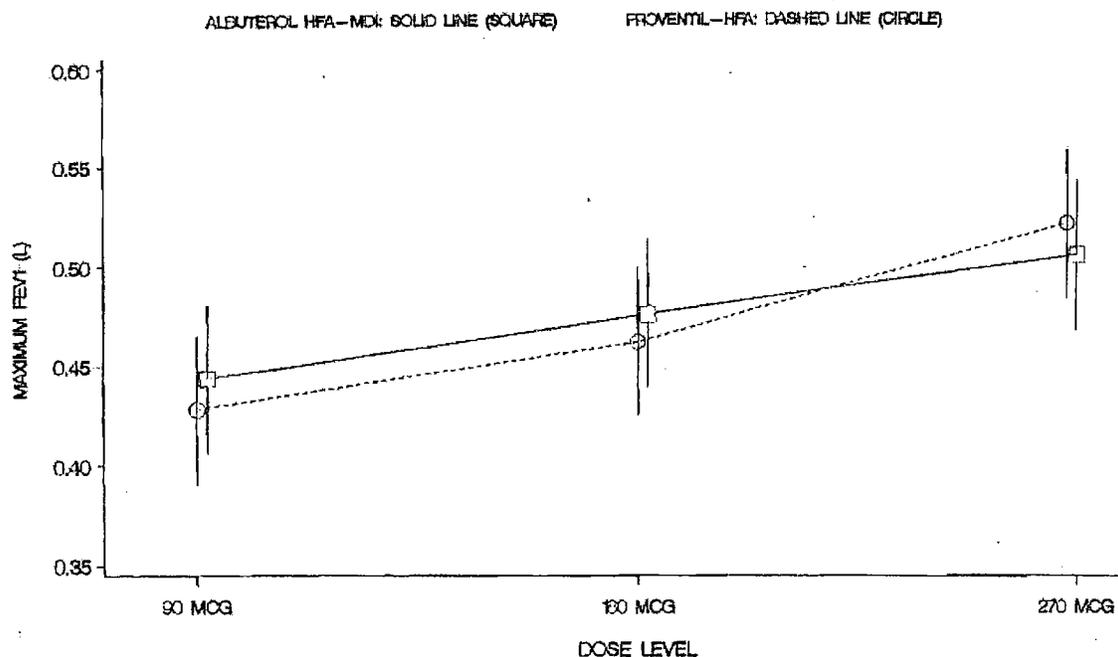


Figure 11. BNP-301-4-105, Baseline-adjusted maximum FEV₁ (L) by dose level, PP population

Source: M5, v 1.10, Figure 14A.5.2.1, p 500144

11.2.2.2.3. Other efficacy measures

The applicant states that bioequivalence between Albuterol-HFA-MDI and Proventil HFA could not be established based on the FEV₁ AUEC₀₋₆ data in this study. They state that the

potency ratio (with 90% confidence intervals), as estimated via bootstrap sampling, was 1.13. However, the derived confidence intervals of 0.77-1.91 exceeded the protocol-defined confidence intervals of 0.67-1.50, precluding any conclusion of bioequivalence between the two products. [M5, v 1.10, 500055]

The applicant also performed a number of post-hoc efficacy analyses, comparing Albuterol-HFA-MDI with Proventil HFA. These analyses included baseline-adjusted percent predicted FEV₁ AUEC₀₋₆, baseline-adjusted maximum percent predicted post-dose FEV₁, time to maximum FEV₁, time to response onset (15% increase in FEV₁ over baseline), and duration of response as measured both from the time of dosing and the time of response onset. The baseline-adjusted percent predicted FEV₁ AUEC₀₋₆, and baseline-adjusted maximum percent predicted post-dose FEV₁ analyses yielded no new information. There were no significant differences between products for time to maximum FEV₁ or time to response onset. The paired raw median time to maximum response was 0.98 and 0.76 hours, 0.90 and 1.01 hours, and 0.88 and 0.76 hours for the 90, 180, and 270mg doses of Albuterol-HFA and Proventil HFA, respectively. The paired raw median time to response onset was 0.36 and 0.31 hours, 0.20 and 0.28 hours, and 0.25 and 0.14 hours for the 90, 180, and 270mg doses of Albuterol-HFA and Proventil HFA, respectively. There were no significant differences between products for duration of response either from the time of dosing or from the time of response onset. [M5, v 1.10, 500062-5]

11.2.2.3. Safety Outcomes

11.2.2.3.1. Extent of exposure

The maximum cumulative dose of albuterol received on-site by the 58 enrolled patients is shown in Table 53. The total person-day exposure was 153 and 150 person-days for Albuterol-HFA-MDI and Proventil HFA, respectively. [M5, v 1.10, 500068]

Table 53. BNP-301-4-105, Maximum cumulative albuterol dose

Maximum cumulative albuterol dose (mcg)	Number of patients
0	1*
180	3
270	3
450	2
630	1
720	1
1080	47
Total	58
*Patient discontinued after one treatment period at which the assigned treatment was placebo	

Source: M5, v 1.10, 500068

11.2.2.3.2. Clinical adverse events

Of the 58 patients enrolled, 27 (47%) reported 51 adverse events (AEs), excluding the 16 episodes of bronchoconstriction during treatment periods. No trends in adverse events are noted. The events were distributed almost equally among treatment groups and periods. Twenty-one patients (41%) experienced an adverse event that was considered severe in

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intensity (5 placebo, 4 Albuterol-HFA-MDI 90 mcg, 5 Albuterol-HFA-MDI 180 mcg, 0 Albuterol-HFA-MDI 270 mcg, 1 Proventil HFA 90 mcg, 4 Proventil HFA 180 mcg, 2 Proventil HFA 270 mcg). None of the severe AEs were considered by an investigator to be related to study drug. AEs that occurred in patients by treatment group are listed in Table 54. Not surprisingly, the most common type of adverse event was headaches.

Table 54. BNP-301-4-105, Adverse events by treatment group, ITT

	Total	Placebo			Albuterol-HFA-MDI			Proventil HFA		
Albuterol dose (mcg)		0	90	180	270	90	180	270		
Number of patients	58	51	52	51	50	50	50	50	50	
Number of events	51	8	8	9	5	6	8	7		
Body as a Whole										
Abdominal pain	1	0	0	0	0	0	1	0		
Abscess	2	0	0	1	0	0	0	1		
Accidental injury	2	0	0	1	0	0	0	1		
Allergic reaction	4	0	0	3	0	0	0	1		
Back pain	2	0	0	1	0	1	0	0		
Chest pain	1	0	0	1	0	0	0	0		
Fever	1	0	0	0	0	0	1	0		
Flu syndrome	2	0	1	0	0	0	0	1		
Headache	7	2	0	1	1	2	1	0		
Cardiovascular system										
Hypertension	1	0	1	0	0	0	0	0		
Digestive system										
Dyspepsia	1	1	0	0	0	0	0	0		
Gastroenteritis	1	1	0	0	0	0	0	0		
Tooth disorder	2	0	0	0	1	0	1	0		
Musculo-skeletal system										
Bone disorder	2	0	0	0	0	0	2	0		
Bone pain	1	0	0	0	0	0	0	1		
Nervous system										
Paresthesia	1	0	0	1	0	0	0	0		
Respiratory system										
Asthma	4	0	1	0	2	0	1	0		
Bronchitis	2	1	1	0	0	0	0	0		
Cough increased	1	1	0	0	0	0	0	0		
Pharyngitis	2	0	0	0	0	1	1	0		
Pneumonia	1	0	1	0	0	0	0	0		
Rhinitis	1	0	0	0	0	1	0	0		
Sinusitis	5	2	1	0	0	1	0	1		
Upper respiratory infection	3	0	2	0	0	0	0	1		
Urogenital system										
Dysmenorrhea	1	0	0	0	1	0	0	0		

Source: M5, v 1.10, Table 12.2.2(3), p 500071; Table 12.2.2(4), p 500072

11.2.2.3.2.1. Drug-related clinical adverse events

Only one of the 51 adverse events was considered by the investigator to be related to study drug. This event was a case of hypertension in a patient (Patient No 021, Investigator No 3281) following treatment with Albuterol-HFA-MDI. However, upon further investigation, this patient was being treated with testosterone gel for a pre-existing low testosterone level. Screening BP was 128/84 (off testosterone). Elevated BPs ranging from a systolic of 130 to 156 mmHg and a diastolic of 87 to 102 mmHg were noted in all treatment periods, of which the first six were on testosterone treatment. The highest systolic BP was 165 mmHg 5 hours

post-treatment with Proventil HFA 270 mcg. Post-study, the patient's Bp was said to have normalized. [Source: M5, v 1.10, p 500076]

11.2.2.3.2.2. Serious adverse events, Deaths, and Discontinuations

There were no deaths. There were two serious adverse events during the study, both asthma exacerbations requiring hospitalization, and neither considered by the investigator to be related to study drug. Patient 004 (Investigator 3272) experienced an asthma exacerbation four days after completion of the study, but within the 30-day post-study period. Patient 024 (Investigator 3275) experienced an asthma exacerbation possibly related to pneumonia or atelectasis following Period 2 treatment with Albuterol-HFA-MDI 90 mcg [M5, v 1.10, p 500077]

11.2.2.3.3. Vital signs and Physical examinations

Of the 54 patients who received at least one study treatment and had an exit physical examination, 33 had no changes in the examination. For the 21 patients who had physical examination changes, 15 had changes in pre-study abnormalities of the eyes, ears, nose, and throat related to an existing concomitant condition [M5, v 1.10, p 500078]. The study report did not present the data on which patients experienced which changes. Therefore, the Division requested shift tables for physical examination changes for patients who had an abnormality or a change during the study. Review of these tables reveals that most changes related to EENT changes, such as conjunctival erythema, nasal congestion, or pale and/or edematous nasal mucosa [Submission of August 7, 2003, Tab 8].

The study report states that, since this study was considered an efficacy study, no formal analysis of post-drug vital signs (blood pressure or heart rate) was undertaken [M5, v 1.10, p 500078]. However, a review of a summary table of serial mean changes from baseline in blood pressure and heart rate by treatment group [M5, v 1.10, Table 14A.3.1.3 (Per Protocol) and 14B.3.1.3 (MITT), p 500134 and 500253] revealed no differences of note between treatments for either the Per Protocol or the MITT populations. In addition, review of shift tables for systolic & diastolic blood pressure and heart rate showed no trends toward differences between the two active drug products [Submission of August 7, 2003, Tab 7].

11.2.2.3.4. Laboratory Adverse Events

Except for pregnancy tests, clinical laboratory tests were only performed at screening. There were no pregnancies. [M5, v 1.10, p 500077]

11.2.2.3.5. Medical device incidents or malfunctions

There were no device incidents or malfunctions noted in the study report.

11.2.3. Discussion

This was a multi-center, randomized, evaluator blind, placebo-controlled, seven-treatment-seven-period, seven-sequence, single-dose crossover bronchodilation study comparing Albuterol-HFA-MDI 90, 180, or 270 mcg, Proventil HFA 90, 180, or 270 mcg, and placebo administered at 2 to 7 day intervals in 47 moderate-to-moderately severe asthmatics (FEV₁ 50-75% predicted with reversible bronchoconstriction of $\geq 15\%$). The primary variable was

the baseline-adjusted change in FEV₁ average area-under-the-effect curve over 0-6 hours following dosing (AUEC₀₋₆). The secondary variable was the baseline-adjusted maximum FEV₁ value observed post-dose (FEV₁ max). Both the primary and secondary analyses were based on a per-protocol population, and included comparisons of the mean difference between each active group and placebo at each dose level, the mean difference between active groups at each dose level, and the within-product difference of 1 versus 2, 1 versus 3, and 2 versus 3 actuations (i.e. dose response). In addition, the dose-response of Albuterol-HFA-MDI was compared to Proventil HFA.

Fifty-eight patients were randomized, 19 males (32.8%) and 39 females (67.2%), predominantly Whites (81% Whites, 14% Blacks, and 5% "Other"). Forty-seven completed the study, of whom 16 did not complete every treatment (14 due to bronchospasm). The frequency of concomitant use of inhaled corticosteroids was not stated.

The primary efficacy analyses and treatment comparisons for the baseline-adjusted mean FEV₁ AUEC₀₋₆ for the per-protocol population were statistically significant ($p < 0.0001$) for all dose comparisons between Albuterol-HFA-MDI and placebo as well as between Proventil HFA and placebo. Comparison between similar doses of active drugs showed only small differences which were not statistically significant. Comparison of doses within each drug product showed a trend to more effect with higher doses. For Albuterol-HFA-MDI there was no statistically significant differences between doses, but for the Proventil HFA, there was a statistically significant difference between the 270 mg dose compared to both the 90 mg ($p = 0.0006$) and 180 mg ($p = 0.0290$) doses. Results for gender subgroups were statistically significant for all active treatments compared to placebo.

The secondary efficacy analyses and treatment comparisons for the baseline-adjusted maximum FEV₁ (L) for the per-protocol population were statistically significant ($p < 0.0001$) for all dose comparisons between Albuterol-HFA-MDI and placebo as well as between Proventil HFA and placebo. Comparison between similar doses of active drugs showed only small differences which were not statistically significant. Comparison of doses within each drug product showed a trend to higher maximum FEV₁ with increasing doses. For Albuterol-HFA-MDI there was no statistically significant differences between doses, but for the Proventil HFA, there was a statistically significant difference between the 90 mg and the 270 mg dose ($p = 0.0052$).

The applicant also sought but was unable to show bioequivalence between the test (Albuterol-HFA-MDI) and reference (Proventil HFA) products. The potency ratio (with 90% confidence intervals) was calculated to be 1.13, but the derived confidence intervals of 0.77-1.91 exceeded the protocol-defined confidence intervals of 0.67-1.50.

There were no trends in adverse events, with AEs distributed almost equally among treatment groups and periods. There were two serious adverse events, both asthma exacerbations. There were no deaths or pregnancies. No device incidents or malfunctions were noted in the study report.

11.2.4. Conclusions

This single dose, multiple dose level study supports the conclusion that the bronchodilation effects of Albuterol-HFA-MDI at the dosage levels typically used are substantially similar to

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those of Proventil HFA. However, since this was a single-dose study that did not include ECG, PK, or safety labs with dosing, safety of use is minimally supported.

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11.3. Study IX-101-105: Twelve-week therapeutic equivalence and safety study of Albuterol-HFA-BOI compared to Albuterol-CFC-MDI and placebo-HFA-BOI

Protocol #: IX-101-105

Title: A study to assess the therapeutic equivalence, efficacy, and safety of a Norton Healthcare Ltd HFA-propelled, breath-operated, metered dose, Salbutamol Inhaler (Salbutamol-BOI-HFA)

Study Dates: December 24, 1996 to July 03, 1997

Sites: Respiratory medicine specialists in Poland (5) and Russia (10)

Principal Investigators: Professor Vladimir Nonikov
Department of Respiratory Diseases
Central Clinical Hospital
Marshala Timoshenko 15
121356 Moscow
Russia

Professor Michal Pirozynski
Head of Department of Bronchology
Institute of Tuberculosis and Lung Diseases
ul. Plocka 26
01 138 Warsaw
Poland

IRB: Ethics Committees at the University Medical School of Warsaw, University Medical School of Lodz, and Medical and Sanitary Unit No 7 of "Kirovsky Factory" and several other hospital ethics committees in Russia (not translated to English).

Source: M5, v 1.67, p 500001, 500197-239

11.3.1. Protocol**11.3.1.1. Objective/Rationale**

The stated objectives of the study were: (1) to assess the therapeutic equivalence of Salbutamol-HFA-BOI and Salbutamol-CFC-MDI, (2) to evaluate the efficacy of Salbutamol-HFA-BOI relative to Placebo-HFA-BOI, and (3) to evaluate the safety profile of Salbutamol-HFA-BOI with respect to Salbutamol-CFC-MDI and Placebo-HFA-BOI. [M5, v 1.67, p 500014, 500084]

11.3.1.2. Summary of the Study Design

This was a multi-center, randomized, double-blind, double-dummy, placebo- and active-controlled parallel-group comparison of Salbutamol-HFA-BOI, Salbutamol-CFC-MDI, and placebo-HFA-BOI in 203 outpatients with mild-to-moderate (FEV₁ 50-80% predicted) non-seasonal asthma. [M5, v 1.67, p 500014, 36, 84]

11.3.1.3. Population

11.3.1.3.1. Inclusion criteria [M5, v 1.67, p 500023, 87-8]

Patients were included in the study if they met each of the following criteria:

1. Male or female outpatients, 18 to 65 years of age. Females of childbearing potential were included if conscientiously practicing an acceptable method of contraception (barrier methods, oral birth control pills, IUDs, or depot progesterone) and have a negative urine pregnancy test at each visit.
2. A minimum of three month history of regular asthmatic symptoms, characterized by intermittent airway obstruction, wheezing or chronic cough, and indicative of a need for daily use of β_2 -agonist therapy.
3. An FEV₁ at screening of 50-80% predicted for age, height, and gender, and reversible airway obstruction as verified by a $\geq 15\%$ increase in FEV₁ within 30 minutes of a 200 mcg does (two actuations) of Salbutamol-CFC-MDI.
4. Willing and able to give fully informed written consent to study participation.
5. Able to comply with the procedural requirements of the protocol including self-measurement of PEF, symptoms, and medication use.

11.3.1.3.2. Exclusion criteria [M5, v 1.67, p 500023-4, 88-9, 123, 129]

Patients were excluded in the study if they met each of the following criteria:

1. Any history of smoking within the previous six months, or a past history in excess of five pack-years.
2. Allergy or sensitivity to salbutamol or other components of the study medications.
3. Exposures to any investigational drug within the previous three months.
4. Past or current serious medical condition that might interfere with the patients' ability to comply with study procedures, pose a threat to the integrity of the data, or adversely influence the well-being of the patients as a result of their participation. In particular, chronic bronchitis, emphysema, active tuberculosis, bronchiectasis, cystic fibrosis, cardiac arrhythmias, uncontrolled hypertension, hepatic, renal, or endocrine dysfunction, stroke, uncontrolled diabetes, hyperthyroidism, and convulsive disorders were to be considered.
5. Clinically significant deviation from normal for biochemical and hematological parameters (eosinophilia of up to 1,000/mm³ was acceptable), and 12-lead ECG at screening.
6. Dosage of any required (a) inhaled corticosteroids, cromoglycate, and/or nedocromil and (b) intranasal corticosteroids and/or cromoglycate that had not been stable for at least one month prior to screening and, for inhaled steroids, dosages that exceeded the following limits:
 - budesonide up to 800 mcg/day
 - beclomethasone dipropionate up to 1000 mcg/day
 - fluticasone up to 500 mcg/day
 - flunisolide up to 1500 mcg/day

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- Patients requiring subsequent dosage adjustment of these products were required to be withdrawn from the study. (Amendment #2, February, 1997, p 5000129)
7. Current or anticipated treatment with monoamine oxidase inhibitors, tricyclic antidepressants, sympathomimetics, beta-blockers, or anticholinergics.
 8. Hospitalization or emergency room treatment for asthma within the previous three months.
 9. Patients whose asthma was suspected to have been exclusively seasonal.
 14. Known or suspected alcohol or other substance abuse.
 15. Any respiratory tract infection (including sinusitis) within the previous month.
 16. Known tendency to develop hypokalemia.
 17. Pregnancy or lactation.
 18. Inability to tolerate the required washout periods for medications (Amendment 1, p 500123) [see next section below]. Patients who were using short-acting β_2 -agonists were eligible, but were not to use these drugs for six hours prior to the screening lung function tests.
 19. Treatment with systemic steroid therapy within the previous three months (Amendment 1, p 500123).

11.3.1.3.3. Concomitant, Excluded, and Rescue Medications, Washout Periods

Medications not allowed, and washout period for medications allowed and disallowed prior to screening and/or each treatment are shown in Table 55. Female patients were allowed to continue oral contraceptives. Restrictions included prohibition from strenuous exercise 12 hours prior to all clinic visits, change in exercise routine during the study, exposure to cold air within one hour of dosing, and consumption of xanthine-containing foods or beverages within 8 hours prior to each clinic visit. Rescue medication included dry-powder salbutamol disks (Ventodisks[®]) used in a Diskhaler[®] (GlaxoWellcome Ltd, UK). [M5, v1.67, p 500025-7, 101-2]

Table 55. IX-101-105, Excluded drugs, Minimum drug washout periods

Medication	Excluded during study	Washout prior to screening and each treatment
Inhaled β_2 -agonists Short-acting (albuterol, pirbuterol, terbutaline) Long-acting (e.g. salmeterol)*	✓	6 hours 2 weeks
Oral β_2 -agonists*	✓	2 weeks
Oral or injectable corticosteroids	✓	3 months
Oral theophyllines	✓	1 week
Oral and intranasal decongestants		1 day
Anticholinergics Inhaled (e.g. ipratropium) Oral		24 hours 7 days
Antihistamines Hydroxyzine Astemizole	✓	4 days 3 months

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Medication	Excluded during study	Washout prior to screening and each treatment
Terfenadine, Loratadine All others	✓	2 weeks 24 hours
Aspirin & other nonsteroidal anti-inflammatory drugs	✓	1 week
Beta-blockers by any route	✓	
MAO inhibitors	✓	
Tricyclic antidepressants	✓	
* Patients receiving oral and long-acting β_2 -agonists could be switched to short-acting β_2 -agonists during the pre-study washout period.		

Source: M5, v 1.67, p 500024, 88, 126

11.3.1.3.4. Subject withdrawal [M5, v 1.67, p 500025, 104-5]

Patients were to be discontinued from the study if any of the following occurred:

1. Occurrence of any adverse event sufficiently severe to warrant withdrawal as judged by the Investigator and/or Sponsor.
20. Onset of any serious condition (including exacerbation of asthma requiring administration of any restricted anti-asthma medications) or the need to administer any medication that might pose a hazard to the patient or affect the validity of the efficacy data.
21. Desire by the patient to withdraw at any time for any reason.
22. Non-compliance with the protocol and/or lack of willingness or commitment to cooperate in all phases of the study.

Patients who did not complete all study-related procedures and evaluations were to be considered to have discontinued prematurely from the study.

11.3.1.3.5. Protocol amendments

The protocol was amended twice, on October 7, 1996 and February 1, 1997. In both instances, the major changes were to the list of excluded medications and washout periods. [M5, v 1.67, p 500123-31]

11.3.1.4. Conduct/Study Procedures

The study included a run-in period during which patients were treated with Salbutamol-CFC-BOI and placebo-CFC-MDI, and a treatment period during which patients were randomized to one of three treatment groups as shown in Table 56. Double-blinding was maintained by use of a double-dummy technique. The study protocol schedule of events and product lots used are summarized in the Table 57 and in Table 58, respectively. [M5, v 1.67, p 500028-9, 89-90]

Table 56. IX-101-105, Dosing and Blinding Methodology

Treatment	Dose	Inhalers	Dose Regimen	Blinding
Placebo-HFA-BOI	0 mcg albuterol QID	Placebo-HFA-MDI Placebo-HFA-BOI	2 actuations QID 2 actuations QID	Double-blind
Salbutamol-HFA-BOI	200 mcg albuterol QID	Salbutamol-HFA-BOI Placebo-HFA-MDI	2 actuations QID 2 actuations QID	Double-blind

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Treatment	Dose	Inhalers	Dose Regimen	Blinding
Salbutamol-CFC-MDI	200 mcg albuterol QID	Salbutamol-CFC-MDI Placebo-CFC-BOI	2 actuations QID 2 actuations QID	Double-blind

Source: M5, v 1.67, p 500026, 90

Table 57. IX-101-105, Study Flow Chart

Event	Visit Day	Screen	1	2	3	4	5	FU
		Day -14±3	0	21±3	42±3	63±3	84±3	PRN
Written informed consent		✓						
Demographic and medical history		✓						
Clinical examination		✓						✓ ^d
Vital signs			✓ ^a					
Lung function tests		✓	✓ ^b					
12-lead ECG		✓		✓			✓	✓ ^d
Blood chemistry and hematology ^e		✓					✓	✓ ^d
Electrolyte screen ^f			✓	✓	✓	✓		
Urinalysis ^g		✓					✓	✓ ^d
Urine pregnancy (females)		✓	✓	✓	✓	✓	✓	✓ ^d
Peak flow meter + BOI/MDI use training		✓	✓	✓	✓	✓		
Concomitant medication		✓	✓	✓	✓	✓		
Dispense run-in medication		✓						
Randomization			✓					
Post-medication PEF by patient		✓ ^c						
Asthma symptom scores		✓	✓	✓	✓	✓	✓	
Issue study & rescue medication			✓	✓	✓	✓		
Ease of use questionnaire		✓					✓	
Adverse events			✓	✓	✓	✓	✓	✓ ^d
Compliance check			✓	✓	✓	✓	✓	
Retrieve study materials			✓	✓	✓	✓	✓	

a Vital signs at 0, 1, and 6 hours post-dosing.

b FEV₁ 15 minutes before, and 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, and 6 hours after dosing.

c PEF measurements twice daily.

d Optional follow-up as required.

e Clinical laboratory tests included a complete blood count with differential and serum chemistries: glucose, sodium, potassium, chloride, BUN, creatinine, total protein, albumin, total bilirubin, calcium, phosphorous, alkaline phosphatase, ALAT (SGPT), ASAT (SGOT), and LDH.

f Electrolyte screen included random glucose and potassium.

g Urine dipstick for blood, protein, and glucose.

Sources: M5, v1.67, p 500016, 110, 114

Table 58. IX-101-105, Investigational Product Lots

Product	Strength/Quantity per Actuation	Manufacturer	Lot/Batch Number	Expiry Date
Placebo-HFA-BOI	0	Norton (Waterford) Ltd, Ireland	RD-96-003	08/98
Placebo-HFA-MDI	0	Norton (Waterford) Ltd, Ireland	96-002	08/98
Placebo-CFC-BOI	0	Norton (Waterford) Ltd, Ireland	95600	09/97
Salbutamol-HFA-BOI	100 mcg	Norton (Waterford) Ltd, Ireland	RD-96-004	08/98
Salbutamol-CFC-MDI	100 mcg	Norton (Waterford) Ltd, Ireland	96952	09/99
MDI Actuators		Not specified		
BOI Actuator Unit		Not specified		

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Product	Strength/Quantity per Actuation	Manufacturer	Lot/Batch Number	Expiry Date
BOI Actuator Main Body Assembly		Not specified		
Ventodisks [®] for rescue use	200 mcg	GlaxoWellcome Ltd, UK	10054521	07/99

Source: M5, v 1.67, p 500027

11.3.1.5. Safety Evaluations

Safety variables at screening included physical examination, pulmonary function studies, clinical labs including urine pregnancy tests, 12-lead ECG, and vital signs. During the study, patients were monitored with home AM and PM PEF measurements, on-site pre- and post-dose PFTs, vital signs, and serum electrolytes and urine pregnancy tests. End-of-study evaluations included a physical examination, clinical labs, urinalysis, 12-lead ECG, pregnancy test, and adverse events. Clinical laboratory tests are shown in Table 57. Adverse events were evaluated for intensity and causality. [M5, v 1.67, p 500629]

11.3.1.6. Efficacy and Compliance Evaluations [M5, v 1.67, p 500093-4]

Efficacy and compliance evaluations included spirometry at each clinic visit, daily diary information, and an ease of use questionnaire. The ease of use questionnaire was completed at the end of the inhaler training session at the screening visit, and again at the final study visit. Patients were asked complete a diary card twice daily including AM and PM post-dosing PEF, daytime asthma symptoms, overnight asthma symptoms, the number of night-time awakenings due to asthma, and the amount of rescue medication used in the preceding 12 hours. Asthma symptom scores were recorded immediately upon waking and prior to going to bed. Asthma symptoms of wheeze, shortness of breath, cough, and tightness of chest were each scored on a 0-3 scale, where:

- 0 = No symptoms
- 1 = Symptom occurred but did not interfere with daily activity or sleep
- 2 = Symptom occurred but was sometimes annoying or interfered with daily activity or interfered with but did not prevent sleep
- 3 = Symptom occurred even at rest and was annoying or interfered with daily activity or sleep.

11.3.1.7. Pharmacokinetic Evaluations

No pharmacokinetic evaluations were performed in this study.

11.3.1.8. Statistical Plan

11.3.1.8.1. Definition of study populations

For this study, the protocol defined the study population to be used for analyses to include patients who were randomized and completed 35 days or more of treatment (Per Protocol population). The study report states that the Per-Protocol population was used for all therapeutic equivalence analyses, while the ITT population was used for safety and efficacy evaluations. However, since there were multiple timepoints at which efficacy was assessed

and an LOCF was not used, in effect a Per-Protocol population was used for the efficacy analyses. [M5, v 1.67, p 500036, 41, 106-7]

11.3.1.8.2. Primary endpoint and analysis

The primary outcome variable was the average FEV₁ change over 0-6 hours post-dosing. This was computed by subtracting the pre-dose FEV₁ from each post-dose measurement, then computing the AUC₀₋₆ using the trapezoidal rule and dividing by 6 hours. For each patient, the study endpoint was the average FEV₁ response observed at visit days 14, 35, 56, 77, and 98. LOCF was used for patients who failed to complete the study.

The primary efficacy endpoint was an analysis of variance including factors for treatment, center, and treatment-by-center using a two-sided t-test and an alpha of 0.05. Neither the protocol nor the study report discusses adjustments for multiple comparisons. [M5, v 1.67, p 500034-5, 105]

The primary equivalence endpoint was between Salbutamol-HFA-BOI (test) and Salbutamol-CFC-MDI (reference), with the comparison assessed as equivalent if the 90% confidence intervals for the difference between the two treatments fell within $\pm 33\%$ of the expected response for the reference product. [M5, v 1.67, p 500034-5, 106]

11.3.1.8.3. Secondary endpoints and analyses

Secondary analysis included pre-dose FEV₁, maximum FEV₁ response, and between-visit day averages of PEF, as well as tabular summaries of FEV₁ response at each evaluation time by treatment, and tabular summaries of cough, wheeze, nighttime awakenings, and use of rescue medication. [M5, v 1.67, p 500035, 106]

11.3.1.8.4. Sample size considerations

Sample size was based on demonstration of therapeutic equivalence between test and reference rather than a comparison between test and placebo. Sample size was calculated based on a previous salbutamol study, in which the average FEV₁ response over 0-6 hours was 0.381 L for the 200 mcg dose with an estimated SD of 0.334 L. Fifty completed patients per arm was calculated to provide an 80% probability that the two-sided 90% confidence intervals for FEV₁ response difference between Salbutamol-CFC-MDI and Salbutamol-HFA-BOI would fall between $\pm 33\%$ of the expected response for Salbutamol-CFC-MDI (0.117L). Since the difference between test and placebo BOI products was expected to be larger than 0.017L, the sample size was expected to yield close to 100% power for an efficacy assessment. [M5, v 1.67, p 500036, 106]

11.3.2. Results

11.3.2.1. Description of Study Population

11.3.2.1.1. Disposition

A total of 236 patients were enrolled, of whom 203 were randomized to treatment, and 182 completed the study. Patient disposition is shown in Table 59, with reasons for discontinuation shown in descending order of frequency. Eleven patients in the Placebo-

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HFA-BOI group withdrew compared to eight in the Salbutamol-HFA-BOI group and two in the Salbutamol-CFC-MDI group.

Table 59. IX-101-105, Patient disposition

Disposition	Sal-HFA-BOI	Sal-CFC-MDI	Placebo-HFA-BOI	Total
ITT population	69	68	66	203
Completed	61 (88.4%)	66 (97.1%)	55 (83.3%)	182 (89.7%)
Per Protocol	60 (87.0%)	66 (97.1%)	54 (81.8%)	180 (88.7%)
Discontinued ^a	8 (11.6)	2 (2.9)	11 (16.7)	21
Adverse event	3 (4.3)	1 (1.5)	4 (6.1)	8 (3.9)
Consent withdrawn	3	0	2	5 (2.5)
Protocol violation	1	0	4	5 (2.5)
Lost to follow-up	1	1	0	2 (1.0)
Other	0	0	1	1 (0.5)
Lack of efficacy	0	0	0	0
Malfunction of inhaler	Not stated	Not stated	Not stated	Not stated

Source: M5, v 1.67, Table 10-2, p 500062; p 500061

11.3.2.1.2. Demographics and baseline characteristics

Demographics and baseline characteristics of the study population are shown in Table 60. Treatment groups were relatively well balanced at randomization. Overall there were more females (66%) than males (34%) enrolled, and Whites (100%) were the only Race represented. FEV₁ and % reversibility of FEV₁ at screening and FEV₁ at baseline were comparable among treatment groups, although baseline FEV₁ was slightly higher for the Placebo-HFA-BOI group. Use of corticosteroids and other asthma medications were comparable among treatment groups.

While the patient listings were not specifically reviewed, the Study report states that baseline medical history, concomitant medication, vital signs, and physical examinations were comparable between treatment groups. [Source: M5, v 1.67, p 500038-41]

Table 60. IX-101-105, Patient demographics and baseline characteristics

Disposition		Sal-HFA-BOI n = 69	Sal-CFC-MDI n = 68	Placebo-HFA-BOI n = 66	Total n = 203
Age, years:	Mean (SD)	42.4 (10.8)	42.5 (13.6)	40.6 (12.2)	41.8 (12.2)
	Range	19 - 64	20 - 65	18 - 64	18 - 65
Gender:					
Males	N (%)	24 (34.8)	22 (32.4)	23 (34.8)	69 (34.0)
Females	N (%)	45 (65.2)	46 (67.6)	43 (65.2)	134 (66.0)
Race:					
White	N (%)	69 (100.0)	68 (100.0)	66 (100.0)	203 (100.0)
Black	N (%)	0	0	0	0
Other	N (%)	0	0	0	0
Qualifying:					
FEV ₁ , L	Mean (SD)	2.06 (0.57)	2.06 (0.53)	2.16 (0.64)	2.09 (0.58)
% reversibility	Mean (SD)	26.3 (10.1)	25.4 (10.2)	26.9 (13.2)	26.2 (11.2)
Baseline (Visit 1, randomization):					

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Disposition		Sal-HFA-BOI n = 69	Sal-CFC-MDI n = 68	Placebo-HFA-BOI n = 66	Total n = 203
FEV ₁ , L	Mean (SD)	2.07 (0.62)	2.08 (0.55)	2.20 (0.69)	
Baseline asthma medication use:					
Corticosteroids	N (%)	29 (42)	32 (47)	28 (42)	
Other	N (%)	22 (32)	22 (32)	25 (38)	

Source: M5, v 1.67, Tables 4, 7A, p 500038, 41; v 1.68, Tables 3.1-2, 4, 7, p 500388-9, 399, 418

11.3.2.1.3. Study populations

The Per-Protocol population (therapeutic equivalence analyses) included 180 patients. The ITT population (safety and efficacy evaluations) included 203 patients. [M5, v 1.67, p 500041]

11.3.2.1.4. Compliance

While the protocol stated that medication compliance would be assessed by weighing returned canisters, the applicant made no formal analysis of compliance. The data was provided as a listing in the Appendix of the study report, and as such, does not provide helpful information regarding compliance in this study. [Source: M5, v 1.67, p 500041]

11.3.2.2. Efficacy Outcomes

Since the HFA-MDI product was not included in this study, the study was primarily evaluated for safety within the context of this review. Efficacy was only briefly evaluated, and was not reviewed by the Division's Biometrics Reviewer. The reasons for not fully evaluating efficacy include the following:

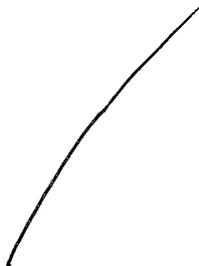
- Only the HFA-BOI product was used in this study.
- While the study states that both therapeutic equivalence between the two active study drugs and efficacy against placebo were study objectives, the study design was that of an equivalence trial.
- Each visit was an endpoint, with no adjustment for multiple endpoints.
- While an analysis was done for last assessment, this was never declared as a primary endpoint.

1 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling



11.3.2.3. Safety Outcomes

11.3.2.3.1. Extent of exposure

The safety population consisted of the 203 patients randomized to treatment. Of these, 182 patients completed 12 weeks of treatment. [M5, v 1.67, p 500054]

11.3.2.3.2. Clinical adverse events

11.3.2.3.2.1. Incidence and types of clinical adverse events

Fewer patients in the Salmeterol-HFA-BOI group experienced an adverse event (AE) than in the other groups: 14 (20.3%) Salmeterol-HFA-BOI; 22 (32.4%) Salbutamol-CFC-MDI, and 20 (30.3%) Placebo-HFA-BOI. The distribution of adverse events is shown in Table 63. Headache was the most frequent AE, followed by flu syndrome and dyspnea. In fact, headache occurred significantly more frequently in the Salbutamol-CFC-MDI group (40.9%) than in either the Salbutamol-HFA-BOI (14.3%) or Placebo-HFA-BOI (15.0%) groups, with a between-active-treatment comparison of $p = 0.031$ (Sal-HFA-BOI to Sal-CFC-MDI). There were no other differences in incidence of AEs that were of note. Most AEs were mild in severity: 16 (59.3%) Salmeterol-HFA-BOI, 23 (69.7%) Salbutamol-CFC-MDI, and 22 (52.4%) Placebo-HFA-BOI. [M5, v 1.67, p 500054-5]

Table 63. IX-101-105, Most frequently reported adverse events and where AEs more frequent in treatment than in placebo*, ITT pop

Adverse event	Salbutamol-HFA-BOI N = 69	Salbutamol-CFC-MDI N = 68	Placebo-HFA-BOI N = 66
Number of adverse events	27	33	42
Patients with adverse event	14 (20.3)	22 (32.4)	20 (30.3)
Most Frequently reported AEs:			
Headache	2 (14.3)	9 (40.9)	3 (15.0)
Flu syndrome	3 (21.4)	6 (27.3)	2 (10.0)
Dyspnea	3 (21.4)	2 (9.1)	5 (25.0)
Other AEs more frequent in active treatment than in placebo*:			
Cough increased	1 (7.1)	2 (9.1)	1 (5.0)
Pharyngitis	1 (7.1)	1 (4.5)	0
Hemoptysis	1 (7.1)	0	0
Rhinitis	1 (7.1)	2 (9.1)	1 (5.0)

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Myalgia	0	1 (4.5)	0
Epistaxis	1 (7.1)	0	1 (5.0)
Eye hemorrhage	0	1 (4.5)	0
Heart block	1 (7.1)	0	0
Tachycardia	0	1 (4.5)	0
Thyroid adenoma	2 (14.3)	1 (4.5)	1 (5.0)
Thyroid disorder	0	1 (4.5)	0
Vertigo	2 (14.3))	0	0
Nausea	1 (7.1)	0	0

* Number of AEs reported higher in either active treatment group than in the control group

Source: M5, v 1.67, Table 10, p 500055 and v 1.68, Table 14.1, Appendix 16.2, p 500520

11.3.2.3.2.2. Serious adverse events, Deaths, and Discontinuations

There was one death. Patient 678 randomized to Placebo-HFA-BOI died 1½ months after starting the study of asystole and pulmonary embolism two days after surgery for ileal torsion. This adverse event was judged by the investigator to not be related to study medication. [M5, v 1.67, p 500054]

Six patients, including patient 678, experienced a serious adverse event (Table 64). Two of these occurred in patients not randomized to treatment. Only one incident of vertigo and nausea (both in patients 651 in the salbutamol-HFA-BOI group) was considered reasonably attributable to study drug.

Eight patients withdrew (discontinued) from the study due to an adverse event (Table 65). The frequency of withdrawals was highest in the placebo group, but none of these was considered attributable to study drug.

Table 64. IX-101-105, Summary of serious adverse events, ITT pop

Patient Number	Treatment Group	Adverse Event	Attribution to study drug	Outcome
S137	Not randomized	Worsening of asthma	No	Resolved
S213		Exacerbation of asthma	No	Resolved
505	Salbutamol-MDI-CFC	Thyroid disorder	No	Resolved
651	Salbutamol-HFA-BOI	Vertigo	Reasonable	Resolved
		Nausea	Reasonable	Resolved
664 678	Placebo-HFA-BOI	Bronchitis	No	Resolved
		Exacerbation of asthma	No	Resolved
		Intestinal obstruction	No	Resolved with sequelae
		Heart arrest	No	Death
		Pulmonary embolus	No	Death

Source: M5, v 1.67, Table 12, p 500056

Table 65. IX-101-105, Withdrawals due to adverse events, ITT pop

Patient Number	Treatment Group	Frequency per group	Adverse Event	Attribution to study drug
548	Salbutamol-HFA-BOI	4.3%	Worsening of asthma	No
573			Exacerbation of asthma	No
651			Vertigo / Nausea	Reasonable
505	Salbutamol-MDI-CFC	1.5%	Thyroid disorder	No

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609	Placebo-HFA-BOI	6.1%	Dyspnea	No
664			Bronchitis / Exacerbation of asthma	No
678			Intestinal obstruction / Pulmonary embolus	No
695			Dyspnea	No

Source: M5, v 1.67, Table 11, p 500055

11.3.2.3.3. Vital signs, ECGs, and Physical examinations

Review of heart and respiratory rate values taken over 6 hours at baseline, 3, 6, 9, and 12 weeks visits showed no significant sustained differences among groups. By visual inspection, there was a trend at each timepoint of 0, 1 and 6 hours and at each visit toward slightly higher systolic and diastolic BPs in the in the range of 2-3 mmHg systolic and 1-2 mmHg diastolic for the Salmeterol-CFC-MDI group compared the other two treatment groups. Two patients experienced changes in ECGs from screening to Visit 2, consisting of ventricular extrasystoles, but there was no pattern to the changes (1 Salbutamol-HFA-BOI and 1 Placebo-HFA-BOI). The only change in physical examinations of note was that for both the active treatment groups there were less patients with chest/lung findings (mostly characterized as a lack of dry rales) than in the placebo group (9 Salmeterol-HFA-BOI, 10 Salmeterol-CFC-MDI, 2 Placebo-HFA-BOI).[M5, v 1.67, p 500063-8

11.3.2.3.4. Laboratory Adverse Events

Review of shift tables for all hematology, chemistry, and urinalysis values from screening to the end of the study showed no significant changes or trends, nor differences between groups. Review of random glucose and potassium from visits at baseline, 3, 6, 9, and 12 weeks showed no significant sustained differences among groups. [M5, v 1.67, p 500056-63]

11.3.2.3.5. Medical device incidents or malfunctions

There were no device incidents or malfunctions noted in the study report.

11.3.3. Discussion

This was a 12-week, multi-center, randomized, double-blind, double-dummy, placebo- and active-controlled parallel-group comparison of Salbutamol-HFA-BOI, Salbutamol-CFC-MDI, and placebo-HFA-BOI in 203 outpatients 18-65 years of age with mild-to-moderate (FEV₁ 50-80% predicted) non-seasonal asthma. The primary objective of the study was to assess the therapeutic equivalence of Salbutamol-HFA-BOI (test) and Salbutamol-CFC-MDI (reference). The primary outcome variable was the average FEV₁ change over 0-6 hours post-dosing. The drug products were assessed as equivalent if the 90% confidence intervals for the difference between the two treatments fell within $\pm 33\%$ of the expected response for the reference product. Secondary objectives were to evaluate the efficacy of Salbutamol-HFA-BOI relative to Placebo-HFA-BOI, and to evaluate the safety profile of Salbutamol-HFA-BOI with respect to Salbutamol-CFC-MDI and Placebo-HFA-BOI. Secondary analysis included pre-dose FEV₁, maximum FEV₁ response, and between -visit day averages of PEF, as well as tabular summaries of FEV₁ response at each evaluation time

by treatment, and tabular summaries of cough, wheeze, nighttime awakenings, and use of rescue medication.

Of the 203 randomized patients, 182 patients completed 12 weeks of treatment. Fewer patients in the Salmeterol-HFA-BOI group experienced an adverse event (AE) than in the other groups: 14 (20.3%) Salmeterol-HFA-BOI, 22 (32.4%) Salbutamol-CFC-MDI, and 20 (30.3%) Placebo-HFA-BOI. Headache was the most frequent AE, followed by flu syndrome and dyspnea. In fact, headache occurred significantly more frequently in the Salbutamol-CFC-MDI group (40.9%) than in either the Salbutamol-HFA-BOI (14.3%) or Placebo-HFA-BOI (15.0%) groups, with a between-active-treatment comparison of $p = 0.031$ (Sal-HFA-BOI to Sal-CFC-MDI). There were no other differences in incidence of AEs that were of note. There was one death in a patient randomized to placebo who experienced a pulmonary embolism two days after surgery for ileal torsion. Six patients experienced a serious adverse event, of which one was the patient who dies and two were in patients not randomized to treatment. Only one incident of vertigo and nausea (both in one patient on salbutamol-HFA-BOI) was considered reasonably attributable to study drug. Eight patients withdrew from the study due to an adverse event, with the frequency of withdrawals highest in the placebo group, and none considered attributable to study drug.

There were no significant sustained differences among groups for laboratory findings. There was a trend at each timepoint (0, 1 and 6 hours) at each visit toward slightly higher systolic and diastolic BPs in the in the range of 2-3 mmHg systolic and 1-2 mmHg diastolic for the Salmeterol-CFC-MDI group compared the other two treatment groups. Since the trend includes time 0 at each visit, and it would be expected for any effects of albuterol to be worn off by the next treatment, the significance of this finding is unclear. There were less patients with the physical examination chest/lung findings (mostly characterized as a lack of dry rales) at the end of the study for both the active treatment groups than in the placebo group (9 Salmeterol-HFA-BOI, 10 Salmeterol-CFC-MDI, 2 Placebo-HFA-BOI). No device incidents or malfunctions were noted in the study report.

Since the HFA-MDI product was not included in this study, the study was primarily evaluated for safety within the context of this review. Efficacy was only briefly evaluated, and was not reviewed by the Division's Biometrics Reviewer.

11.3.4. Conclusions

This 12-week equivalence study compared Salbutamol-HFA-BOI to Salbutamol-CFC-MDI and placebo. Since the HFA-MDI product was not included in this study, the study was primarily evaluated for safety. The only safety finding of note was that the incidence of

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headache occurred significantly more frequently in the Salbutamol-CFC-MDI group (40.9%) than in either the Salbutamol-HFA-BOI (14.3%) or Placebo-HFA-BOI (15.0%) groups, with a between-active-treatment comparison of $p = 0.031$ (Sal-HFA-BOI to Sal-CFC-MDI). There was a trend at each timepoint (0, 1 and 6 hours) at each visit toward slightly higher systolic and diastolic BPs in the in the range of 2-3 mmHg systolic and 1-2 mmHg diastolic for the Salmeterol-CFC-MDI group compared the other two treatment groups. Since both sets of findings were more frequent with Salmeterol-CFC-MDI treatment, these findings do not impact either of the HFA products.

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11.4. Study IXR-107-1-105: Cumulative-dose, single-dose PK/PD crossover study of Albuterol HFA MDI and BOI compared to Proventil HFA MDI

Protocol #: IXR-107-1-105

Title: Comparison of extrapulmonary effects and pharmacokinetics of HFA-propelled Albuterol Inhalation Aerosol (Norton Waterford) by breath-operated and press-and-breathe inhalers when compared to Proventil HFA (Key Pharmaceuticals)

Study Dates: February 13, 2002 to February 28, 2002

Sites: /
/
/IRB: /
/

Source: M5, v 1.7, p 500002, 12

Note: This study was reviewed by the Division's Clinical Pharmacology and Biopharmaceutics Reviewer, Dr. Sinja Kim. Please refer to her review for an in-depth analysis of the safety results.

11.4.1. Protocol**11.4.1.1. Objective/Rationale**

The objective of this study was to compare the extrapulmonary effects and pharmacokinetics of Albuterol HFA administered using a breath-operated (BOI, IVAX Pharmaceuticals, Ireland) and a metered-dose inhaler (MDI, IVAX Pharmaceuticals, Ireland) with an equivalent dose of Albuterol HFA in a marketed formulation using an MDI (*Proventil*[®] HFA, Key Pharmaceuticals, Inc.) over a cumulative dose of 12 puffs (1080 mcg albuterol) in healthy volunteers. [M5, v 1.7, p 500018, 500206]

11.4.1.2. Summary of the Study Design

This study was a repeat of an earlier study, IXL-106-1-105, with a similar study design. Study IXL-106-1-105 was deemed invalid because 56% (9/16) of subjects had positive (non-zero) pre-dose albuterol concentrations across all three treatment periods, and 31% (5/16) of subjects had positive (non-zero) pre-dose albuterol concentrations for two treatment periods. [M5, v 1.7, p 500017]

This was a single-center, randomized, evaluator-blind, active-controlled, three-treatment, three-period, three-sequence, cumulative-dose crossover comparison safety study evaluating the extrapulmonary and pharmacokinetic profiles of Albuterol HFA-MDI, Albuterol HFA-BOI, and Proventil HFA in 15 healthy subjects. Eligible subjects were randomized to receive 2 + 4 + 6 actuations administered at 30 minutes intervals (180 + 360 + 540 for a total

treatment dose of 1080 mcg) of Albuterol-HFA-MDI, Albuterol-HFA-BOI, or Proventil HFA, with a minimum of 6 days between treatments. [M5, v 1.7, p 50004, 19, 206-7, 212]

11.4.1.3. Population

11.4.1.3.1. Inclusion criteria [M5, v1.7, p 500020, 210-11]

Subjects were included in the study if they met each of the following criteria:

1. Male, or non-pregnant, non-nursing females, 18 to 35 years of age at screening. Females of childbearing potential were included if practicing an acceptable method of birth control (barrier methods, oral birth control pills, progesterone implanted rods, IUDs, or *Depo-Provera*®) and have a negative urine pregnancy test at screening and each subsequent clinic visit.
2. Weight within $\pm 15\%$ of ideal body weight for height, frame size, and gender according to the Metropolitan Life Insurance Company Statistical Bulletin, 1983.
3. Non-smoker for at least one year prior to the screening visit and a maximum smoking history of five-pack years.
4. Sitting heart rate >50 and <85 bpm.
5. Sitting blood pressure $>100/65$ and $<130/85$ mmHG.
6. Demonstrate relatively consistent inspiratory flow rates and duration using the *InspirEase*® spacer device at the screening visit.
7. Acceptable medical history, physical examination, and clinical laboratory test results.
8. Provision of written informed consent.

11.4.1.3.2. Exclusion criteria [M5, v 1.7, p 500020-21, 211]

Subjects were excluded in the study if they met each of the following criteria:

1. History of any clinically significant disease, including cardiovascular, pulmonary, renal, neurologic, liver, or endocrine dysfunction, including ECG with evidence of ischemic heart disease.
2. Previous or current history of illicit drug or alcohol abuse or positive drug screen.
3. Known intolerance or hypersensitivity to any component of the MDI formulations.
4. History of allergies or allergic rhinitis.
5. Any current or past medical condition that might significantly affect pharmacodynamic safety responses to the administered drug.
6. Exposures to any investigational drug within 30 days prior to the screening visit.

11.4.1.3.3. Prohibitions

Subjects were required to refrain from strenuous physical activity throughout each treatment period. During each treatment period, no food or beverage other than water was permitted from 8 hours prior to the first dose until the last sample for potassium and glucose measurement was collected approximately 4 hours post-dose. Subjects were prohibited from consuming alcohol, caffeine-containing beverages, chocolate, grapefruits, and/or grapefruit juice for 48 hours prior to and during each treatment period. No prescription or OTC medications were allowed within the 2-week period prior to the first treatment. During

the course of the study, acetaminophen, ibuprofen, Pepto-Bismol, and Kaopectate were permitted. Females were allowed to continue oral contraceptives. [m5, v 1.7, p 500027, 219-20]

11.4.1.3.4. Subject withdrawal [M5, v 1.7, p 500021, 224]

The following criteria were the basis for subject discontinuation from the study:

1. Occurrence of any adverse event sufficiently severe to warrant withdrawal as judged by the Principal Investigator and/or Sponsor.
2. Increase in heart rate to >175 bpm, and/or the occurrence of palpitations or chest discomfort.
3. Appearance of significant ventricular arrhythmias.
4. Inability to provide a serum sample.
5. Onset of any serious condition or the need to administer any medication that might pose a hazard to the subject or affect the validity of the data.
6. Desire by the subject to withdraw from the study at any time for any reason.
7. Non-compliance with the protocol and/or lack of willingness or commitment to cooperate in all phases of the study.

Subject who did not complete all study-related procedures were considered to have discontinued prematurely from the study.

11.4.1.3.5. Protocol amendments

The original protocol, dated January 17, 2002, was amended on January 31, 2002 prior to enrollment of any subjects. Amendments to the protocol included addition of a blood sample at screening to test for possible albuterol contamination and a change to the pre-dose albuterol determination from one hour pre-dose to 12 hours pre-dose to ensure that subjects did not have measurable pre-dose albuterol levels. [M5, v 1.7, p 500040]

11.4.1.4. Conduct/Study Procedures

Eligible subjects were randomized to receive three treatments as shown below with a minimum of 3 days between treatments, with the treatment sequence defined by a three-sequence randomization code. [M5, v 1.7, p 500019, 23]

Treatment	Number of actuations at 30 minute intervals	Dose of Albuterol (mcg)
Albuterol-HFA-MDI	2 + 4 + 6	180 + 360 + 540 = 1080 mcg
Albuterol-HFA-BOI	2 + 4 + 6	180 + 360 + 540 = 1080 mcg
Proventil®-HFA-MDI	2 + 4 + 6	180 + 360 + 540 = 1080 mcg

Because of the difference in appearance and the lack of a Proventil-HFA-MDI placebo, the study could only be evaluator blinded. Because of the study design, patients were blindfolded for the treatment administration procedure, necessitating a complex training regimen outlined in detail in the protocol. To maintain blinding of the individuals who conducted the evaluations or monitored patients the study, separate unblinded individuals called dosing administrators were used to dose the patient. [M5, v 1.7, p 500025]

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Patients were asked to fast for 8 hours prior to each study dosing. Priming of canisters was performed five times by a routine of shaking for five seconds in an upright position, followed by actuating to waste, then a two-second pause. The BOI device was primed by similarly to the MDI device after unscrewing and removing the top of the canister. Administration of dosing was without a spacer device and with the patient blindfolded. For this reason, patients were required to practice inhalation technique during the screening phase. Each actuation was made at one-minute intervals, with 30 minutes between doses.

The study protocol schedule of events (including timing of PK/PD sampling with respect to dosing) and product lots used are summarized in the Table 45 and in Table 46, respectively.

Table 66. IXR-107-1-105, Study Protocol Event Schedule

Events	Screening (-14 days)	Treatment Periods 1-3	End of study
Informed consent	✓		
Medical/medication history	✓		
Physical examination	✓		✓
12-lead ECG	✓		
Safety laboratory tests (fasting)	✓ ¹		
Albuterol level	✓		
Serum pregnancy test	✓ ²		
Urine pregnancy test		✓ ²	
Vital signs	✓		
Inhalation technique training	✓		
Dose administration		✓	
Serial vital signs (BP and respiratory rate)		✓ ³	
Serial ECG (R-R, QT, and QTc)		✓ ⁴	
Serial serum K ⁺ and glucose levels		✓ ⁵	
Serial blood albuterol levels		✓ ⁶	
Concomitant medications	✓	✓	✓
Adverse events		✓	✓

1 Screening clinical laboratory evaluations included: CBC, Differential, Glucose, Sodium, Potassium, Chloride, Creatinine, BUN, Uric acid, Cholesterol, Total protein, Albumin, Total bilirubin, Calcium, Phosphorus, Alkaline phosphatase, ALAT (SGPT), and ASAT (SGOT), LDH, Urinalysis for: Protein, Glucose, Blood, Drugs of abuse.

2 For females: Serum pregnancy test at screening, urine pregnancy test prior to each dosing period.

3 Serial vital signs: Prior to first dose, 15 minutes after completing of the last actuation of the 2- and 4-actuation doses, 15, 30 minutes, and 1, 2, 3, 4, and 24 hours following completion of the last actuation of the 6-actuation dose.

4 Serial 12-lead ECGs: Prior to first dose, 15 minutes after completing of the last actuation of the 2- and 4-actuation doses, 15, 30 minutes, and 1, 2, 3, and 4 hours following completion of the last actuation of the 6-actuation dose.

5 Serial serum K⁺ and glucose levels: 3-mL blood samples taken prior to first dose, 15 minutes after completing of the last actuation of the 2- and 4-actuation doses, 15, 30 minutes, and 1, 2, 3, and 4 hours following completion of the last actuation of the 6-actuation dose.

6 Serial PK collection: 7-mL blood samples taken 12 hours prior to first dose, 5, 10, 15, and 29 minutes after completing of the last actuation of the 2- and 4-actuation doses, and 5, 10, 15, and 45 minutes, and 1, 2, 3, 4, 6, 8, 12, and 24 hour following completion of the last actuation of the 6-actuation dose.

Source: M5, v 1.7, p 500028, 35-6, 245-6

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Table 67. IXR-107-1-105, Investigational Product Lots

Product	Strength / Actuation	Manufacturer	Lot/Batch Number	Expiry Date
Albuterol-HFA	90 mcg	IVAX Pharmaceuticals, Ireland	AAW13A	6/02
Proventil HFA	90 mcg	Obtained from commercial sources. Manufactured by Key Pharmaceuticals, Inc., Kenilworth, NJ	GBD002A	4/02
MDI  Actuators			01R0010	NA
BOI Actuators			00R0161	NA

Source: M5, v 1.7, p 500022

11.4.1.5. Safety Evaluations

PK / PD (pharmacologic) measurements included serial blood albuterol levels, potassium (K⁺) and glucose measurements, 12-lead ECGs (RR, QT and QTc intervals, T- and U-wave morphology), and vital signs (BP and respiratory rate). Albuterol levels were performed 12 hours prior to each dosing to ensure that levels were not contaminated from previous exposure. Plasma albuterol levels were performed using a validated LC/MS/MS with mass spectrometric detection methodology with a lower limit of quantitation of 2pg/mL. Linearity was established using eleven calibration standards over the range of 2.00 to 4000 pg/mL. [M5, v 1.7, p 500030, 33]

11.4.1.6. Efficacy Evaluations

This was a safety study in healthy subjects. No efficacy evaluations were performed.

11.4.1.7. Statistical Plan

11.4.1.7.1. Safety variables [M5, v 1.7, p 500036-7, 226-7]

The variables determined from the vital signs, ECG, serum potassium and glucose measurements were:

- The mean and mean changes from baseline in systolic blood pressure at 15 minutes after the first and second doses, and at 15 and 30 minutes, and 1, 2, 3, 4, and 24 hours after the last dose.
- The mean and mean changes from baseline in diastolic blood pressure at 15 minutes after the first and second doses, and at 15 and 30 minutes, and 1, 2, 3, 4, and 24 hours after the last dose.
- The mean and mean changes from baseline in QT and QTc intervals (msec) at 15 minutes after the first and second doses, and at 15 and 30 minutes, and 1, 2, 3, 4, and 24 hours after the last dose.
- Heart rate calculated as the RR interval from ECG as: $HR = (60 \times 1000) / RR$ (msec) bpm.
- The variables determined from the plasma albuterol measurements were:
 - The maximum observed plasma concentration (C_{max})
 - The area under the plasma concentration-time curve from time zero to the last detectable plasma concentration (AUC_{0-t}) derived using the trapezoidal rule.

- The area under the plasma concentration-time curve from time zero to the infinity (AUC_8).
- Terminal half-life ($t_{1/2}$).

11.4.1.7.2. Primary safety analyses

The primary comparisons of interest were the comparisons between inhaler treatments of mean changes from baseline at 15 minutes in cardiovascular (systolic and diastolic blood pressure) and selected laboratory parameters (serum glucose and potassium). These comparisons were done separately for the 180, 360, and 540 mcg doses (cumulative doses of 180, 540, and 1080 mcg). [M5, v 1.7, p 500039, 225]

11.4.1.7.3. Statistical methodology

The analyses were based on the per-protocol population, defined as the population of eligible subjects who completed the study. For the safety parameters of interest, t-tests derived from the mixed effects model with fixed effects for the treatment sequence, period, and treatment group, and random effect of subject within sequence. Analyses comparing the three albuterol formulations were done separately for post-dose 1, 2, and 3, with statistical significance declared at the 0.05 level. The mixed effect model was also used for comparisons between formulations of mean changes from baseline in the QT and QTc interval as well as comparisons of the PK parameters obtained post-dose three. A logarithmic transformation was used for the AUCs and C_{max} . Descriptive summaries were provided for all study data, and adverse event were summarized by body system and preferred COSTART term. [M5, v 1.7, p 500039, 62, 227-8]

11.4.1.7.4. Sample size considerations

Sample size was based on a previous study with a similar design using Proventil CFC as the reference product and verified in study IXL-106-1-105. A sample size of 15 subjects (five per sequence) was calculated to result in >80% power to detect differences between formulation groups of at least 20% of the reference product (Proventil HFA) at the 0.05 significance level. [M5, v 1.7, p 500039-40, 225-6]

11.4.2. Results

11.4.2.1. Description of Study Population

11.4.2.1.1. Disposition, Analysis populations, and Protocol violations

Sixteen subjects were randomized, and 15 subjects completed the study (per-protocol population). One subject withdrew from the study at the subject's request. There were no serious protocol violations. [M5, v 1.7, p 500042]

11.4.2.1.2. Demographics and baseline characteristics

The demographics by treatment sequence for the intent-to-treat (ITT) population are shown in Table 68. The baseline laboratory, blood pressure, and ECG parameters of interest for each treatment group in the per protocol population are shown in Table 69. There were no significant differences among treatment groups in these parameters at baseline.

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Table 68. IXR-107-1-105, Patient demographics, ITT pop

	All subjects	1) Alb-HFA-BOI 2) Alb-HFA-MDI 3) Proventil HFA	1) Alb-HFA-MDI 2) Proventil HFA 3) Alb-HFA-BOI	1) Proventil HFA 2) Alb-HFA-BOI 3) Alb-HFA-MDI
N	16	5	6	5
Gender:				
Males, N	9	2	5	2
Females, N	7	3	1	3
Race:				
White, N	9	3	4	2
Other, N	7	2	2	5
Age, years, mean (SD)	23.9 (3.9)	25.6 (6.0)	22.3 (3.4)	24.0 (0.7)
Height, cm, mean (SD)	174 (7.7)	176 (6.0)	177 (9.1)	169 (2.1)
Weight, Kg, mean (SD)	71 (9.8)	73 (5.9)	72 (13.1)	66 (9.0)

Source: M5, v 1.7, Table 11.2(1), p 500043

Table 69. IXR-107-1-105, Baseline laboratory, blood pressure, and ECG parameters by treatment group, PP pop

	Alb-HFA-MDI	Alb-HFA-BOI	Proventil HFA
Glucose, mg/dL	92.9 (1.5)	93.3 (1.7)	93.8 (1.4)
Potassium, mmol/L	4.2 (0.1)	4.1 (0.1)	4.1 (0.1)
Systolic BP, mmHg	113.4 (2.2)	114.6 (1.7)	114.1 (2.2)
Diastolic BP, mmHg	73.1 (1.5)	72.1 (1.7)	73.9 (1.2)
Heart rate, bpm	56.6 (2.2)	58.8 (2.2)	55.3 (2.1)
QT interval, msec	391.5 (7.6)	401.3 (12.3)	395.1 (5.6)
QTc interval, msec	377.7 (7.8)	394.7 (11.3)	377.3 (6.6)

Source: M5, v 1.7, Tables 11.2(2), 11.2(3), 11.2(4), p 500043-4

11.4.2.2. Safety Outcomes

This study was also reviewed by the Division's Clinical Pharmacology and Biopharmaceutics Reviewer, Dr. Sinja Kim. Please refer to her review for an in-depth analysis of the safety results.

11.4.2.2.1. Primary pharmacokinetic measures

Pharmacokinetic parameters are summarized in Table 70. Statistically significant differences are shown in **bold**. The concentration-time curves for all three products substantially overlap, suggesting that the PK parameters are comparable (Figure 13). There were no statistically significant differences between Albuterol-HFA-MDI and Proventil HFA for any parameters. Administration of Albuterol-HFA-BOI resulted in a slightly earlier T_{max} , lower C_{max} , and lower total exposure (AUC_{0-t} and AUC_8) than either Albuterol-HFA-MDI or Proventil HFA. The differences between Albuterol-HFA-BOI and Proventil HFA for AUC_{0-t} and AUC_8 were statistically significant. There were also statistically significant differences between Albuterol-HFA-MDI and Albuterol-HFA-BOI for AUC_{0-t} , and AUC_8 , and C_{max} . However, the 90% confidence intervals for the ratios between all evaluated PK parameters were within 80-120%, implying that these drug products are comparable and that any differences noted may not be clinically relevant.

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Table 70. IXR-107-1-105, PK parameters*, with comparisons, PP pop

PK Parameter	Alb-HFA-MDI 1	Alb-HFA-BOI 2	Proventil HFA 3	Comparison		p-value
AUC _{0-t} (pg/mL*hr)	26730.8	24570.2	26905.3	1 vs 3	0.99	0.8052
				2 vs 3	0.91	0.0018
				2 vs 1	0.92	0.0034
AUC ₈ (pg/mL*hr)	28425.8	25896.4	28395.0	1 vs 3	1.00	0.9675
				2 vs 3	0.91	0.0017
				2 vs 1	0.91	0.0016
C _{max} (pg/mL)	4072.9	3629.8	3870.2	1 vs 3	1.05	0.3001
				2 vs 3	0.94	0.1958
				2 vs 1	0.89	0.0247
T _{max} (hours)	1.85	1.44	1.67	1 vs 3	0.18	0.5122
				2 vs 3	-0.23	0.3919
				2 vs 1	-0.41	0.1368
T _{1/2} (hours)	6.2	5.8	5.9	1 vs 3	0.30	0.1345
				2 vs 3	-0.05	0.8105
				2 vs 1	-0.34	0.0856

* LS mean for each treatment

Source: M5, v 1.7, Adapted from Tables 11.4(2) and 11.4(3), p 500048-9

PLOT OF MEAN PLASMA CONCENTRATION (PG/ML) VS. TIME (HRS) BY TREATMENT GROUP
(LIMIT OF QUANTITATION (LOQ) = 2 PG/ML)

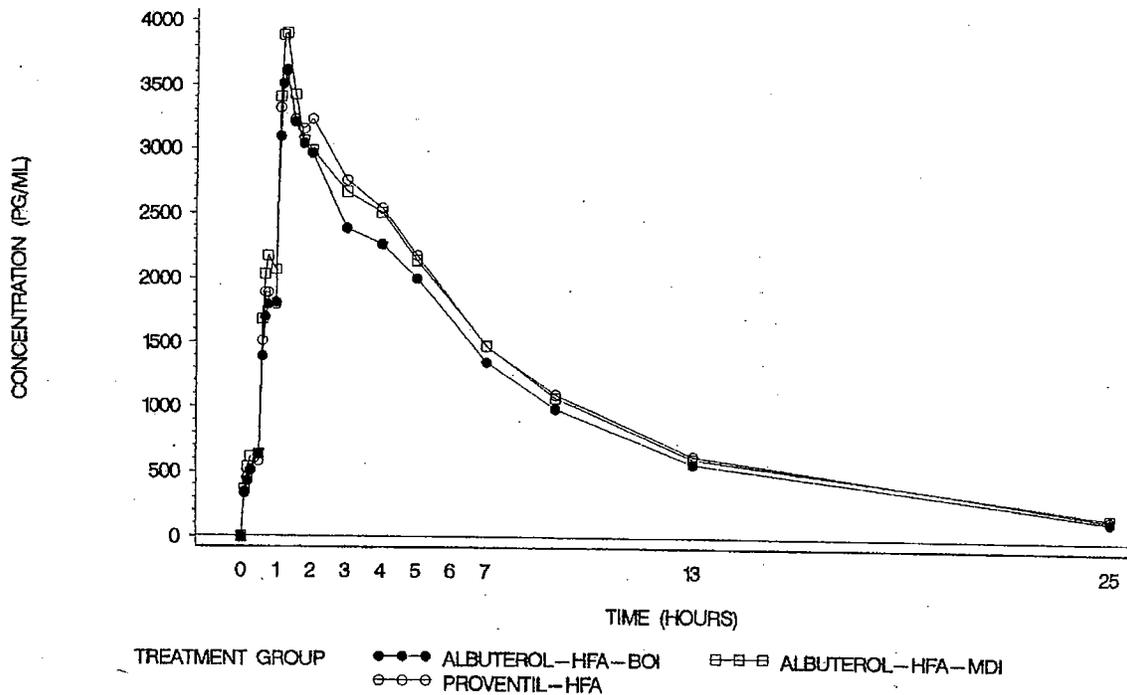


Figure 13. IXR-107-1-105, Mean plasma concentration-time curve by treatment, PP

Source: M5, v 1.7, Figure 14A.5.2, p 500133

11.4.2.2.2. Primary extrapulmonary pharmacodynamic/ pharmacologic measures

Extrapulmonary (pharmacologic) safety measures included systolic and diastolic blood pressure (Table 71 and Figure 14), serum glucose and potassium (Table 72 and Figure 15), and ECG-derived heart rate, QT, and QTc intervals (Table 73 and Figure 16). Except for less of an effect on ECG parameters with Albuterol HFA-BOI treatment, there were no statistically significant differences for these parameters among the three products. None of the differences that were noted were judged to be clinically relevant. All changes in pharmacodynamic parameters were expected based on the known physiologic effects of albuterol drug substance.

Mean changes in both systolic and diastolic BP were comparable among products. Systolic BP rose with treatment and returned to baseline or just below baseline, while diastolic BP initially decreased then rose to just above baseline then gradually lowered below baseline over the treatment period. The highest mean systolic BP increase was 4.5 to 7.5 mmHg at 15 minutes after the final (1080 mcg) dose, and the mean between-treatment differences in systolic BP were less than 8 mmHg at all time points. One subject (#9305) experienced an increase of 30 mmHg 15 minutes after the final dose of Albuterol HFA-MDI. The highest systolic BP was 146 mmHg. Ten subjects had a decrease in diastolic BP of 10 mmHg or more, and one subject (#314) experienced a decrease of 23 mmHg. The highest diastolic BP was 87 mmHg in two subjects (#306, three hours after third dose of Albuterol HFA-BOI; #314, two hours after third dose of Albuterol HFA-BOI). [M5, v 1.7, p 500050-2]

Mean changes in serum glucose and potassium were comparable among products. Serum glucose levels increased and serum potassium decreased with treatment, then both returned to baseline over several hours. The mean increase in serum glucose was 15.4 to 18.0 mg/dL at 30 minutes after the third dose. While there were differences in mean glucose that were statistically significant between Albuterol HFA-MDI and Proventil HFA at the timepoints of 15 minutes after the first and second doses, the actual differences were too small to be clinically relevant (3.0 mg/dL 15 minutes after the first dose, 3.8 mg/dL 15 minutes after the second dose). The largest individual change (#302) was an increase of 35 mg/dL from a baseline of 91 mg/dL 30 minutes after the third dose of Albuterol HFA-MDI. Two subjects had serum glucose levels of 129 mg/dL (#309, 15 minutes after the third dose of Albuterol HFA-MDI; #311, 30 minutes after the third dose of Albuterol HFA-BOI). The maximum decrease in serum potassium level was -0.57 to -0.79 mmol/L at 15-30 minutes after the third dose. The largest individual change (#313) was -1.6 mmol/L from a baseline of 4.6 mmol/L 30 minutes after the third dose of Albuterol HFA-MDI. Nine subjects had potassium levels of less than 3.4 mmol/L, with the lowest recorded value of 2.9 mmol/L (#311, baseline 2.9 mmol/L) at 15 and 30 minutes after the third dose of Albuterol HFA-MDI. [M5, v 1.7, p 500053-5]

Mean changes in heart rate, QT, and QTc intervals were comparable between Albuterol HFA and Proventil HFA, but less so between Albuterol HFA-BOI and the other products. However, these differences may have been explained by variances of baseline between treatments. In general, the heart rate and QTc interval increased, but the uncorrected QT interval decreased with treatment, then all returned to baseline. Both the mean QTc interval and mean heart rates peaked around 15-30 minutes after the final dose (1080 mcg). All

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three products produced peak heart rates of 70-72 bpm, but Albuterol-HFA-BOI started at a slightly higher baseline HR. Albuterol-HFA-BOI raised the heart rate less and had more negative effect on QT interval than the other two products, producing a very small net increase in QTc (+5.00) 15 minutes after the third (1080 mcg) dose. In contrast, the net increase in QTc for Albuterol-HFA and Proventil HFA peaked at 25.4 to 33.3 msec 15-30 minutes after the third dose.

Analysis of QTc outliers did not show any differences among groups. The highest QTc increase and the highest absolute QTc occurred after Proventil HFA administration. However, the maximum mean QTc (mean + SE) did not exceed 420 msec. Five subjects experienced post-dose QTc intervals that exceeded 440 msec with prolongation of QTc by >10 msec (Table 74), but there was no pattern to the elevations. [M5, v 1.7, p 500055-9]

In addition, two subjects had at least one elevated baseline QTc >440 msec (Table 75), but their absolute QTc after treatments did not differ substantially. Both instances of elevated baseline QTc intervals were prior to Albuterol-HFA-BOI administration but not prior to other treatment periods, potentially influencing the QTc results for the Albuterol-HFA-BOI treatment group while not affecting the ECG parameters for the Albuterol-HFA-MDI or Proventil HFA treatment groups. The other potential explainer of these findings is the slightly lower PK results for the Albuterol-HFA-BOI treatment group.

Table 71. IXR-107-1-105, Mean change from baseline* in BP, PP pop

PD Parameter	Dose	Timepoint	Alb-HFA-MDI	Alb-HFA-BOI	Proventil HFA	SE
Systolic BP (mmHg)	180 mcg	15 min	-0.60	-1.87	-0.20	2.08
		540 mcg	15 min	3.73	2.20	2.00
	1080 mcg	15 min	7.53	6.07	4.53	2.31
		30 min	4.67	2.80	3.93	2.03
		1 hour	2.73	-0.73	1.53	1.91
		2 hours	0.33	-1.07	-0.87	1.99
		3 hours	-0.93	-1.67	-1.60	2.52
		4 hours	-1.93	-1.40	-4.53	1.87
		24 hours	4.53	-0.73	0.27	2.16
		Diastolic BP (mmHg)	180 mcg	15 min	-0.80	0.00
540 mcg	15 min			-1.80	-2.27	-4.07
1080 mcg	15 min		-1.53	1.07	-3.00	1.81
	30 min		0.27	0.07	-1.20	1.78
	1 hour		-0.73	-0.67	-1.40	2.02
	2 hours		-1.80	0.13	-3.00	1.67
	3 hours		-2.33	-1.60	-2.60	1.75
	4 hours		-2.60	-2.13	-4.40	1.77
	24 hours		1.27	1.80	-0.53	1.56

* LS mean and SE for each treatment

Source: M5, v 1.7, Tables 11.5.1(1) and 11.5.1(2), p 500050-2

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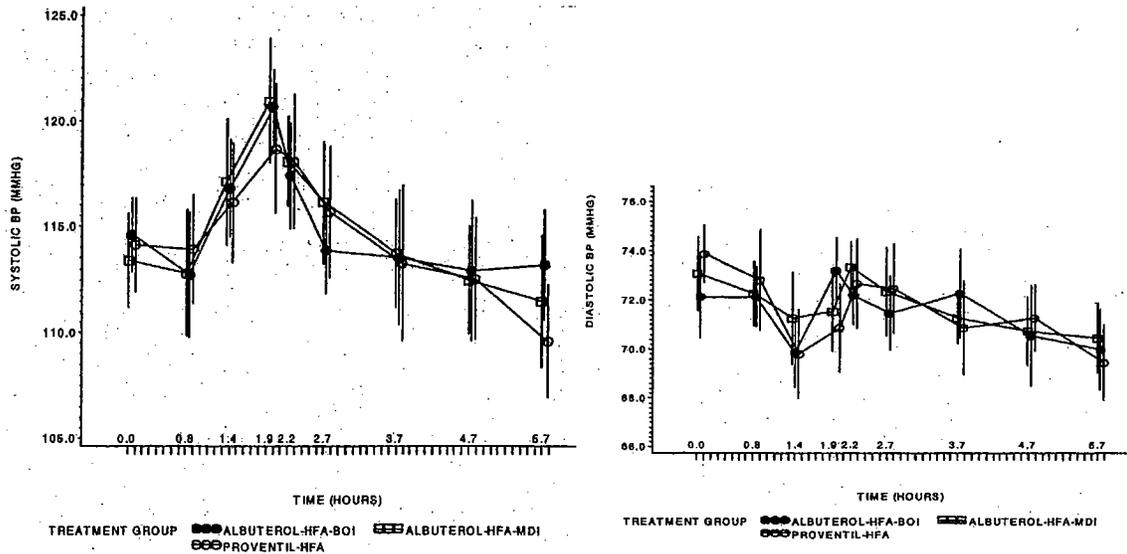


Figure 14. IXR-107-1-105, Systolic and diastolic blood pressure

Source: M5, v 1.7, Figures 11.5.1 (1) and 11.5.1 (2), p 500051-2

Table 72. IXR-107-1-105, Mean change from baseline* in serum glucose and potassium, PP pop

PD Parameter	Dose	Timepoint	Alb-HFA-MDI	Alb-HFA-BOI	Proventil HFA	SE
Glucose (mg/dL)	180 mcg	15 min	2.73	1.40	-0.27	1.09
		540 mcg	11.07	8.33	7.27	1.47
	1080 mcg	15 min	16.47	14.67	13.53	2.12
		30 min	18.00	16.07	15.40	2.04
		1 hour	11.52	10.20	12.73	1.88
		2 hours	6.93	3.87	5.60	1.69
		3 hours	0.87	-0.73	0.33	1.84
		4 hours	-0.73	-3.07	-2.00	1.56
Potassium (mmol/L)	180 mcg	15 min	-0.22	-0.25	-0.16	0.07
		540 mcg	-0.47	-0.45	-0.48	0.10
	1080 mcg	15 min	-0.72	-0.67	-0.57	0.07
		30 min	-0.79	-0.61	-0.62	0.08
		1 hour	-0.62	-0.57	-0.49	0.07
		2 hours	-0.40	-0.21	-0.29	0.09
		3 hours	-0.26	-0.13	-0.13	0.10
		4 hours	-0.19	-0.09	-0.15	0.08

* LS mean and SE for each treatment

Source: M5, v1.7, Tables 11.5.1(3) and 11.5.1(4), p 500053-4

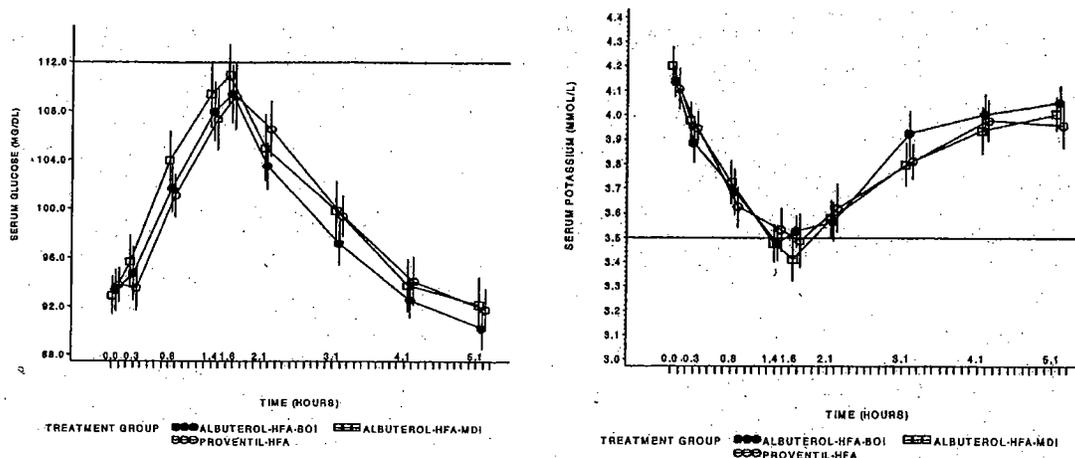


Figure 15. IXR-107-1-105, Serum glucose and potassium

Source: M5, v 1.7, Figures 11.5.1 (3) and 11.5.1 (4) , p 500054-5

Table 73. IXR-107-1-105, ECG parameters, Mean change from baseline * in HR, QT, and QTc, PP pop

PD Parameter	Dose	Timepoint	Alb-HFA-MDI	Alb-HFA-BOI	Proventil HFA	SE
Heart rate (bpm)	180 mcg 540 mcg 1080 mcg	15 min	3.46	2.23	3.18	1.44
		15 min	10.82	9.31	9.71	2.01
		15 min	15.71	11.62	15.19	2.15
		30 min	14.43	11.36	14.63	2.15
		1 hour	10.67	8.35	11.66	1.57
		2 hours	7.99	4.68	6.49	2.10
		3 hours	2.57	2.07	4.57	1.78
QT interval (msec)	180 mcg 540 mcg 1080 mcg	15 min	-6.20	-19.27	-9.27	5.89
		15 min	-17.07	-25.27	-18.93	6.88
		15 min	-22.53	-29.53	-18.73	6.71
		30 min	-20.70	-33.10	-13.10	8.12
		1 hour	-22.30	-22.70	-21.00	8.10
		2 hours	-10.20	-19.50	-11.90	5.89
		3 hours	-2.13	-19.00	-6.13	6.02
QTc interval (msec)	180 mcg 540 mcg 1080 mcg	15 min	5.40	-11.10	2.07	6.10
		15 min	17.60	3.87	12.53	7.83
		15 min	25.40	5.00	28.93	7.42
		30 min	23.87	1.67	33.33	9.48
		1 hour	11.07	4.27	15.93	10.0
		2 hours	15.73	-4.60	9.27	8.16
		3 hours	6.60	-11.90	8.53	7.20
4 hours	4.93	-6.07	6.00	6.63		

* LS mean and SE for each treatment

Source: M5, v 1.7, Tables 11.5.1(5), 11.5.1(6), and 11.5.1(7), p 500056-9

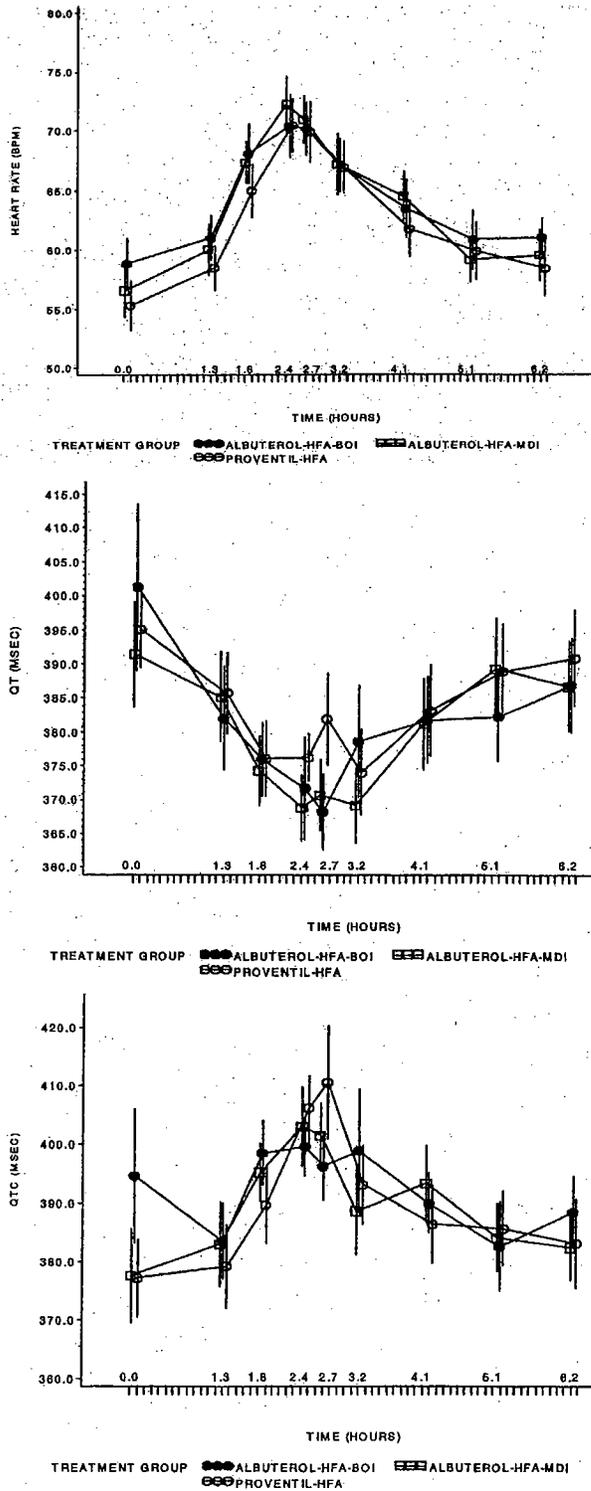


Figure 16. IXR-107-1-105, Heart rate, QT, and QTc

Source: M5, v 1.7, Figures 11.5.1 (5), 11.5.1 (6), and 11.5.1 (7), p 500056-9

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Table 74. IXR-107-1-105, Patients with QTc >440 msec & >10 msec increase from baseline

Patient	Treatment*	Baseline QTc	Elevated QTc	Time	Change from baseline
301	Proventil-HFA	395	442	30 min p dose 3	47
	Albuterol-HFA-BOI	411	441	3 hr p dose 3	30
	Albuterol-HFA-MDI	425			
304	Proventil-HFA	370	510	30 min p dose 3	140
	Albuterol-HFA-BOI	389			
	Albuterol-HFA-MDI	375			
308	Albuterol-HFA-BOI	368	520	1 hr p dose 3	152
	Albuterol-HFA-MDI	333			
	Proventil-HFA	344			
310	Albuterol-HFA-BOI	397			
	Albuterol-HFA-MDI	405	440	30 min p dose 3	35
	Proventil-HFA	400			
9305	Albuterol-HFA-MDI	377			
	Proventil-HFA	365	450	30 min p dose 3	85
	Albuterol-HFA-BOI	406			

*Treatments are listed by order administered

Source: M5, v 1.8, Listing 16.2.6.7, p 500635-47

Table 75. IXR-107-1-105, Patients with a baseline QTc >440 msec & highest QTc on treatment

Patient	Treatment*	Baseline QTc	QTc Max	Time	Change from baseline
309	Proventil-HFA	446	450	1 hr p dose 3	4
	Albuterol-HFA-BOI	505	461	15 min p dose 1	-44
	Albuterol-HFA-MDI	437	446	1 hr p dose 3	9
313	Albuterol-HFA-BOI	481	412	15 min p dose 3	-69
	Albuterol-HFA-MDI	352	409	15 min p dose 3	57
	Proventil HFA	342	409	30 min p dose 3	67

Source: M5, v 1.8, Listing 16.2.6.7, p 500635-47

11.4.2.2.3. Clinical adverse events

Eight of the 16 subjects (50%) reported at total of 21 adverse events, with three subjects accounting for 12 (57%) events. Eight events occurred after Albuterol-HFA-MDI administration, four after Albuterol-HFA-BOI, and nine after Proventil HFA. All adverse events were considered minor and resolved. Adverse events were comparable among treatments, although both Albuterol-HFA-MDI and Albuterol-HFA-BOI were associated with a slightly higher incidence of tremor than Proventil HFA. All except one event of rhinitis were considered by the investigator as possibly related to study medication. [M5, v 1.7, p 500064-5]

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IXR-107-1-105, Adverse events by treatment group

	Albuterol- HFA-MDI n = 16	Albuterol- HFA-BOI n = 15	Proventil HFA n = 15
Total AEs	8	9	4
Headache	1	1	1
Vasodilatation	1	1	0
Flatulence	0	1	0
Dizziness	0	1	0
Nervousness	1	1	1
Tremor	4	3	1
Dyspnea	1	0	0
Pharyngitis	0	0	1
Rhinitis	0	1	0

Source: M5, v 1.7, Table 12-2(1), p 500065

11.4.2.2.3.1. Serious adverse events, Deaths, and Discontinuations

There were no deaths, no serious adverse events, and no withdrawals due to adverse events. [M5, v 1.7, p 500065]

11.4.2.2.4. Vital signs and Physical examinations

Vital signs performed during the study are discussed above. Vital signs were comparable among treatment groups at a timepoint of 24 hours after treatments. [M5, v 1.7, p 500066]

11.4.2.2.5. Laboratory Adverse Events

There were no laboratory adverse events. Laboratory evaluations were performed at screening, and not repeated. [M5, v 1.7, p 500066]

11.4.2.2.6. Medical device incidents or malfunctions

There were no device incidents or malfunctions noted in the study report.

11.4.3. Discussion

This was a single-center, randomized, evaluator-blind, active-controlled, three-treatment, three-period, three-sequence, cumulative-dose crossover comparison safety study evaluating the extrapulmonary and pharmacokinetic profiles of Albuterol-HFA-MDI, Albuterol-HFA-BOI, and Proventil HFA in 15 healthy subjects. Eligible subjects were randomized to receive 2 + 4 + 6 actuations administered at 30 minutes intervals (180 + 360 + 540 for a total treatment dose of 1080 mcg) of Albuterol-HFA-MDI, Albuterol-HFA-BOI, or Proventil HFA, with a minimum of 6 days between treatments. Even though this was a single-dose study with no placebo control, the high-dose PK/PD safety data captured in the study makes it a 'pivotal' study. Therefore, the study was reviewed by both the Division's Pharmacology & Biopharmaceutics and Medical Reviewers, with the comparative data between Albuterol-HFA-MDI and Proventil HFA of primary interest.

Sixteen subjects were randomized, one withdrew, and 15 subjects completed the study (per protocol population). There were no significant differences among treatment groups in PK

parameters at baseline. With treatment, the concentration-time curves for all three products substantially overlapped, suggesting that the PK parameters are comparable. There were no statistically significant differences between Albuterol-HFA-MDI and Proventil HFA for any parameters. Administration of Albuterol-HFA-BOI resulted in a slightly earlier T_{max} , lower C_{max} , and lower total exposure (AUC_{0-t} and AUC_8) than either Albuterol-HFA-MDI or Proventil HFA. The differences between Albuterol-HFA-BOI and Proventil HFA for AUC_{0-t} and AUC_8 were statistically significant. There were also statistically significant differences between Albuterol-HFA-MDI and Albuterol-HFA-BOI for AUC_{0-t} , and AUC_8 , and C_{max} . However, the 90% confidence intervals for the ratios between all evaluated PK parameters were within 80-120%, implying that these drug products are comparable and that any differences noted may not be clinically relevant.

Pharmacologic parameters included systolic and diastolic blood pressure, serum glucose and potassium, and ECG parameters of heart rate, QT and QTc intervals. All changes in pharmacologic parameters were expected based on the known physiologic effects of albuterol drug substance. Mean changes in systolic and diastolic BP and serum glucose and potassium were comparable among products. Mean changes in heart rate, QT, and QTc intervals were comparable between Albuterol-HFA and Proventil HFA, but not between Albuterol-HFA-BOI and the other products. Albuterol-HFA-BOI raised the heart rate less and had more negative effect on QT interval than the other two products, producing a very small net increase in QTc (+5.00) 15 minutes after the third (1080 mcg) dose. In contrast, the net increase in QTc for Albuterol-HFA and Proventil HFA peaked at 25.4 to 33.3 msec 15-30 minutes after the third dose. Analysis of QTc outliers (QTc ≥ 440 msec with a >10 msec change) did not show any differences among groups. Adverse events were comparable among treatments, although both Albuterol-HFA-MDI and Albuterol-HFA-BOI were associated with a slightly higher incidence of tremor than Proventil HFA.

The smaller effect on QTc interval noted for Albuterol-HFA-BOI compared to either Albuterol-HFA-MDI or Proventil HFA may be explained by several observations. First, there was high variability of QTc results. Second, there was only one baseline ECG measurement prior to each treatment, making the baseline measurements far less reliable (generally at least three baseline measurements are recommended). In fact, two subjects had elevated baseline QTc intervals >440 msec prior to Albuterol-HFA-BOI administration but not prior to other treatment periods. These differences may have influenced the QTc results for the Albuterol-HFA-BOI treatment group, while not affecting the ECG parameters for the Albuterol-HFA-MDI or Proventil HFA treatment groups.

There were no device incidents or malfunctions noted in the study report.

11.4.4. Conclusions

In this cumulative-dose PK/PD crossover safety study, there were no significant differences among the three products noted for pharmacokinetic or pharmacologic parameters, except that Albuterol-HFA-BOI was associated with slightly less total exposure (PK) and produced less of an increase in QTc interval than the other products studied. None of the differences were judged to be clinically relevant. The 90% confidence intervals for the ratios between all evaluated PK parameters were within 80-120%, implying that all three drug products are

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comparable. No safety trends were noted that are not already known pharmacodynamic effects of albuterol.

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12. SYNOPSES OF SUPPORTING STUDIES

12.1. Study IXR-106-1-105: Cumulative-dose, single-dose PK/PD crossover study of Albuterol HFA MDI and BOI compared to Proventil HFA MDI

Protocol #: IXR-106-1-105
Title: Comparison of extrapulmonary effects and pharmacokinetics of HFA-propelled Albuterol Inhalation Aerosol (Norton Waterford) by breath-operated and press-and-breathe inhalers when compared to Proventil HFA (Key Pharmaceuticals)
Study Dates: September 8, 2001 to September 30, 2001
Sites:

Source: M2, v 1.3, p 500382-4

Study IXL-106-1-105 was deemed invalid because 56% (9/16) of subjects had positive (non-zero) pre-dose albuterol concentrations across all three treatment periods, and 31% (5/16) of subjects had positive (non-zero) pre-dose albuterol concentrations for two treatment periods [M5, v 1.7, p 500017]. For this reason, the study was repeated as study IXL-107-1-105, with a similar, if not identical, study design. Therefore the study design will not be repeated here. The major difference between the two studies was in study IXL-107-1-105 the dosing was separated by six days instead of the three days in this study. Please refer to study IXL-107-1-105 for further study design information.

12.2. Study IX-105-105: Safety and tolerability of Albuterol HFA MDI compared to Albuterol CFC-MDI in asthmatics, ages 7-18 years

Protocol #: IX-105-105
Title: A double-blind evaluation of the safety and tolerability of a new HFA-propelled salbutamol metered-dose inhaler compared with conventional CFC-propelled salbutamol metered-dose inhaler in children with asthma
Study Dates: June 8, 1998 to November 17, 1998
Sites: Eight hospitals/specialist clinic sites in Moscow (6) and St. Petersburg (2), Russia

Source: M2, v 1.3, p 200399-400

The primary objective of the study was: "to evaluate the safety and tolerability of salbutamol-MDI-HFA, a new product, compared with salbutamol-MDI-CFC, a currently marketed product."

This was a multiple-center, randomized, double-blind, active-controlled, non-placebo-controlled, comparison safety study evaluating the European version of Albuterol-HFA-MDI (Salbutamol-HFA-MDI) compared to the European version of Albuterol-CFC-MDI

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(Salbutamol-CFC-MDI) in 138 pediatric patients with mild-to-moderate asthma. Inclusion/exclusion criteria included: FEV₁ 50-80% predicted, minimum history of 3 months duration, stable for at least 4 weeks prior to screening, took beta₂ agonists for therapy, demonstrable reversible bronchoconstriction of $\geq 10\%$ from baseline 30 minutes after 200 mcg salbutamol-CFC-MDI, non-smoker, ages 7-18 years. After a 2-week run-in, eligible patients were randomized to receive 6 weeks of Salbutamol-HFA-MDI (batch RD-97-004) or Salbutamol-CFC-MDI (batch 970882). Clinic visits were at screening and at Weeks 0, 3, and 6. As a safety study, there was no primary efficacy variable. The study utilized PEFR measurements at each clinic visit as the primary variable for assessing the equivalent safety of Salbutamol-MDI-HFA and Salbutamol-CFC-MDI. Secondary safety variables included PEFR measurements taken away from the clinic following the first and last daily doses of study drug. Other safety evaluations included adverse events, pre- and post-study physical examinations, pre- and post-dosing vital signs (heart rate, blood pressure, Lead II ECG) at each clinic visit, and incidence of paradoxical bronchospasm at each clinic visit.

Despite the fact that as a safety study there was no declared primary efficacy variable, the study evaluated the maximum of the 5 post-dose morning PEFR measurements determined at the end of 6 weeks of treatment. Equivalence was declared if the 95% CIs for the ratio of treatments was contained completely within the 90-111% bounds. On this basis, the study purported to show equivalence between Salbutamol-CFC-MDI and Salbutamol-HFA-MDI. However, this reviewer judged that the information regarding therapeutic equivalence was of no particular value to the application, and to the review of Albuterol-HFA-MDI.

No serious adverse events occurred, and one patient on Salbutamol-HFA-MDI withdrew due to an AE of respiratory disorder and headache. Non treatment-emergent adverse events were reported by 4 (6%) and 8 (11%) of patients on HFA-MDI and CFC-MDI treatments, respectively. Such AEs that occurred in $\geq 3\%$ of patients in either treatment group were headache and respiratory disorder. Treatment-emergent adverse events were reported by 13 (19%) and 14 (20%) of patients on HFA-MDI and CFC-MDI treatments, respectively. Such AEs that occurred in $\geq 3\%$ of patients in either treatment group were influenza-like symptoms, headache, asthma, coughing, respiratory disorder, and rhinitis.

12.3. Study IX-100-105: Cumulative dose-response therapeutic equivalence 4-period crossover study of Albuterol HFA MDI compared to Albuterol CFC-MDI in asthmatics

Protocol #: IX-100-105
Title: A cumulative dose-response study to evaluate the therapeutic equivalence of a new salbutamol inhalation aerosol containing a replacement HFA-propellant in breath-operated and traditional metered-dose devices and existing salbutamol-CFC products
Study Dates: January 16, 1997 to May 19, 1997
Sites:

Source: M2, v 1.3, p 200386-8

The objective of the study was: "to evaluate the therapeutic equivalence of salbutamol-HFA and salbutamol-CFC inhalation aerosols."

This was a single-center, randomized, evaluator-blind, cumulative dose-response, 4-period crossover study evaluating Salbutamol-HFA-MDI (batch RD 96-004/2) and Salbutamol-HFA-BOI (batch RD 96-004) compared to Salbutamol-CFC-MDI (Salamof[®]-MDI, batch 6F102) and the reference Ventolin[®] CFC MDI (batch 10170994) in 25 patients with mild-to-moderate asthma. Inclusion/exclusion criteria included: FEV₁ 50-80% predicted, stable for at least 4 weeks prior to screening, took beta₂ agonists for therapy, demonstrable reversible bronchoconstriction of ≥15% from baseline 30 minutes after 200 mcg salbutamol-CFC-MDI, non-smoker x 6 months, age ≥18 years. Patients were randomized to receive each of the four treatments separated by 4-7 days. Each treatment consisted of an ascending cumulative dose of study drug consisting of 1, 2, 4, and 8 actuations at 30 minute intervals. Cumulative doses were 100m 300, 700, and 1500 mcg respectively.

The primary efficacy variable was peak FEV₁, and the secondary efficacy variable was PEF_R at each dose of treatment. Therapeutic equivalence was declared at a given dose level if a 90 or 95% Confidence Limit (CL), expressed as a ratio of test to reference, showed that the test compounds (Salbutamol-HFA-MDI and -BOI) were contained within ±30%, ±20%, ±10%, or ±5% of the reference compound (Salbutamol-CFC-MDI). Secondly, therapeutic equivalence was declared if similar ratios were found for the comparison of Ventolin (test) to Salbutamol-CFC-MDI (reference). For each treatment relative to pre-dose values, mean FEV₁ and PEF_R values increased with each dose increment. The applicant states that therapeutic equivalence was established for all comparisons, with all three test treatments within 5% of the reference treatment for both the primary and secondary outcome variables.

Safety variables included adverse events, serum glucose and potassium 5 minutes prior to and 25 minutes after each dose, pre- and post-dose vital signs and lead II ECG, pre- and post-treatment laboratory measurements, and pre- and post-study physical examinations. There were no adverse events of note. As expected, there were increases in mean heart rate and mean systolic and diastolic blood pressure. Mean serum potassium decreased and glucose values increased slightly with treatment. Unfortunately, this study did not contain PK data to allow review as a systemic exposure safety study.

12.4. Study SAMM 57: Postmarketing safety and tolerability of Albuterol HFA MDI in asthmatic patients in general practice

Protocol #: SAMM 57
 Title: A post-marketing study to evaluate the safety and tolerability of Salamol CFC-Free[™] (HFA-134a) metered dose inhaler in asthmatic patients in general practice
 Study Dates: May 9, 2000 to October 23, 2001

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Sites: 96 general practitioners in the United Kingdom

Source: M2, v 1.3, p 200407-9

The primary objective of the study was: "to compare the safety and tolerability in normal clinical use of a new chlorofluorocarbon-free (CFC-free) salbutamol metered dose inhaler (MDI; Salamol CFC-Free™) with salbutamol CFC MDI, in patients with asthma."

This was an open, observational cohort, comparative, parallel group, Phase IV, safety assessment study in adults and children ≥ 7 years with mild-to-moderate asthma. Patients currently on salbutamol CFC MDI were randomized in a 3:1 ratio to either salbutamol HFA MDI or salbutamol CFC MDI. There were no formal efficacy assessments. Safety assessments were made at baseline and at the end of three months of treatment, including asthma exacerbations, adverse events, hospital admissions and visits, withdrawals, and changes to concomitant medications.

Overall, this reviewer found very little safety information of value in this study. Three patients in the salbutamol HFA MDI treatment group, and none in the salbutamol CFC MDI treatment group were withdrawn due to an asthma exacerbation. Five patients experienced serious adverse events, none of which were judged to be related to study medication. The only hospitalization during the study was for one patient who was hospitalized for elective surgery. Two-hundred and twenty-six (30.6%) and ninety-six (35.4%) of patients experienced adverse events in the salbutamol HFA MDI and salbutamol CFC MDI groups, respectively. A broad spectrum of adverse events were reported, with no new AEs reported or rare AEs identified. Treatment-emergent, treatment related adverse events were reported for 25 (3.4%) and seven (2.6%) of patients in the salbutamol HFA MDI and salbutamol CFC MDI groups, respectively. The most common events felt to be related to study drugs were lower respiratory infections and asthma exacerbations, with asthma exacerbations reported in a higher proportion of patients on salbutamol HFA MDI treatment (28, 3.8%) than on salbutamol CFC MDI (5, 1.8%). Overall time to onset of exacerbations was similar between the groups.

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13. DETAILED LABELING CHANGES OR REVISED DRUG LABEL

While the label was reviewed for content and inclusion or exclusion of information, detailed labeling negotiations were not carried out during this review cycle. Please see the Conclusions and Recommendations section of this review for overall labeling comments.

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14. OTHER RELEVANT MATERIALS

No other relevant materials were submitted or reviewed.

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**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Peter Starke
11/21/03 05:33:43 PM
MEDICAL OFFICER
MO Review first NDA cycle

Badrul Chowdhury
11/24/03 09:13:03 AM
MEDICAL OFFICER
I concur

MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION: NDA #21-457, N-000	TRADE NAME: Volare™ HFA Inhalation Aerosol
APPLICANT/SPONSOR: Ivax Research, Inc. 4400 Biscayne Boulevard Miami, FL 33137	USAN NAME: Albuterol sulfate HFA MDI
	CATEGORY: Bronchodilator
	ROUTE: Orally inhaled
MEDICAL OFFICER: Peter Starke, MD	PDUFA DATE: 30 November 2003
TEAM LEADER: Eugene Sullivan, MD	60-DAY FILING DATE: 1 April 2003
	REVIEW DATE: 1 April 2003

SUBMISSIONS REVIEWED IN THIS DOCUMENT

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
30 January 2003	31 January 2003	N-000	

REVIEW SUMMARY:

This submission is a new NDA for Volare™ (albuterol sulfate) HFA Inhalation Aerosol (MDI) for the treatment and prevention of bronchospasm with reversible obstructive airway disease. The submission includes 3 pivotal studies and 5 supporting studies. The submission is a paper submission, with statistical files submitted electronically. The application contains a number of deficiencies, primarily related to multiple tables of contents within the document. Because of these deficiencies, it was difficult to find everything within the application to perform the Filing and Planning review process. Nevertheless, when the reviewer tried to find an item it appeared to be present. However, the table of contents pointing to that item was often incomplete.

OUTSTANDING ISSUES:

The applicant has made a commitment to address all deficiencies in the application.

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS: X FILEABLE NOT FILEABLE
OTHER ACTION:

1. General Information

This submission is a 505(b)(2) NDA application for Volare™ (albuterol sulfate) HFA Inhalation Aerosol (MDI) for the treatment and prevention of bronchospasm with reversible obstructive airway disease. [REDACTED] IVAX Research, Inc., of Miami, Florida is submitting the application, but Volare was developed and will be manufactured by Ivax Pharmaceuticals, Inc., located in Waterford, Ireland. Both companies are wholly owned subsidiaries of IVAX Corporation.

The main difference between the proposed drug product and the currently marketed (reference) product (Proventil HFA) is the absence of oleic acid in the proposed formulation. In addition, the ethanol concentration in the proposed formulation is [REDACTED], compared to approximately [REDACTED] for Proventil HFA.

2. Regulatory and Foreign Marketing History

2.1. Regulatory History

The IND for albuterol-HFA-MDI was originally submitted on March 3, 2000 as [REDACTED]

[REDACTED]

IND 60,549 was passed with Amendments to the Division of Pulmonary and Allergy Drug Products (DPADP) for evaluation in July of 2000. Baker Norton changed the drug product actuator design from the original drug product. [REDACTED]

[REDACTED] Baker Norton used an actuator with a smaller orifice size (0.22 mm) that is currently approved for use with this product in the United Kingdom. The change in actuator means an increase in respirable dose [REDACTED] to 50%, and an increase in respirable fraction [REDACTED] to 0.60.

The Baker Norton albuterol-HFA-MDI is marketed in Europe with two different actuators, one push-and-breathe (MDI), and the other breath-actuated (BOI). Both drug products contain the same canister and drug formulation of albuterol and HFA propellant. [REDACTED]

[REDACTED] Baker Norton previously studied their albuterol-HFA-MDI and albuterol-HFA-BOI in Europe and South Africa (but the canister size differed from the current formulation to allow for blinding of studies).

When the IND was passed with Amendments to the Division of Pulmonary and Allergy Drug Products (DPADP) in July of 2000, Baker Norton indicated that it would await the suggestions of this Division prior to initiation of any studies. A teleconference was held with

Baker Norton on August 15, 2000, to discuss the IND proposal. Results of that discussion are contained in the Medical Officer's Review of August 22, 2000. At that time the Division agreed that it was safe to proceed with the proposed IND study, but discussed with Baker Norton the need for a drug development plan

Baker Norton met with the Division on October 13, 2000 to discuss their drug development plan. At the time, deficiencies in the plan included limited long-term (12-week) data that could be used to support efficacy and safety. In particular, the 12-week European study used only the BOI product. In addition, the plan did not include information on device performance evaluations

The Division met with IVAX for a pre-NDA meeting on November 8 and 14, 2001. At that time, the Division stated that an ISS that was part of a common technical document was acceptable. However the proposed ISE was not acceptable. The Division stated submission of the study reports alone would not be acceptable, and that a full ISE should include all the pivotal studies with a full rationale and explanation of efficacy, including differences between the two drug products and differences with the comparator drug product. The nature of the proposed application was deemed "minimalistic," since it lacked a 12-week efficacy and safety study. Therefore, the Division strongly suggested that IVAX include the 12-week European safety and efficacy study as a pivotal study. IVAX was reminded about the Pediatric Rule. Feedback was given regarding the general formatting of the application.

2.2. Foreign Marketing History

Both the albuterol-HFA-MDI and albuterol-HFA-BOI product configurations were approved for marketing in the United Kingdom starting in April of 2000. A previous submission stated

that

However, a marketing history was not submitted with the application.

3. Items Required for Filing and Reviewer Comments

3.1. Reviewer Comments

This is a paper NDA submission comprising 102 volumes. The datasets are submitted electronically, and the statistical reviewer will comment on issues related to this electronic portion of the submission.

Indexes and references are very confusing. The document submitted in the Common Technical Document (CTD) format. The clinical sections are Modules 1 and 2, and part of Module 5. Each module has a volume number associated with that module. In addition, each volume has a volume number out of the total number of volumes submitted, starting with volume 1.000 up to volume 1.102. Each module contains a Table of Contents (TOC), and the first volume contains a Master TOC. However, there are a number of deficiencies, particularly in the TOCs within the application. Because of these deficiencies, it was difficult to find everything within the application to perform the Filing and Planning review process. Nevertheless, when the reviewer tried to find an item it appeared to be present. These issues were discussed with the applicant on several occasions during the course of the preparation of the Filing and Planning review, and the applicant has made a firm commitment in writing to address all the issues that have been raised. Some of the issues found include:

- No foreign marketing history present.
- Need statistical reviewer's guide, noting where sections may be located (paper and electronic)
- Jackets are not per guidance – Need to be re-jacketed
- Master TOC is not per guidance, refers to consecutive volume number instead of the Module Volume number - The Master TOC should have Module, Module Volume, and Tab divider identifier listed
- Module TOCs do not have pagination - Module TOCs should have Module, Module Volume, Tab divider identifier, (and page numbers) listed
- Tab dividers within a Module do not completely conform to the Module TOC, i.e. not every tab has a TOC - Each Tab needs a TOC for that section that includes the Module, Module Volume, Tab divider, and page
- CRF section has no sub-tabs, spans 7 volumes, 8 attachments, and has no location identifiers or pagination - Add appropriate section TOC with page numbers, sub-tabs
- Paper submission: Where are CRTs?
- Clinical did not receive all of Module 5
- Module 5 does not have the appropriate TOC - The TOC at the beginning of Module 5 is the CTD TOC, starting with Module 2. Module 5 requires a Module TOC, with pagination.

- References to Study BNP-301-4-167 appear in Section 5.3.4, Human PD Studies, and Section 5.3.5, Efficacy and Safety Studies. However, the study report is not in section 5.3.5, but is only in section 5.3.4, and section 5.3.5 has a blank section
- Section 5.2, Tabular listing of clinical studies, does not have a column for Location of Study Report completed
- If a Section spans multiple Volumes, request the Section TOC be repeated at the front of the Volume in order to aid the reviewer

3.2. Necessary Elements (21 CFR 314.50)

Please note that since the document is in a Common Technical Document (CTD) format, the format is different from those in a typical NDA application.

Table 1. Necessary Elements

Item	Type	Status
	Application Form (FDA 356h)	Present
	Formatting for Electronic Filing	NA
	Format	NA
	Table of Contents / Indexes	NA
	Labeling	NA
1	Index / Table of Contents	Not complete
2	Samples and Labeling	
	Proposed Package Insert	Present
	Proposed Label	Present
	Proposed Medication Guide	Present
3	Summary	
	Labeling	Present
	Marketing History	Not found
	Chemistry, Manufacturing, & Controls (CMC)	Present
	Nonclinical Pharmacology and Toxicology	Present
	Human Pharmacokinetics and Bioavailability	Present
	Clinical	Present
	Benefits vs Risks	Present
4	CMC	Present
	Environmental Impact statement	Present
5	Nonclinical Pharmacology and Toxicology	Present
6	Human Pharmacokinetics and Bioavailability	Present
8	Clinical	
8.5	Controlled studies	Present
8.7	Uncontrolled studies	Present
8.8	Integrated Summary of Effectiveness (subsets for age, gender, and race)	CTD summary present

Item	Type	Status
8.9	Integrated Summary of Safety Potential for Abuse	CTD summary present Not needed
8.11	Benefits vs Risks	Present
8.12	Statements of Good Clinical Practice: Statement that all clinical studies were conducted in accordance with IRB and Informed Consent procedures Auditing information	Present
9	Safety Updates	Not at this time
10	Statistics	Present
11	Case Report Tabulations	None found
12	Case Report Forms (for patients who died or did not complete studies)	Present
13	Patent Information	Present
14	Patent Certification	Present
16	Investigator Debarment Certification	Present
17	Field copy certification (if applicable)	Present
18	User Fee Cover Sheet	Present
19	Financial Disclosure	Present
20	Other Claimed Marketing Exclusivity Pediatric Use	No request present Deferral requested

3.3. Decision

This application is fileable.

4. Clinical Studies

This submission includes three pivotal efficacy and safety studies, and five supporting studies, shown in Table 2 and Table 3.

Table 2. Summary of Pivotal Studies

Study	Design / Population	Formulation	Dose (mcg)	N	Evaluations
BNP 301-4-167 Efficacy & Safety US (32)	6-week, multi-center, randomized, double-blind / double-dummy vs placebo, evaluator-blind vs Proventil HFA, placebo-controlled, parallel group multiple-dose, incorporating two 3-week life-of-device tests Mild-to-moderate asthmatics (FEV ₁ 50-85% predicted) with airway reversibility FEV ₁ ≥12% after 180 mcg albuterol, ≥12y	Placebo-HFA-BOI/MDI	QID	345	Efficacy: FEV ₁ AUEC ₀₋₆ on Days 1, 22, 43
		Albuterol-HFA-BOI	180 QID	58	
		Albuterol-HFA-MDI	180 QID	173	
		Proventil®-HFA	180 QID	58	
			180 QID	56	
BNP 301-4-105 Efficacy &	7-day, multi-center, randomized, evaluator-blind, placebo-controlled, 7-sequence, 7-period crossover, single-	Placebo-HFA-MDI	0	58	Efficacy: FEV ₁ AUEC ₀₋₆
		Albuterol-HFA-MDI	90		
		Albuterol-HFA-MDI	180		

Study	Design / Population	Formulation	Dose (mcg)	N	Evaluations
Safety US (5)	dose Moderate to severe asthmatics (FEV ₁ 50-75% predicted) with airway reversibility FEV ₁ ≥15% after 180 mcg albuterol, 18-50y	Albuterol-HFA-MDI Proventil [®] -HFA Proventil [®] -HFA Proventil [®] -HFA	270 90 180 270		
IX-101-105 Safety Russia (10) Poland (5)	12-week, multi-center, randomized, placebo-controlled, double-blind, double-dummy, parallel group multiple-dose Mild-to-moderate asthmatics (FEV ₁ 50-80% predicted) with airway reversibility FEV ₁ ≥15% after 200 mcg albuterol, 18-65y	Placebo-HFA-BOI Albuterol-HFA-BOI Albuterol-CFC-MDI	QID 200 QID 200 QID (200mcg ex-valve)	203 55 61 66	Efficacy: FEV ₁ AUEC ₀₋₆ at 0, 3, 6, 9, 12 weeks

Source: Module 5, volume 1.1B

Table 3. Summary of Supporting Studies

Study	Design / Population	Formulation	Dose (mcg)	N
IXR-107-1-105 PK/PD US	Single-center, randomized, evaluator-blind, active-controlled, 3-period crossover, cumulative-dose study in healthy subjects	Albuterol-HFA-MDI Albuterol-HFA-BOI Proventil [®] -HFA 2 + 4 + 6 actuations	180 + 360 + 540 = 1080 mcg	16
IXL-106-1-105 PD US	Single-center, randomized, evaluator-blind, active-controlled, 3-period crossover, cumulative-dose study in healthy subjects	Albuterol-HFA-MDI Albuterol-HFA-BOI Proventil [®] -HFA 2 + 4 + 6 actuations	180 + 360 + 540 = 1080 mcg	16
IX-100-105 PD South Africa	Single-center, randomized, evaluator-blind, active-controlled, 4-period crossover, cumulative-dose study in mild-to-moderate asthmatics 1 + 2 + 4 + 8 actuations	Albuterol-HFA-MDI Albuterol-HFA-BOI Ventolin [®] -CFC-MDI Albuterol-CFC-MDI	100 + 200 + 400 + 800 = 1600 mcg ex-valve	25
IX-105-105 Safety Russia (8)	6-week randomized, placebo-controlled, active-controlled study in mild-to-moderate asthmatics age 7-18 years	Placebo-HFA-BOI Albuterol-HFA-BOI Albuterol-CFC-MDI	QID 200 QID 200 QID	138
SAMM57 Safety UK	12-week open-label, general practice, observational cohort, 3:1 allocation ratio HFA:CFC in mild-to-moderate asthmatics age ≥ 7 years	Albuterol-HFA-MDI Albuterol-CFC-MDI	At the patient's existing prescribed dose	1009

Source:

5. DSI Review / Audit

Since this is a new drug product, it is suggested that a DSI audit be undertaken. Appropriate sites will be chosen for review.

6. Trade Name Review

Since this is a new product, a Trade Name review was suggested, and has been sent.

7. Timeline for Review

Table 4. Timeline for Review

Milestone	Target Date for Completion
Stamp Date	January 31, 2003
60-day Filing date	April 1, 2003
Draft Review	September 1, 2003
Wrap-up Meeting	October 1, 2003
PDUFA Date	November 30, 2003

8. Comments to Applicant

1. A marketing history was not found in your submission. Please submit a marketing history for your product.
2. Assure that the TOC for all pivotal and supporting studies are complete and include locations for all appendices, tables, etc.
3. Jackets are not per guidance - Re-jacket.
4. Master TOC is not per guidance, refers to consecutive volume number instead of the Module Volume number. The Master TOC should have Module, Module Volume, and Tab divider identifier listed.
5. Module TOCs do not have pagination. Module TOCs should have Module, Module Volume, Tab divider identifier, (and page numbers) listed.
6. Tab dividers within a Module do not completely conform to the Module TOC; i.e. not every tab has a TOC. Each Tab needs a TOC for that section that includes the Module, Module Volume, Tab divider, and page.
7. If a Section spans multiple Volumes, we request that the Section TOC be repeated at the front of the Volume in order to aid the reviewer.
8. Specific issues to be addressed:
 - a. Clinical did not receive all of Module 5.
 - b. CRF section has no sub-tabs, spans 7 volumes, 8 attachments, and has no location identifiers or pagination - Add appropriate section TOC with page numbers, sub-tabs.
 - c. Module 5 does not have the appropriate TOC - The TOC at the beginning of Module 5 is the CTD TOC, starting with Module 2. Module 5 requires a Module TOC, with pagination.
 - d. References to Study BNP-301-4-167 appear in Section 5.3.4, Human PD Studies, and Section 5.3.5, Efficacy and Safety Studies. However, the study report is not in section 5.3.5, but is only in section 5.3.4, and section 5.3.5 has a blank section.
 - e. Section 5.2, Tabular listing of clinical studies, does not have a column for Location of Study Report completed.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Peter Starke
4/1/03 05:07:21 PM
MEDICAL OFFICER

Eugene Sullivan
4/2/03 08:52:12 AM
MEDICAL OFFICER