PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE

DECEMBER 20, 2002

CLINICAL BRIEFING DOCUMENT

NDA 20-959

EBASTINE 10 AND 20 MG TABLETS FOR SAR AND PAR

APPLICANT:

ALMIRALL PRODESFARMA, SA

DIVISION DIRECTOR MEMORANDUM

Date: November 14, 2002

From: Badrul A. Chowdhury, MD, PhD
               Acting Director, Division of Pulmonary and Allergy Drug Products

To: Members, Pulmonary-Allergy Drugs Advisory Committee

Subject: Overview of the FDA background materials for NDA #20-959, application for
               ebastine10 mg and 20 mg tablets for the relief of symptoms associated with
               seasonal and perennial allergic rhinitis in patients 12 years of age and older

Thank you for your participation in the Pulmonary-Allergy Drugs Advisory Committee
(PADAC) meeting to he held on December 20, 2002. As members of the PADAC you
provide important expert scientific advice and recommendation to the US Food and Drug
Administration (the Agency) on the regulatory decision making process related to the
approval of a drug product for marketing in the United States. The upcoming meeting is to
discuss the NDA from Almirall Prodesfarma, seeking an approval for ebastine 10 mg and 20
mg tablets for the relief of symptoms associated with seasonal and perennial allergic rhinitis
(SAR and PAR) in patients 12 years of age and older.

Allergic rhinitis is a relatively non-serious but common disease. An estimated 10-30% of
adults in the United States have allergic rhinitis. Alhough the disease itself is not serious, it
has major consequence to the US population. Symptoms of allergic rhinitis include sneezing,
nasal itch, nasal discharge, nasal obstruction, and ocular symptoms such as redness, itch, and
tearing. Allergic rhinitis is classified as seasonal or perennial based on timing or periodicity
of symptoms. The drug classes currently approved in the United States for the treatment of
allergic rhinitis include antihistamines, nasal topical corticosteroids, decongestants, and
cromolyn. Oral antihistamines with or without a decongestant, and nasal topical
corticosteroids are considered as first line drugs for the relief of allergic rhinitis symptoms.
Newer antihistamines, such as cetirizine (Zyrtec), desloratadine (Clarinex), fexofenadine
(Allegra), and loratadine (Claritin) are usually the antihistamine of choice over the older
antihistamines. Many antihistamines are available without prescription in the Unites States.
Ebastine, if approved, would provide another choice among the newer antihistamines for the
relief of allergic rhinitis symptoms.

The newer antihistamines have advantages over the older antihistamines because they offer
reduced sedation and have relatively less anticholinergic effects. However, a rare but serious
and potentially fatal cardiac arrhythmia called *Torsades de Pointes* has been reported with
some of the newer antihistamines. Two such drugs, terfenadine (Seldane) and astemizole
(Hismanal), were marketed in the United States and subsequently withdrawn from the market
when it was realized that these drugs caused *Torsades de Pointes* in a some rare susceptible
patients. Terfenadine and astemizole are predominantly metabolized by the hepatic CYP3A4
enzymes. Concomitant use of terfenadine or astemizole with other drugs metabolized by the

hepatic CYP3A4 enzymes resulted in very high concentrations of the parent drugs and precipitated *Torsades de Pointes* in these patients. Other currently marketed newer antihistamines (cetirizine, desloratadine, fexofenadine, and loratadine) are believed to be free of this effect both due to intrinsic properties of the drugs and a general lack of important drug-drug interactions.

Torsades de Pointes is a rare cardiac arrhythmia that is usually not captured in the limited database of a typical clinical drug development program. However, prolongation of cardiac repolarization, identified on surface ECG as the prolongation of QTc interval, is a validated surrogate of a drug's risk in causing *Torsades de Pointes*.

Ebastine is metabolized by the CYP3A4 enzymes, and when a therapeutic dose of ebastine is given together with therapeutic doses of other drugs metabolized by the CYP3A4 enzymes (i.e., drugs that can inhibit CYP3A4), the plasma concentration of ebastine substantially increases and the QTc interval prolongs. The Applicant's contention is that the QTc prolonging effect of ebastine is small and not clinically relevant. The focus of this PADAC meeting is to discuss the clinical relevance of the pharmacokinetic interaction of ebastine with drugs metabolized by the CYP3A4 enzymes, and the resulting QTc effect, particularly in the context of the proposed indication.

The background materials included for the PADAC meeting include several documents prepared by the Agency, several published articles, and the Applicant's original and current proposed product labels of ebastine. The documents prepared by the Agency include a clinical briefing document, a summary of the spontaneous adverse event reporting on ebastine from some countries around the world where ebastine is currently marketed, and a pharmacometric analyses of a drug interaction cardiac safety study of ebastine (EBS 25). The published articles include review articles on allergic rhinitis, a review on the assessment of QT prolongation and proarrhythmia by non-antiarrhythmic drugs, and some original articles on the historical use of QT prolonging drugs with contraindicated drugs in clinical practice in the United States. The documents prepared by the Agency contain findings and opinions based on reviews of the Applicant's submissions. These represent preliminary findings, and do not represent the final position of the Agency. Indeed, an important piece of our thinking on this application will be the opinions and the input that we receive from you at this meeting. Subsequent sections of this memorandum summarize the regulatory history, efficacy data, safety data, and cardiac safety data of ebastine, and the key issues and questions for discussion at the PADAC meeting.

Regulatory history
Ebastine was first marketed in Spain in 1990. Subsequently ebastine has been approved for marketing in over 70 countries around the world, mostly at the 10 mg QD dose.

The original NDA submission seeking approval for marketing of ebastine 10 mg and 20 mg tablets in the United States was originally submitted to the Agency by Rhone-Poulenc Rorer (RPR) on March 31, 1998. A regulatory decision to not approve the application was taken by the Agency on March 23, 1999, because of concerns with cardiac safety of ebastine. The Agency concluded that ebastine at high doses prolonged the QTc interval (based on Bazett's

correction for heart rate), and that ebastine had significant pharmacokinetic interactions with drugs metabolized by CPP3A4 enzymes. The decision to not approve ebastine was taken by the Agency without the PADAC involvement.

The QTc data in the original submission was based on Bazett's method of correction for heart rate. The Applicant later questioned the validity of the Bazett's method because ebastine was noted to cause a slight increase in heart rate, and at higher heart rates, Bazett's formula tends to overcorrect the QTc interval. Subsequently, the Applicant reanalyzed the QT data using various other methods of QT correction, such as Fridericia's method, linear regression method, and an individual patient correction method called Malik's method (referred as QTcM). The Applicant contends that the QTcM is the most appropriate method for QT correction for heart rate. Over the years the Applicant also conducted additional efficacy studies and cardiac safety studies with ebastine. On the business side, Almirall Prodesfarma took over the US marketing rights to ebastine from RPR subsequent to the merger of RPR with another company to form Aventis.

In a May 10, 2001, meeting with the Agency, Almirall requested that the Agency discuss the application for ebastine at an Advisory Committee meeting. The Agency suggested that before an Advisory Committee meeting the Applicant should conduct at least one definitive study to characterize the cardiac safety of ebastine. Specifically, the Agency pointed out that all the cardiac safety studies of ebastine so far had been conducted in healthy young males. Post-pubertal, pre-menopausal women may be at higher risk of QT prolongation and its consequences than men. As a result of that discussion, the Applicant conducted an ebastine-ketoconazole drug interaction cardiac safety study (EBS 25) in healthy female volunteers. Study EBS 25 was designed by taking into consideration all previously conducted cardiac safety studies, and the Applicant's concerns regarding possible flaws in previous studies. Study EBS 25 was meant to be the pivotal cardiac safety study of ebastine. Almirall resubmitted the NDA to the Agency on August 20, 2002. The resubmission contains reanalysis of the previously conducted cardiac safety studies, and some new cardiac safety and comparative efficacy studies.

Allergic rhinitis efficacy and safety studies
The efficacy and safety of ebastine for the treatment of SAR and PAR was assessed in two pivotal SAR studies (EBA 124, and EBA 132), three pivotal PAR studies (EBA 109, EBA 110, and CR 2714), one onset of action SAR study (EBA 133), and six comparative SAR efficacy studies. Four of the comparative SAR efficacy studies (CM 030, CM 031, EBA 402, and EBS 28) were conducted in the United States and used fixed doses of ebastine. The primary goal of the pivotal SAR and PAR studies was to show superiority of ebastine over placebo. The primary goal of the comparative studies was to show an efficacy advantage (and therefore presumably a public health benefit) of ebastine over loratadine because of the potential cardiac safety burden of ebastine. Loratadine is one of the many antihistamines available in the United States for treating allergic rhinitis.

The duration of treatment in the pivotal SAR and PAR studies was three weeks, except for study CR 2714 where the duration of treatment was 12 weeks. The duration of treatment for the four US comparative efficacy studies was four weeks. A total of 685 patients were

enrolled in the pivotal SAR studies, 709 patients were enrolled in the pivotal PAR studies, and 2594 patients were enrolled in the US comparative efficacy studies. Efficacy in these studies was assessed by patient scoring of various rhinitis symptoms, such as nasal discharge, nasal stuffiness, sneezing, itchy nose, and itchy and watery eyes. In the pivotal SAR and PAR studies ebastine at a dose of 20 mg QD was statistically superior to placebo in relieving rhinitis symptoms. In some studies, ebastine 10 mg QD also was statistically superior to placebo. In the comparative SAR studies, both ebastine and loratadine were statistically superior to placebo, ebastine 20 mg QD tended to be superior to loratadine 10 mg QD, and ebastine 10 mg QD tended to be similar to loratadine 10 mg QD in relieving rhinitis symptoms.

The safety of ebastine in these pivotal efficacy studies and in other supporting efficacy studies was assessed by recording of adverse events, clinical laboratory measures, physical examinations, and ECG recordings. Ebastine was generally well tolerated in these studies. Notable adverse events reported by patients that were more common in ebastine treated arms compared to placebo arms were somnolence (3.2% in ebastine 10 mg QD and ebastine 20 mg QD, and 2.2% in placebo arms) and dry mouth (2.6% in ebastine 20 mg QD, 4.8% in ebastine 10 mg QD, and 2.3% in placebo arms).

High dose and drug interaction cardiac safety studies
The cardiac safety of ebastine was evaluated in three high dose studies (EBA 126, EBA 136, and EBS 21), and seven pharmacokinetic-pharmacodynamic drug interaction studies (EBA 130, EBA 138, EBA 127, EBA 137, EBA 148, EBS 24, and EBS 25). The Applicant also submitted one drug interaction study (EBA 145) to assess the QTc effect of loratadine given with ketoconazole. In two drug interaction studies, interaction of ebastine and erythromycin was examined (EBA 130, and EBA 138). In five drug interaction studies, interaction of ebastine and ketoconazole was examined (EBA 127, EBA 137, EBA 148, EBS 24, and EBS 25). Three of the studies used single doses of ebastine (EBS 21, EBA 127, and EBA 130) and therefore were not informative. Study EBS 24 was also not informative because this study was conducted on only 6 subjects and had an unusual crossover design. Some of the larger multiple dose cardiac safety studies are briefly discussed below.

Study EBA 126 assessed the QTc effects of ebastine 10, 20, 40, and 80 mg QD for 8 days compared to placebo in a parallel design (n=77). This study was conducted in two periods. In the first period ebastine 10, 20, and 40 mg QD was assessed, and in the second period ebastine 80 mg QD was assessed. All doses of ebastine appeared to cause prolongation of mean QTc (corrected by Bazett's and Fridericia's methods) by 5-13 msec over baseline on days 6, 7, and 8, and for the 10, 20, and 40 mg QD doses the QTc effect appeared to be dose proportional.

Study EBA 136 assessed the QTc effects of ebastine 60 mg and 100 mg QD for 7 days, compared to placebo and terfenadine 360 mg/day (3 times the therapeutic dose) in a crossover design (n=32). On Bazett's corrected QTc, a dose dependent prolongation of mean QTc was seen (mean change over baseline was 1.4 msec for placebo, 3.7 msec for ebastine 60 mg, and 10.3 msec for ebastine 100 mg). On Fridericia's or linear regression correction of QTc, ebastine did not appear to prolong the mean QTc.

Study EBA 138 assessed the pharmacokinetic and QTc effects of ebastine 20 mg QD and erythromycin 800 mg TID administered together for 10 days in a crossover design (n=30). Co-administration of ebastine and erythromycin increased the ebastine Cmax by about 2-fold and ebastine AUC by about 3-fold, and prolonged the mean QTc (corrected by Bazett's, Fridericia's, linear regression, or Malik's methods) by 5-11 msec over baseline compared to ebastine alone or erythromycin alone.

Study EBA 137 assessed the pharmacokinetic and QTc effects of ebastine 20 mg QD and ketoconazole 400 mg QD administered together in a parallel group design (n=55). Ebastine was given for 13 days and ketoconazole was given for the last 8 days of ebastine treatment. Co-administration of ebastine and ketoconazole increased the ebastine Cmax by about 16-fold and ebastine AUC by about 42-fold, and prolonged the mean QTc (corrected by Bazett's, Fridericia's, linear regression, or Malik's methods) by 6-10 msec compared to co-administration of placebo and ketoconazole.

Study EBA 148 assessed the pharmacokinetic and QTc effects of ebastine 20 mg QD or loratadine 10 mg QD and ketoconazole 400 mg QD administered together in a 2-period cross-over design (n=43). Within each period the design was similar to study 137. Ebastine or loratadine was given for 13 days and ketoconazole was given for the last 8 days of ebastine treatment. Co-administration of ebastine and ketoconazole increased the ebastine Cmax by about 6-fold and ebastine AUC by about 16-fold, and prolonged the mean QTc (corrected by Bazett's, Fridericia's, linear regression, or Malik's) by 4-5 msec compared to co-administration of loratadine and ketoconazole.

Study EBS 25 assessed the pharmacokinetic and QTc effects of ebastine 20 mg QD and ketoconazole 400 mg QD administered together in a 2-period crossover design (n=24). Ebastine or placebo was given for 13 days and ketoconazole was given for the last 8 days of ebastine or placebo treatment. This was the pivotal cardiac safety study and the only cardiac safety study conducted in females. Co-administration of ebastine and ketoconazole increased the ebastine Cmax by about 16-fold and ebastine AUC by about 44-fold, and prolonged the mean QTc (corrected by Malik's method) by 10.7 msec compared to co-administration of placebo and ketoconazole. By Bazett's corrected QTc the mean prolongation was by 16.9 msec.

In most of the cardiac safety studies the number of subjects who were QTc outliers (identified by pre-defined QTc criteria) were greater in the ebastine arms compared to the placebo arms. Several subjects had QTc prolongation of 30 msecs or more over baseline. In study EBS 25, eight out of 23 subjects had one or more ECGs with 30 msec or more prolongation of QTcM over baseline on days 12 and 13 when ebastine was administered with ketoconazole, but not when placebo was administered with ketoconazole.

Key issues and questions
The purpose of the PADAC meeting is to discuss the adequacy of the efficacy and safety data submitted originally by RPR and now by Almirall to support the approval of ebastine for allergic rhinitis in the United States. The main issues for the PADAC to consider are the

safety and overall risk-benefit assessment of ebastine for the treatment of allergic rhinitis symptoms. While all clinical data submitted by the Applicant is open for discussion, we are asking for a detailed deliberation on the cardiac safety of ebastine, particularly because the Applicant contends that the QTc effects of ebastine are small and clinically not relevant. The Applicant acknowledges that ebastine when co-administered with drugs metabolized by CYP3A4 prolongs the QTc slightly, which the Applicant concludes is not clinically relevant. The Applicant also contends that with higher systemic exposure of ebastine, the QTc does not increase further but plateaus after a slight prolongation.

The proposed product label submitted with the original NDA for ebastine contained the QTc (corrected by Bazett's method) results of one high dose cardiac safety study (EBA 136) and two drug interaction cardiac safety studies (EBA 137, EBA 138), and had precautionary statements on the use of ebastine in certain patients, such as long QT syndrome, hypokalemia, treatment with any drug known to produce increase in QT or inhibit CYP3A4. The Applicant now contends that ebastine has no clinically relevant QTc effects. The currently proposed product label refers to three drug interaction cardiac safety studies (EBA 137, EBA 138, and EBS 25) but concludes that the changes in the QTc interval seen in these studies were not clinically relevant. The precautionary statements on the use of ebastine by certain high risk patients have also been removed from the label.

At the PADAC meeting, the Applicant will present an overview of the efficacy and safety data on ebastine, followed by the Agency's presentation. The Agency's presentation will include the safety and efficacy data of ebastine, the spontaneous adverse event reporting on ebastine from some countries around the world, and published historical data on the use QT prolonging drugs with contraindicated drugs in clinical practice in the United States. Since a large part of the PADAC discussion is expected to cover the cardiac safety of ebastine, the Agency will highlight the salient pharmacokinetic and QTc effects of ebastine. The spontaneous adverse event reporting on ebastine is limited and not particularly revealing. Note, however, that experience to date in the Agency suggest that adding labeling precautions against the use of QTc prolonging drugs with contraindicated drugs (e.g., terfenadine and erythromycin) have not been particularly successful in extinguishing these practices in the United States.

Please keep in mind the following questions that will be discussed and deliberated upon following the presentations and discussion.

1. Do the cardiac safety data adequately characterize the QTc effects of ebastine?
    a) If not, what further cardiac safety data should be obtained?
    b) If ebastine were to be approved for marketing in the United States, which of the cardiac safety data should be obtained prior to approval?

2. Is the safety database (other than cardiac safety) for ebastine for the treatment of seasonal and perennial allergic rhinitis adequate?
    a) If not, what further safety data should be obtained?
    b) If ebastine were to be approved for marketing in the Unites States, which of the safety data should be obtained prior to approval?

3. Does the risk-benefit assessment support the approval of ebastine for the treatment of seasonal and perennial allergic rhinitis in the United States?
    a) If not, what further data can be obtained to support the approval?
    b) If yes, how should the label reflect the potential safety concerns?

Please note that the questions above are preliminary and may change prior to the meeting. Final questions will be available at the meeting. We intend that all the questions above should generate a binary yes or no answer, and will be voted on by the voting members of the Committee.

We look forward to a very interesting meeting and again thank you for your time and commitment in this important public health service.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

they do not wish to place any statements regarding drug-drug interaction QTc prolongation warnings in the product label. The PADAC is asked to evaluate the information as it relates to the risk/benefit ratio in light of the known difficulties in effectively labeling drugs for serious, life-threatening adverse events, when the drug is intended to be prescribed for very common, uncomfortable, but relatively minor, non-life-threatening diseases such as allergic rhinitis.

1.2. Brief Overview of Clinical Program and this Briefing Document

The original NDA application, dated March 31, 1998, contained 42 studies, listed in Table 1. Of these, there were five efficacy studies in SAR and PAR patients that were considered pivotal. The application contained one onset-of-action study, three open-label safety studies, fourteen pharmacokinetic studies, eight pharmacodynamic studies, seven cardiac safety studies (two high-dose and five drug-interaction), and a number of other supporting studies.

The complete response submission, dated August 20, 2002, contained 21 studies that were either ongoing at the time of the original submission or were conducted after the original submission. These studies are outlined in Table 2. These include: six SAR studies, one environmental exposure unit (EEU) onset-of-action SAR study, seven non-cardiac clinical pharmacology studies, four cardiac safety studies (one high-dose and three drug-interaction), and two marketing support studies. The six comparative SAR efficacy studies submitted as part of the complete response were designed to compare ebastine against loratadine to show an efficacy advantage (and therefore a public health benefit) because of the safety burden of QT prolongation. The complete response submission also included a re-analysis of the QTc data from the newly submitted and previously submitted cardiac safety studies. However, the key cardiac safety study submitted was study M/EBS/25.

Study M/EBS/25 was the "pivotal" drug-interaction cardiac safety study. This study was the most carefully performed cardiac safety study, and was designed with FDA input. The study was designed to take into account the applicant's concerns regarding possible flaws in previous studies, and to address the cardiotoxicity concerns stated by the FDA when ebastine was not approved. To take into account the individual variability of QT interval and the effect of heart rate changes on corrected QT, the applicant used the QTcM method of QTc calculation. To obtain individual correction factors, a very large number of ECGs were done both at baseline and throughout the study. Unlike most of the other studies, this was a randomized, double-blind, 2-way crossover design comparing ebastine versus placebo. It was the only drug-interaction cardiac safety study in female subjects. Pharmacokinetic and pharmacokinetic/pharmacodynamic (QTcM) analyses were carried out by both the sponsor and the FDA. The analyses yielded information with more breath and precision than the other studies, and confirmed findings of prolongation of QTc and more outliers with prolonged QTc than were seen previous studies. Therefore, it is suggested that the reader pay particular attention to the results of study M/EBS/25 (review starts on page 213).

For the sake of brevity, not all of the studies that were submitted are reviewed in this briefing document. Brief outlines of the Chemistry, Manufacturing and Controls, Nonclinical Pharmacology and Toxicology, and Human Pharmacokinetics and

2. CLINICAL BACKGROUND

2.1. Introduction, Trade Name, Proposed Indication and Dosage

This NDA was submitted in support of ebastine 10 mg and 20 mg tablets with the proposed indication for the relief of nasal and non-nasal symptoms associated with seasonal and perennial allergic rhinitis in adults and children 12 years of age and older. The proposed trade name for this drug product is KESTINE. The proposed dosage is one 20 mg tablet once daily, although the proposed label also states that "in some patients, 10 mg once daily may be sufficient. In patients with severe hepatic insufficiency, a dosage of 10 mg KESTINE is recommended."

Ebastine is a synthetic second-generation H_1 receptor antagonist. The response to antigen in allergic rhinitis is characterized by an early phase response caused by IgE mediated degranulation of mast cells and basophils with release of histamine, followed by a late phase inflammatory response mediated by various cells and inflammatory mediators. Most of the symptoms of allergic rhinitis, namely sneezing, rhinorrhea, lacrimation, and itching of the eyes, nose, and throat are largely mediated by histamine through the H_1 receptor. While the first-generation antihistamines have good efficacy, they produce adverse effects related to anticholinergic activity and sedation. The second-generation antihistamines have the advantage of being designed to have reduced anticholinergic and sedative effects. However, some rare but serious cardiotoxic adverse events have been reported with some of the second-generation antihistamines. Since this is of significant concern, a background is necessary to sufficiently evaluate the risk-benefit ratio of ebastine and the concerns regarding cardiotoxicity. Therefore, cardiac safety data are the major focus of this briefing document.

2.2. Important Milestones in Product Development

2.2.1. Pertinent Regulatory History

NDA 20-959 for Ebastine Tablets 10 mg and 20 mg was originally submitted to the Division of Pulmonary Drug Products by Rhone-Poulenc Rorer (RPR) on March 31, 1998. A regulatory action to not approve the application ('not approvable' action) was taken on the NDA on March 23, 1999 because of concerns with the cardiac safety of ebastine. The not approvable letter also contained a list of Chemistry, Manufacturing, and Controls (CMC) and Clinical Pharmacology and Biopharmaceutics (CPB) deficiencies. Subsequently, RPR merged into Aventis Pharmaceutical Products Inc., which turned the rights to ebastine, including NDA 20-959, to Almirall Prodesfarma, SA in May of 2000.

Specifically ebastine at high doses was noted by FDA review to prolong the QT interval, and ebastine had interactions with drugs metabolized by CYP3A4 enzymes such as ketoconazole and erythromycin. When ebastine was given along with ketoconazole or erythromycin, ebastine levels in plasma were substantially increased, and the QT interval was prolonged. The applicant's initial submission of cardiac safety data was based on correction of QT values by a formula called the Bazett's formula (QTcB). After the NDA was not approved, the applicant questioned the validity of that correction method because

ebastine was noted to cause some increase in heart rate, and the most appropriate methodology for correcting QT for changes in heart rate is open to interpretation. Subsequently the applicant submitted re-analyses of cardiac safety data using alternate methods of QT correction, such as Fridericia's method (QTcF), QTc by linear regression, Framingham correction, and an individual patient correction method called Malik's correction (QTcM). The applicant also conducted more cardiac safety studies, and comparative efficacy studies. The Agency reviewed all subsequent submissions and had meetings with the applicant to discuss these issues on August 10, 1999, January 18, 2000, and May 10, 2001. The applicant now holds the position that there is no cardiac effect of ebastine, or very small if at all.

In the May 10, 2001, meeting the applicant specifically requested that the Agency discuss the application in an Advisory Committee meeting. The Agency pointed out that such a meeting would not be fruitful at that time because the subsequent re-analyses and new data did not change the FDA's viewpoint and the conclusion reached in the original NDA review. The Agency suggested that the applicant consider conducting a well-designed definitive study or studies to better characterize the cardiac safety of ebastine before proposing an Advisory Committee discussion. Specifically the Agency pointed out that the cardiac safety of ebastine in women had not been studied at all. In follow up to the May 10, 2001, meeting the applicant proposed a new cardiac safety study (M/EBS/25) in a submission dated July 3, 2001.

The new cardiac safety study (M/EBS/25, review starts on page 213) was submitted on August 20, 2002 as part of a Class II NDA resubmission (complete response) to the 'not approvable' action. In addition to the single major deficiency in the risk-benefit profile, the 'not approvable' letter also outlined many CMC and CPB deficiencies to be addressed prior to approval. The complete response contains responses to the CMC and CPB deficiencies, and the applicant states that all deficiencies have been addressed. The applicant also performed and submitted a re-analysis of data from a number of the previous cardiac safety studies. They claim that the data demonstrate that, at therapeutic doses, ebastine alone does not prolong the QT interval, and that modest increases in individual QTc interval prolongation is seen at very high doses or with CYP3A4 inhibitor co-administration, and the QT prolongation plateaus near 12ms. In addition, they claim an advantage over other available treatments, as demonstrated by four new comparative efficacy studies against loratadine submitted with this application. (v 2.1, Cover letter)

2.2.2. Proposed Labeling (Package Insert)

In the original NDA, Rhone-Poulenc Rorer's cardiac consultants gave the following opinion regarding labeling of ebastine for cardiac safety:

> "due to interaction... ...precautionary statement be included in the labeling regarding use in... ...long QT syndrome, hypokalemia, treatment with any drug known to produce an increase in QTc or inhibit CYP450-3A4 cytochrome such as azole antifungals and macrolide antibiotics." (v 21, p 272)

The original product label submitted by RPR to the NDA only partially addressed this safety issue. The proposed product label contained several paragraphs that discussed the increased

exposure and QTc changes seen in high dose and drug-interaction cardiac safety studies in the **CLINCIAL PHARMACOLOGY** section. The proposed label also contained the drug-drug interaction **PRECAUTION** that "The interactions of ebastine with ketoconazole and ebastine with erythromycin have been evaluated." However, the proposed product label contained a statement that "No clinically relevant or statistically significant cardiac effects, including prolongation, have been observed at recommended doses of ebastine when administered alone."

The proposed product label submitted by Almirall with the complete response differs significantly. The drug-drug interaction **PRECAUTION** has been removed. The **OVERDOSAGE** section contains information from the single dose-high dose study M/EBS/21), and only the QTcF results are included even though both QTcB and QTcF were co-primary endpoints in this study. The **CLINCIAL PHARMACOLOGY** section contains a statement that drug-drug interactions having been studied, with the conclusion that there is no clinically relevant changes in the safety profile of ebastine, and no clinically significant effect on QTc prolongation. The effects on QT are summarized by the statement that:

> *"Effects on QT:* The cardiac effects of ebastine have been extensively investigated in clinical studies. No clinically relevant or statistically significant cardiac effects, including QT and QTc corrected by heart rate interval prolongation, have been observed at recommended doses of ebastine."

For reference, the proposed product label included with the original NDA and the complete response are appended to this document.

2.2.3. Foreign Marketing History

Ebastine was first marketed in Spain in 1990. Since 1995, ebastine has been approved for marketing in 78 countries, mostly as the 10 mg tablets. Currently ebastine is marketed in Spain by Almirall Prodesfarma, and by licensees or Almirall Prodesfarma affiliates. Worldwide registration at the time of the NDA submission is shown in Table 3, and worldwide registration at the time of the submission of a complete response to the 'not approvable' letter (with an update as of October 22, 2002) is shown in Table 4. (v 2.1, p 83-6; Submission of October 22, 2002, v 1, p 1-7)

At the time of the original NDA submission, only 10 mg tablets were commercially available; a 20 mg dose would be administered by taking 2 tablets of 10 mg each, and a 5 mg dose would be administered by taking one half of a 10 mg tablet (v 1, p 172-174; 6/19/98 correspondence). Currently 5 mg, 10 mg and 20 mg are commercially available. In addition, a syrup (1 mg/ml) and a combination product with pseudoephedrine are also commercially available.

Ebastine 10 mg is approved in many countries in Europe, South America, Africa, the Pacific Rim countries, Japan, South Korea, and Pakistan (for a complete list, see Table 4). Several of these countries allow OTC status for the 10 mg tablets, including Sweden, Finland, and Russia. (v 2.1, p 083-6; Submission of 10/22/02, v 1, p 1-7)

Ebastine 20 mg tablets are approved in 8 countries: Argentina, Chile, the Czech Republic, Estonia, Hungary, Mexico, Slovakia, and Spain. Applications for marketing approval of the 20 mg tablets have been filed in 15 countries, including Belgium, Denmark, Germany,

Greece, Iceland, Ireland, Italy, Sweden, Luxembourg, Netherlands, Poland, Portugal, United Kingdom, Venezuela, and Norway. This list includes the European Union countries, where an application was submitted in early 2002. Although Germany approved marketing of ebastine, the label has an extensive list of contraindications that lists drugs metabolized by the cytochrome P450 3A4 enzyme, cardiac arrhythmia, electrolyte abnormalities, and other diseases or concomitant drugs that can lead to electrolyte changes (German regulatory agency letter dated December 3, 1997).

Applications for marketing approval of ebastine syrup (1 mg/ml) are approved in 24 countries, and currently pending in the Russian Federation, Turkey, and the United Arab Emirates. The combination of ebastine and pseudoephedrine are marketed in 10 countries, with applications for marketing filed in another 9 countries. (v 2.1, p 083-6; Submission of 10/22/02, v 1, p 1-7)

The applicant states that ebastine has not been withdrawn from any market, and no warnings or correspondence relating to safety have been issued by any regulatory agencies (v 1, p 172-174; 6/19/98 correspondence; v 2.1, p 83).

Table 3. Worldwide registration status of ebastine tablets and syrup as of May 1998

Status	Formulation, dose	Countries
Launched	Tab. 10 & 20 mg	Argentina, Bulgaria, Colombia, Denmark, Finland, Iceland, Malta, Netherlands, Norway, Pakistan, Russia, Slovak Republic, Singapore, Sweden, Ukraine, Venezuela
	Tab. 5 & 10 mg	Japan, Korea, Mexico, Peru, Spain, Uruguay
	Tab. 5, 10 & 20 mg	Pakistan, Chile
	Tab. Combination*	Spain
Approved	Tab. 10 & 20	Bangladesh, Belarus, Belgium, Brazil, Czech Republic, Cyprus, Ecuador, France, Kazakhstan, Luxembourg, Romania
Applied for	Tab. 10 & 20 mg	Austria, Australia, Azerbaijan, Bolivia, China, Costa Rica, Croatia, Egypt, Estonia, Greece, Guatemala, Hong Kong, Hungary, India, Indonesia, Ireland, Italy, Kenya, Kirgistan, Latvia, Lithuania, Morocco, Paraguay, Philippines, Poland, Portugal, Switzerland, Thailand, Turkey, United States, Uzbekistan, Vietnam, Zimbabwe
	Tab. 10 mg	Canada, South Africa
Launched	Syp. 2.5 & 5 mg	Brazil
	Syp. 5 & 10 mg	Colombia, Uruguay
	Syp. 2.5, 5 & 10 mg	Korea, Spain
Approved	Syp. 2.5, 5 & 10 mg	Argentina, Ecuador
	Syp. 5 & 10 mg	Columbia, Mexico, Peru
* 10 mg ebastine, 120 mg pseudoephedrine		
Source: v 1, p 172-174; 6/19/98 correspondence		

Table 4. Worldwide registration status of ebastine tablets and syrup as of August 2002

Status	Formulation, dose	Countries
Approved	Tab. 10 mg	Armenia, Austria, Azerbaijan, Bahrain, Bangladesh, Belarus, Belgium, Bolivia, Brazil, Bulgaria, Chile, China, Columbia, Costa Rica, Croatia, Cyprus, Denmark, Dominican Republic, Ecuador, El Salvador, Egypt, France, Georgia, Germany, Greece, Guatemala, Hong Kong, Iceland, Ireland, Israel, Italy, Kazakhstan, Kenya, Kuwait, Kyrgyzstan, Latvia, Lebanon, Lithuania, Luxembourg, Macao, Malta, Moldavia, Netherlands, Nicaragua, Norway, Pakistan, Panama, Paraguay, Peru, Philippines, Poland, Romania, Singapore, South Africa, South Korea, Thailand, Turkmenistan, Ukraine, United Kingdom, Uruguay, Uzbekistan, Venezuela, Vietnam, Yemen, Zimbabwe
	Tab. 5 & 10 mg	Japan, Taiwan
	Tab. 5, 10 & 20 mg	Argentina
	Tab. 10 & 20 mg	Chile, Czech Republic, Estonia, Hungary, Mexico, Portugal, Slovakia, Spain
	Tab. 10 mg OTC	Finland, Russia, Sweden
	Tab. Combination*	Argentina, Brazil, Colombia, Corea del Sur, Ecuador, Guatemala, Mexico, Peru, Spain, Venezuela
	Syrup 1 mg/ml	Argentina, Bolivia, Brazil, Chile, Columbia, Costa Rica, Cyprus, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Lebanon, Mexico, Nicaragua, Panama, Paraguay, Peru, Spain, Uruguay, Venezuela
Applied for	Tab. 10 mg	Turkey, Iraq, Taiwan, India
	Tab. 20 mg	Belgium, Denmark, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Netherlands, Norway, Poland, Portugal, Sweden, United Kingdom, Venezuela
	Tab Combination*	Bolivia, Chile, Costa Rica, Dominican Republic, El Salvador, Honduras, Nicaragua, Paraguay, Panama
	Syrup 1 mg/ml	Russian Federation, Turkey, UAE
* 10 mg ebastine, 120 mg pseudoephedrine		
Source: v 2.1, p 083-6; Submission of October 22, 2002, v 1, p 1-7, 84-5		

Clinical Background

2.3. State of Armamentarium for Indication(s)

Allergic rhinitis is estimated to affect from 10 to 30 percent of adults and up to 40 percent of children.[1] This translates to between 20 to 40 million Americans who are affected, with a reported loss of 3.8 million days missed from school or work per year. The prevalence of allergic rhinitis makes it the sixth most common chronic disease in the United States. Symptoms typically include sneezing, nasal itch, rhinorrhea, nasal obstruction, post-nasal drip, and ocular symptoms such as itch, redness, and tearing. The disease is classified as either seasonal or perennial based on timing or periodicity of symptoms. A number of drugs are available to treat these symptoms, among them the class of drugs known as antihistamines.

Four second-generation H_1 receptor antagonists are currently approved for marketing in the US. These include Allegra (fexofenadine), Claritin (loratadine), Clarinex (desloratadine), and Zyrtec (cetirizine). None of these products have any concerns for clinically significant prolongation of QT interval associated with their use, as they are generally believed to be free of intrinsic QT effect and they are not substrates for CYP3A4 (lack any concerns for drug-drug interaction). In addition, for individuals in whom sedation is not an issue, there are many prescription and non-prescription (OTC) first-generation oral antihistamines available.

In addition to antihistamines, several classes of treatments are available to treat nasal and or ocular symptoms of allergic rhinitis. These include oral and intranasal decongestants, nasal saline washes, nasal and ocular cromolyn, intranasal glucocorticoids, and ocular antihistamines. Nasally inhaled corticosteroids are generally considered the most effective medication class for controlling symptoms of allergic rhinitis.[2] Table 5 and Table 6 show the current American Academy of Allergy Asthma and Immunology recommendations for the treatment of seasonal and perennial allergic rhinitis.

To provide an overview of the treatment of allergic rhinitis, several documents are included along with this Clinical Briefing Document. These include the "Executive Summary of the Joint Task Force Practice Parameters on Diagnosis and Management of Rhinitis" and the "Joint Task Force Summary Statements on Diagnosis and Management of Rhinitis".[1,3]

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[1] Agency for Healthcare Research and Quality (May, 2002) "Management of Allergic and Nonallergic Rhinitis." Evidence Report/Technology Assessment, Number 54, AHRQ Publication No. 02-E024.

[2] Dykewicz, M.S. and Fineman, S. (1998) "Executive Summary of the Joint Task Force Practice Parameters on Diagnosis and Management of Rhinitis." Ann Allergy Asthma Immunol 81(Part II): 463-8.

[3] Dykewicz, M.S. Fineman, S. & Skoner, D.P. (1998) "Joint Task Force Summary Statements on Diagnosis and Management of Rhinitis." Ann Allergy Asthma Immunol 81(Part II): 474-7.

Table 5. AAAAI* stepwise approach to pharmacotherapy for seasonal allergic rhinitis

Severity	Daily Medication	Quick-relief Medication
Intermittent symptoms	None	Rapid-onset non-sedating H_1 antihistamine OR Topical nasal antihistamine CONSIDER: Nasal cromolyn sodium as a preventive measure before anticipated allergen exposures.
Persistent mild-to-moderate disease *Consider referral to an allergy/immunology or otolaryngolic allergy specialist for consultation or co-management.*	Oral non-sedating H_1 antihistamine (with or without a decongestant combination). **OR** Topical nasal corticosteroid. **CONSIDER:** Topical nasal antihistamine; nasal cromolyn sodium. If there are prominent eye symptoms: topical ocular antihistamine with or without vasoconstrictor, topical ocular mast cell stabilizer, and/or ocular NSAID.	
Severe disease *Referral to an allergy/immunology or otolaryngolic allergy specialist for consultation or co-management is recommended.*	Topical nasal corticosteroid. **AND:** Oral non-sedating H_1 antihistamine (with or without a decongestant combination). **CONSIDER:** Topical nasal antihistamine; nasal cromolyn sodium. **AND, if needed:** A short course (3-10 day) of oral corticosteroids. If there are prominent eye symptoms: topical ocular antihistamine with or without vasoconstrictor, topical ocular mast cell stabilizer, and/or ocular NSAID.	

* Source: The American Academy of Allergy Asthma and Immunology, Inc. (2000) "The Allergy Report, Volume II: Diseases of the Atopic Diathesis." page 20. URL: http://www.theallergyreport.org/

Table 6. AAAAI* stepwise approach to pharmacotherapy for perennial allergic rhinitis

Severity	Daily Medication	Quick-relief Medication
Intermittent symptoms	None	Rapid-onset non-sedating H_1 antihistamine OR Topical nasal antihistamine CONSIDER: Nasal cromolyn sodium as a preventive measure before anticipated allergen exposures.
Persistent mild-to-moderate disease *Consider referral to an allergy/immunology or otolaryngolic allergy specialist for consultation or co-management.*	Oral non-sedating H_1 antihistamine (with or without a decongestant combination). **AND/OR:** Topical nasal corticosteroid. **CONSIDER:** Topical nasal antihistamine.	
Severe disease *Referral to an allergy/immunology or otolaryngolic allergy specialist for consultation or co-management is recommended*	Topical nasal corticosteroid **AND:** Oral non-sedating H_1 antihistamine (with or without a decongestant combination) **AND, if needed:** A short course (3-10 day) of oral corticosteroids.	

* Source: The American Academy of Allergy Asthma and Immunology, Inc. (2000) "The Allergy Report, Volume II: Diseases of the Atopic Diathesis." page 21. URL: http://www.theallergyreport.org/

2.4. Important Issues with Pharmacologically Related Agents

The second-generation antihistamines have the advantage of having reduced anticholinergic and sedative effects. However, some rare but serious cardiotoxic adverse events, including a type of ventricular arrhythmia called *Torsades de Pointes*, have been reported with some of the second-generation antihistamines. Two of these products have been withdrawn from marketing because they prolong the QT interval, particularly when co-administered with certain other drugs that are broken down by the same enzyme system (CYP3A4) in the liver. These drugs were Seldane (terfenadine), which was approved for marketing in the US in May of 1985, and Hismanal (astemizole), which was approved for marketing in December 1988. The propensity of these drugs to prolong the QT interval is now well documented, but was not established at the time of marketing approval. At that time, Seldane was one of the top 5 prescriptions (by new prescription frequency) in the US. From the original report of a case of *Torsades de Pointes* published in JAMA in 1990 until the time of marketing withdrawal in 1998, a series of articles were published in highly respected and widely read journals and a series of steps were taken to alert the prescribing community to the risks of these drugs when co-administered with macrolide antibiotics or imidazole antifungals such as erythromycin and ketoconazole.[4,5] These included a Dear Doctor letter (August, 1990), Medical Letter (1992), Mailgram and black-box warning (July, 1992), JAMA article by Dr. Nightingale (August, 1992) and articles in 1993 by Honig et al., Woosley et al., Peck et al. and Crane and Shih.[6,7,8,9] It was well documented that none of these warnings significantly affected the prescription patterns of these drugs, and concurrent use of Seldane and macrolide antibiotics and imidazole antifungals continued to occur.[10]

2.5. Materials Submitted

Please see Section 1.2 on page 14 for an overview of the clinical program for ebastine. The original NDA comprised 373 volumes (340 volumes submitted on April 3, 1998, and 33 volumes submitted on July 31, 1999 as safety update). The Class II resubmission (complete response) to the 'not approvable' action (submitted August 20, 2002) comprised 240

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[4] Monahan, B. P., C. L. Ferguson, et al. (1990). "Torsades de Pointes occurring in association with terfenadine use." JAMA **264**(21): 2788-90.

[5] Nightingale, S. L. (1997). "From the Food and Drug Administration." JAMA **277**(5): 370.

[6] Honig, P. K., D. C. Wortham, et al. (1993). "Terfenadine-ketoconazole interaction. Pharmacokinetic and electrocardiographic consequences." JAMA **269**(12): 1513-8.

[7] Woosley, R. L., Y. Chen, et al. (1993). "Mechanism of the cardiotoxic actions of terfenadine." JAMA **269**(12): 1532-6.

[8] Peck, C. C., R. Temple, et al. (1993). "Understanding consequences of concurrent therapies." JAMA **269**(12): 1550-2.

[9] Crane, J. K. and H. T. Shih (1993). "Syncope and cardiac arrhythmia due to an interaction between itraconazole and terfenadine." Am J Med **95**(4): 445-6.

[10] Thompson, D. and G. Oster (1996). "Use of terfenadine and contraindicated drugs." JAMA **275**(17): 1339-41.

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volumes. In addition to the clinical program, the complete response includes responses to CMC and CPB deficiencies, which were included in the NAL.

The FDA also received responses to several requests for further information. The responses were dated October 22, 2002 (3 volumes) and October 30, 2002 (1 volume). The information requests included a Safety Update Report for the first half of 2002, full reports and line listings for the 53 cardiac and 33 hepatic serious adverse events (SAEs) reported in the Integrated Summary of Safety (v 2.203, p 147-8), full reports for SAEs reported in the Safety Update Report (SUR) for 2002, and full reports for all SAEs that resulted in death.

2.6. Conduct of the Review and Data Documentation

In the conduct of the original Clinical Review, the pivotal efficacy studies and safety information from all submitted studies were reviewed. In addition, separate reviews were conducted by review disciplines in the following areas: Chemistry, Manufacturing and Controls, Pharmacology/Toxicology, Clinical Pharmacology and Biopharmaceutics, and Statistics. The conduct of the review of the complete response and the preparation of the clinical briefing document was more limited, but more highly coordinated among review disciplines. The four US comparative efficacy studies, the new and re-analyzed cardiac safety studies, as well as all submitted safety information were reviewed, and included in this document. Other studies included in the complete response (including EEU onset of action, food effect, psychomotor and memory response, safety-related performance, antihistaminic and anti-allergy effects, marketing, and European comparative studies) were either reviewed in depth or evaluated for safety signals, but the individual study reviews are not included in this document. Individual review disciplines conducted reviews of the data submitted. While the individual reviews are not included in this briefing package, information of clinical relevance is included. In addition, the Office of Drug Safety evaluated the limited available information regarding postmarketing safety. This clinical briefing document represents an effort on the part of the Division of Pulmonary and Allergy Drug Products to fully reflect all the salient data from all review disciplines in one document.

Throughout this document, reference to the NDA is made to indicate the source of information, including v for volume, and p for page number. Since there were two major submissions, the applicant used a 2 preceding the volume number for the volumes in the complete response. That convention is followed in this document.

2.7. Data Quality and Integrity

Two sites from the efficacy studies and 3 sites from the cardiac safety studies were reviewed by the DSI during the initial NDA cycle. The sites were chosen based on the importance of the sites to the NDA. Sites included one for EBA 124 (SAR efficacy study), one for EBA 109 (PAR efficacy study), one for EBA 137 (ebastine-ketoconazole interaction cardiac safety study), one for EBA 138 (ebastine-erythromycin interaction cardiac safety study), and one for EBA 136 (high dose cardiac safety study). The center reviewed by DSI in study EBA 136 was also the central referral center where ECGs from other cardiac safety studies and all efficacy and open-label studies were sent for final reading and interpretation. One of the centers was also the site for 3 other cardiac safety studies (EBA 126: High dose cardiac

safety study, EBA 127: Ebastine- ketoconazole interaction cardiac safety study, and EBA 130: Ebastine-erythromycin interaction cardiac safety study).

Representative data from the NDA were provided to the DSI team for comparison with the original data source. The DSI entry of the data matched every number in the submitted NDA verifying the data integrity. No major deviations from pertinent federal regulations and/or good clinical investigation practices governing conduct of clinical investigations and the protection of human subjects were identified by the DSI team for any of the sites that would compromise the NDA database. One minor deficiency was noted for the site of an ebastine-ketoconazole interaction study. At this site, QTc of 55 subjects were verified. All had correct entries, except patient 14 who had one set of different values. The QT and QTc was reported as 0.449 and 0.389 rather than the original values of 0.488 and 0.417 (Source: DSI letter to the investigator dated September 3, 1998). This deviation was not of a nature that could impact this NDA. This investigator conducted the ebastine and ketoconazole drug interaction cardiac safety study (EBA 137) which had showed a positive interaction between the drugs.

2.8. Ethical Standards, and Financial Disclosure

No ethical issues or issues regarding financial disclosure were raised during either review cycle. The applicant has indicated that all clinical trials were conducted in accordance with accepted ethical standards.

3. CHEMISTRY, MANUFACTURING AND CONTROLS

The active component of ebastine (RP 64305) is a synthetic piperidine derivative designated as 4-diphenylmethoxy-1-[3-(4-terbutylbenzoyl)-propyl]piperidine with the empirical formula of $C_{32}H_{39}NO_2$, and a molecular weight of 469.62. The molecular structure of ebastine is shown in Figure 1. Ebastine is a white to almost white odorless powder that is practically insoluble in water. KESTINE is intended to be marketed as a round, white, film-coated tablet for oral administration containing 10 or 20 mg of ebastine. The quantitative composition of the to be marketed formulations and RPR's investigational formulations used in the pivotal US clinical trials were the same and is given in Table 7 (v 1, p 140, 176-184).
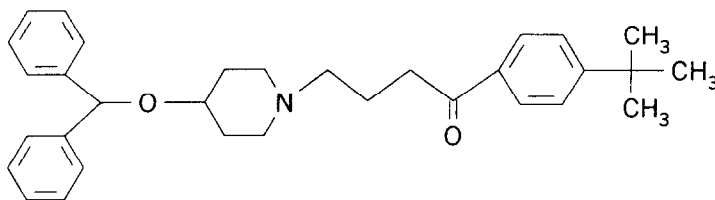
Figure 1. Molecular structure of ebastine

Table 7. Quantitative composition of ebastine tablets*

Component	Commercial		RPR investigational			
	10 mg	20 mg	1 mg	5 mg	10 mg	20 mg
Tablet core (in mg):						
Micronized RP 64305	10.5	20.0	1.0	5.0	10.0	20.0
Lactose monohydrate fine powder	88.5	177.0	48.25	44.25	88.5	177.0
Microcrystalline cellulose USNF	20.0	40.0	10.0	10.0	20.0	40.0
Pregelatinized starch USNF	5.2	10.4	2.6	2.6	5.2	10.4
Croscarmellose sodium USNF	5.0	10.0	2.5	2.5	5.0	10.0
Magnesium stearate USNF	1.3	2.6	0.65	0.65	1.3	2.6
Total tablet core weight (mg):	130.0	260.0	65.0	65.0	130.0	260.0
Tablet coating (in mg & percentage):						
Hydroxypropylmethylcellulose USP	1.725	2.85	60%	60%	60%	60%
Polyethylene glycol 6000 USNF	0.575	0.95	20%	20%	20%	20%
Titanium dioxide USP	0.575	0.95	20%	20%	20%	20%
Total tablet coating weight (mg):	2.875	4.75				
* As submitted to the original NDA						
Source: v 1, p 181, 184						

4. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

This section briefly summarizes the nonclinical pharmacology and toxicology of ebastine and its major metabolite, carebastine. The information in this section is based on data from both the original NDA and the complete response, and was written jointly by the Medical and Pharmacology /Toxicology review teams.

4.1. Mechanism of action

Ebastine, like other second generation H_1 antihistamines, does not cross the blood-brain barrier to the same extent as the first generation agents. Ebastine is a relatively selective histamine H_1 receptor antagonist and is relatively nonsedating. Table 8 shows the H_1 receptor affinity for ebastine, carebastine, and other metabolites. Carebastine has been shown to have good antihistaminic properties, and two other minor metabolites also have good H_1 receptor affinity. In *in vitro* assays, both ebastine and carebastine have a high affinity for H_1 receptor in the guinea pig cerebellum and inhibit ^3H-mepyramine binding with a Ki of 7.1 nM and 7.9 nM, respectively. Both are twice as potent as terfenadine (Ki=14.3), but less potent than astemizole (ki=1.7 nM). Ebastine and carebastine show a weak affinity for the $5\text{-}HT_2$ receptor, and does not bind to the following receptors: adrenergic $\alpha1$, dopaminergic D2, benzodiazepine, muscarinic, cholecystokinin, NMDA, CGRP, neuropeptide Y, neurotensin, opiate, somatostatin, NK1, vasopressin V1, VIP, bradykinin B2, or Ca^{++} channels (v 1, p 212).

Table 8. Revised table of effects of ebastine and its metabolites on H_1 receptors and HERG-potassium current*

Compound	H_1 binding (nM)	HERG IC_{50} (μM)
Ebastine	48 ± 6	0.33
Carebastine	27 ± 4	6.00
HO-ebastine	14 ± 3	0.44
Diphenyl-norpyraline	81 ± 17	1.29
Benzhydrol	>10,000	>30
4HO-benzhydrol	>10,000	>30
4HO,3MeO-benzhydrol	>10,000	>30
4HO,3MeO-carebastine	878 ± 53	8.9
4HO-benzhydroxypiperidine	523 ± 59	10.0
4HO-carebastine	140 ± 26	>30
4HO,3MeO-benzhydroxypiperidine	2,833 ± 1,492	>30
* Revised table as presented in complete response		
Source: v 2.1, p 99		

4.2. Pharmacokinetics

Studies involving oral administration of ebastine in mice, rats, rabbits, and dogs show that ebastine is rapidly absorbed and extensively converted to carebastine by enzymatic oxidation of one of the methyl groups of the terbutyl moiety. This biotransformation takes place in the small intestine and in the liver. Subsequently one of the phenyl rings of carebastine undergoes oxidation resulting in the formation of a phenolic derivative of carebastine. These metabolites are excreted as non-conjugated derivatives. In rats and dogs,

following oral and intravenous administration of ^{14}C-ebastine, about 60-90% of the dose appears in feces and 4-10% in the urine over a period of 7 days. The percentages are same following both routes of administration, suggesting the presence of biliary excretion in both species. (v 1, p 220-229)

4.3. Toxicology

In oral single-dose toxicity studies in mice and rats, no lethality was observed at 4000 mg/kg and the LD_{50} by the intraperitoneal route was 486 mg/kg. In oral repeat-dose toxicity studies, the NOAEL in rats was 100 mg/kg/day for 13 weeks and 15 mg/kg/day for 1 year, and in dogs was 50 mg/kg/day for 13 weeks and 15 mg/kg/day for 1 year. The main observations associated with ebastine was lymphocyte depletion in lymphoid organs in rats and dogs, and pulmonary histiocytosis and decreased number of ovarian corpus lutea in rats. (v 1, p 215-217)

4.4. Mutagenicity and carcinogenicity

Ebastine was not mutagenic or clastogenic in the Ames, CHO/HGRPT-locus, and Mouse Micronucleus assays. Ebastine was not carcinogenic in rats and mice. (v 1, p 218)

4.5. Reproductive and developmental studies

Ebastine was not teratogenic at oral doses up to 300 mg/kg in rats and up to 120 mg/kg in rabbits and did not affect fertility in rats. Decreased fetal weight was observed at 300 mg/kg and not at 150 mg/kg in rats. In the postnatal study in rats, decreased pup and litter weights occurred at oral dosages of 140 mg/kg, and not at 70 mg/kg. (v 1, p 217)

4.6. Neuropharmacological effects

In rats and mice, ebastine had no significant effect on behavioral and related parameters as evaluated in the Irwin test and on conditioned avoidance, the electroencephalograph, muscle tone and spontaneous motor activity. Ebastine did not manifest anticonvulsant and anti-dopaminergic activities and did not produce catalepsy. (v 1, p 1212)

4.7. Cardiac conduction studies

The electrophysiological effects of ebastine and carebastine were studied in isolated rabbit Purkinje fibers *in vitro*. In normal and low potassium solution (4 mM and 2.7 mM K^+) ebastine (at concentration of 1 nM to 1 μM) and carebastine (at a concentration of 1 nM to 10 μM) produced a concentration-dependent prolongation of action potential duration (APD) without impairment of the maximum rate of depolarization. The rank order of activity at 10 mM in increasing the APD_{90} for ebastine and other antihistamines indicative of their ability to block cardiac K^+ channels was: astemizole > carebastine = terfenadine > cetirizine > ebastine = loratadine = fexofenadine. (v 1, p 213)

The effect of ebastine and other non-sedating antihistamines on cardiac conduction has been reported by various groups. Some controversy exists as to whether ebastine prologs QTc interval in experimental animals. Published works by Hey *et al* (Schering-Plough Research Inc., US marketer of loratadine) show that ebastine prolongs QT interval; whereas the works

of Gras *et al* (Almirall Laboratories, marketer of ebastine) contradicts the findings.[11,12,13,14] Hey *et al* showed that intravenously administered ebastine (3 to 50 mg/kg) caused dose-related prolongation of QTc in anesthetized guinea pigs in a manner comparable to that seen with terfenadine (1 to 10 mg/kg). Ebastine was about 1/5 times as potent as terfenadine (on a mg/kg basis) for a comparable level of QTc prolongation. In these studies, carebastine (up to 50 mg/kg IV), or loratadine (up to 100 mg/kg IV) caused no QT prolongation. Hey *et al* also showed accentuation of QTc prolongation by ebastine (10 mg PO, approximately 20 mg/kg) in conscious guinea pigs pretreated with ketoconazole (200 mg PO, approximately 400 mg/kg). Loratadine (10 mg PO, approximately 20 mg/kg) had no effect on QTc interval in guinea pigs pretreated with ketoconazole. Gras *et al* showed no interaction between ebastine and ketoconazole. In conscious guinea pigs pretreated with ketoconazole (400 mg/kg PO), ebastine (20 mg PO), terfenadine (120 mg/kg PO), and loratadine (20 mg/kg PO) did not induce QTc prolongation above that seen with ketoconazole alone. It is important to note that the positive control, terfenadine, was negative. These differences are difficult to reconcile. However, the effects of ebastine on cardiac potassium channels are more compelling, and are discussed in the next section.

4.8. Effects on cardiac potassium channels

During an action potential in human heart, the depolarizing current is carried by the Na^+ and Ca^{++} channels, and the repolarizing current is carried by the K^+ channel. Genotyping of the hereditary long-QT syndrome (LQT) has been instrumental in understanding these channels (Table 9). The syndrome has an incidence of 1 in 10,000 to 1 in 15,000 with a 10 year mortality of about 50% from *Torsade de Pointes* and other ventricular tachyarrythmias.[15,16,17] The frequency of cardiac events is higher among subjects with mutations of the LQT1 locus or the LQT2 locus than among those with mutations of the LQT3 locus.[18] Of the various repolarizing (inward rectifying) potassium channels (I_K) that have been identified in human heart, I_{Ks}, I_{Kr}, and I_{Kur} ("s" denotes "slow", "r" denotes

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[11] Hey, J. A., M. del Prado, et al. (1996). "Terfenadine, astemizole, and ebastine produce QTc interval prolongation in an experimental model predictive of adverse clinical ECG effects." Ann Allergy Asthma Immunol 76(5): 476.

[12] Hey et al. (1996). Drug Research 46:153, 159, 834.

[13] Gras, J. and J. Llenas (1999). "Effects of H1 antihistamines on animal models of QTc prolongation." Drug Saf 21(Suppl 1): 39-44; discussion 81-7.

[14] Gras, J., J. Llenas, et al. (1996). "The role of ketoconazole in the QTc interval prolonging effects of H1-antihistamines in a guinea-pig model of arrhythmogenicity." Br J Pharmacol 119(2): 187-8.

[15] Ackerman, M. J. and D. E. Clapham (1997). "Ion Channels -- Basic Science and Clinical Disease." N Engl J Med 336(22): 1575-1586.

[16] Ackerman, M. J. (1998). "The Long QT Syndrome: Ion Channel Diseases of the Heart." Mayo Clinic Proceedings 73(3): 250.

[17] Vincent, G. M., MD (1998). "The molecular genetics of the Long QT Syndrome: Genes causing fainting and sudden death." Annual Rev. Medicine 49(1): 263-274.

[18] Zareba, W., A. J. Moss, et al. (1998). "Influence of the Genotype on the Clinical Course of the Long-QT Syndrome." N Engl J Med 339(14): 960-965.

"rapid", and "ur" denotes "ultrarapid") have been well characterized. I_{Ks} is formed by the co-assembly of KvLQT1 and MinK proteins, and I_{Kr} is formed by the HERG (human ether-a-go-go-related gene) protein. These are the main I_K channels in the human ventricle. I_{Kur} is mainly located in human atria and does not play an important role in ventricular repolarization. From drug safety standpoint, I_{Kr} has received much attention because some other non-cardiac drugs that have been associated with development of *Torsade de Pointes* and death were found to block this channel.

Table 9. Currently recognized human LQTS genes

Subtypes	Chromosome	Gene	Channel	Incidence	Cardiac event*
LQT1	11p15.5	KvLQT1	K (I_{Ks})	≈ 50 %	63 %
LQT2	7q35-36	HERG	K (I_{Kr})	30-40 %	46 %
LQT3	3q21-24	SCN5A	Na	5-10 %	18 %
LQT4	4q25-27	?	?	?	?
LQT5	21	KCNE1/MinK	K (I_{Ks})	?	?
* Syncope, aborted cardiac arrest requiring defibrillation, and death from birth to age 40 years (Ref. N Engl J Med 1998; 339:960)					
Ref: Modified form Ann Rev Med 1998; 49:263					

A comprehensive study on suppression of potassium channels by ebastine was published by Ko *et al* from Georgetown University, Washington, DC.[19] The five members of the potassium channel family known to be expressed in human heart were studied by the whole-cell patch-clamp technique. The five potassium channels were I_{Kr} (delayed rectifying, rapid), I_{Ks} (delayed rectifying, slow), I_{to} (transient outward, also called the shaker), I_{Kped} (rapidly activating delayed rectifier, the noninactivating component of I_{to}), and I_{K1} (inward rectifying). In the patch clamp study, the I_{kr} channel was examined in both the HERG-expressing X. laevis oocytes and guinea pig ventricular myocytes; the I_{ks} and I_{k1} were studied in the guinea pig ventricular myocytes, and the I_{to} and I_{kped} were studied in the rat heart. The results of the study showed that ebastine had significant suppressive effects on the I_{kr} (both models), I_{ks} and I_{kped} channels, but it was less effective in blocking the I_{to} and I_{k1} channels. The suppressive effect of ebastine was equivalent or somewhat weaker than that of terfenadine and much stronger than that of loratadine. The applicant takes issue with this study, stating that "the quoted Kd values for inhibition for the various K^+ channels are...values for 50% inhibition of the maximum inhibition and not 50% of complete inhibition. This gives rise to potential misinterpretations of potency when the former is considerably less than 100%. Indeed, the 300 nM value quoted for 50% maximal inhibition by ebastine corresponds to only 23% inhibition of total channel activity." (v 2.1, p 93)

The applicant has studied the potassium current by the whole-cell configuration of the patch-clamp technique in heterologous cells transfected with some of the cloned human potassium channel genes (results submitted in volume 11). Terfenadine and loratadine were found to be potent inhibitors of hkv1.5 expressed in mouse Ltk cells (Table 10), and terfenadine, and ebastine were found to be strong inhibitors of potassium current in CHO cells expressing the HERG gene (Table 11). Data from HERG system are more relevant since HERG is well

[19] Ko, C. M., I. Ducic, et al. (1997). "Suppression of Mammalian K+ Channel Family by Ebastine." J Pharmacol Exp Ther 281(1): 233-244.

characterized as the human I_{Kr}, whereas the hkv1.5 is more abundant in human atria and is possibly the I_{Kur}. HERG currents were also found to be several times more sensitive to inhibition by terfenadine than the hkv1.5 currents.[20]

More recent studies used HERG channel transferred into human embryonic kidney (HEK-293) cells. The applicant claims that this model offers considerable improvement in accuracy for measurement of HERG channels. However, a reanalysis using this model (Table 12) reveals confusing results. IC_{50} for ebastine was 331nM, which was a little less potent than terfenadine (208 nM) and loratadine (200 nM). Since loratadine is non-arrhythmogenic, and terfenadine is arrhythmogenic, it is difficult to reconcile the results. To do so, the applicant suggests that one must consider the availability of free compound based on standard dosing and resultant plasma concentrations, yielding a 'HERG/Free compound ratio.' Using this scenario, the applicant argues that ebastine is the least likely of the antihistamines tested to affect HERG channels. However, under this scenario, both cetirizine and fexofenadine would be the most potent. Since this too did not fit the clinical data, the applicant did an *in vivo* study in rats to address the differences in accumulation of antihistamines into cardiac tissue. Rats were administered antihistamines orally for 5 days at a dose calculated to achieve steady-state concentrations substantially higher than in humans. The ratio between the HERG IC_{50} and the plasma level of the free compound at steady state C_{max} (μM) and the ratio between the HERG IC_{50} and the C_{max} in the rat heart at steady state were determined. Under this scenario, ebastine and carebastine fare the best of all the antihistamines with high ratios suggesting that the putative arrthymogenic potential of ebastine was lower than terfenadine (Table 12). (v 2.1, p 94-7)

Table 8 shows the effects of ebastine and its metabolites on H_1 receptors and HERG-potassium current. The applicant synthesized each of the metabolites for this testing. Carebastine is seen to have antihistaminic activity, with less HERG effects. The only metabolites that showed significant HERG activity were hydroxyebastine and diphenylnorpyraline, and the applicant states that these compounds appear fleetingly or in such low concentration as to be insignificant. (v 2.1, p 98-9)

Table 10. Effect of antihistamines and their metabolites on hkv1.5 currents (CHO cells)

Compound	Concentration	n	% inhibition
Terfenadine	3 μM	5	69.3
Terfenadine carboxylate	3 μM	4	0.03
Ebastine	1 μM	6	8.1
	3 μM	4	13.0
Carebastine	3 μM	5	4.8
Loratadine	3 μM	5	68.2
Source: v 11, p 52			

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[20] Reviewed in Current Drugs (1997) 2: 331.

Table 11. Effects of antihistamines and their metabolites on HERG-potassium current (CHO cells)

Compound	Effect on HERG	IC_{50} (μM)
Terfenadine	Strong reduction, hardly reversible	0.13
Terfenadine carboxylate	No effect	-
Ebastine	Reduction, hardly reversible	1
Carebastine	Some reduction at 10 μM, hardly reversible	> 10
Loratadine	No effect	-
Descarboethoxy loratadine	No effect	-
Source: v 11, p 85		

Table 12. Revised table of effects of antihistamines and their metabolites on HERG-potassium current (HEK-293 cells)

Compound	HERG IC_{50} (μM)	HERG IC_{50} / Free Compound [a]	HERG IC_{50} / Cardiac Compound [b]
Astemizole	0.026	371	0.03
Loratadine	0.200	833	4.76
Terfenadine	0.208	473	0.37
Ebastine	0.331	1273	6.37
Mizolastine	0.427	33	-
Cetirizine	1.300	28	2.34
Desloratadine	1.500	222	2.23
Carebastine	6.000	455	6.99
Fexofenadine	12.700	64	6.10

[a] Ratio of HERG IC_{50} to plasma C_{max} (μM) of the free compound at steady state in rats.
[b] Ratio of HERG IC_{50} to C_{max} (μM) in the rat heart at steady state.
Source: v 2.1, p 96

5. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

This section briefly summarizes the human pharmacokinetics and pharmacodynamics of ebastine and its major metabolite, carebastine. The information in this section is based on data from both the original NDA and the complete response, and was written jointly by the Medical and Clinical Pharmacology and Biopharmaceutics review teams. Pharmacokinetic analysis was part of many of the cardiac safety studies, and further details may be found in the individual study reviews. To address certain deficiencies listed in the 'not approvable' letter, the applicant developed a more sensitive analytical methodology for measurement of ebastine and carebastine, and conducted several new Clinical Pharmacology and Biopharmaceutics studies (EBA 151 in the elderly, EBA 147 in renal impaired patients, EBA 146 in hepatic impaired patients, and RP64305-601 for evaluation of food effects).

5.1. Pharmacokinetics

5.1.1. Ebastine

Ebastine is rapidly absorbed following oral administration and undergoes extensive first pass metabolism to its carboxylic acid active metabolite, carebastine, which appears to be the major circulating species in the blood. Both ebastine and carebastine are highly (~98%) protein bound in the circulation. Following a single oral dose of 10 mg or 20 mg of ebastine to healthy volunteers, maximum ebastine plasma concentrations of 1.1 ng/mL and 3.75 ng/mL were achieved within 1 and 1.4 hours, respectively, and maximum carebastine concentrations of 95 ng/mL and 157 ng/mL were achieved by 4.9 hours and 5.5 hours, respectively. Ebastine steady-state was achieved within 4 to 5 days of repeated dose administration, with steady-state AUC_{0-24} reaching 4.2 and 17.9 ng*hr/mL following multiple administration of ebastine 10 mg and 20 mg, respectively. The elimination half-life of ebastine ranges from 2.6 to 6.4 hours following single and multiple doses of 10 mg and 20 mg ebastine, respectively. The effect of food on the pharmacokinetics of ebastine has not been addressed. (v 1, p 141, 231-234; v 2.1, p 96, 106; Clinical Pharmacology and Biopharmaceutics review)

5.1.2. Carebastine

The active metabolite carebastine is further metabolized to numerous other (mostly inactive) metabolites (see Table 8). Carebastine exhibits linear pharmacokinetics over the ebastine 10 mg to 20 mg dose range, and steady-state is achieved within 5 to 7 days of repeated dose administration. Human pharmacokinetic parameters for carebastine at steady state are shown in Table 13. In one study (severely limited by the fact that there was only one time point performed at steady-state) submitted to the complete response, food did not affect ebastine levels, and carebastine levels were only increased by 10%. However, in a study submitted to the original NDA using ebastine 10 mg dosage, food increased the Cmax and AUC of carebastine bioavailability by 40% to 50% and 30% to 40%, respectively. Food effects for carebastine using the 20 mg dosage have not been studied. (v 2.1, p 106-122; Clinical Pharmacology and Biopharmaceutics review)

Table 13. Carebastine pharmacokinetic parameters following repeat dose ebastine administration*

Parameter	10 mg ebastine	20 mg ebastine
$AUC_{(0-24)}$ (ng•hr/mL)	2305 (28.7)	4813 (43.4)
C_{max} (ng/mL)	129 (26.8)	281 (41.8)
T_{max} (hrs)	4.86 (25.4)	4.93 (31.3)
$t_{1/2}$ (hrs)	19.9 (21.6)	20.7 (22.8)
* Expressed as mean (percent coefficient variation)		
Source: v 1, p 141		

5.1.3. Metabolism and Elimination

In vitro studies with human liver microsomes suggested that while CYP3A4 (79% inhibition) may be the major route of enzymatic activity for ebastine metabolism, there could be involvement of a variety of other isoforms, such as 1A1 (55% inhibition), 1A2 (55% inhibition), 2C9 (42% inhibition), 2D6 (30% inhibition) and 2E1 (58% inhibition).

In addition, data from a mass balance study indicated that carebastine might not be the only major circulating metabolite as the sponsor claims (see Figure 2). Urine and fecal data from a human mass balance study documented the presence of more than 30 different conjugated and unconjugated metabolites. On average, 65.9% of the radioactivity administered to the human volunteers is excreted in urine. In urine carebastine represents only 0.6% of the dose administered, while ebastine is not detected. Fecal excretion of radioactivity represents on average 30% of the administered dose. In feces carebastine represents 5.9% of the administered dose, while unchanged ebastine represents only 1.1%. (v 1, p 141; v 2.1, p 106-122; Clinical Pharmacology and Biopharmaceutics review)

Concurrent administration of ebastine with other CYP3A4 inhibitors is associated with significantly increased plasma concentrations of ebastine and only slightly increased concentrations of carebastine. Co-administration with ketoconazole increased ebastine Cmax by about 16-fold and AUC by about 44-fold, whereas ketoconazole increased carebastine Cmax by about 1.7-fold and AUCt by about 1.4-fold, but its clearance was dramatically decreased. Neither ebastine nor carebastine inhibit P450 isoforms (CYP1A2, 2A6, 2C9, 2C19, 2E1, 2D6, and 3A4) *in vitro*. (v 2.1, p 106-122; Clinical Pharmacology and Biopharmaceutics review)

In high-dose studies, the Cmax of ebastine increased proportionally with the dose whereas the AUC increased more than proportionally, suggesting a saturation of the metabolic pathway. In contrast, both the Cmax and AUC of carebastine increased less than proportionally with the dose of ebastine (Clinical Pharmacology and Biopharmaceutics review).
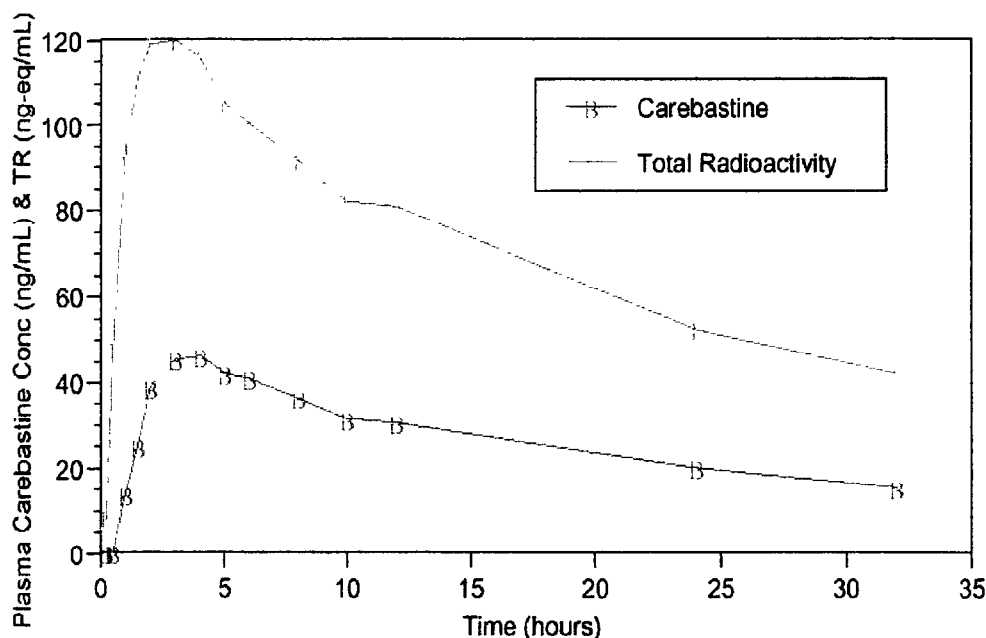
Figure 2. Mean plasma carebastine concentration (ng/mL) and total radioactivity (ebastine ng-equiv/mL) versus time profile

Data from mass balance of ^{14}C ebastine (10 mg) in 4 healthy males
Source: Office of Clinical Pharmacology and Biopharmaceutics, FDA

5.1.4. Special Populations

The applicant has not conducted a formal study to evaluate the effect of gender on the pharmacokinetic of ebastine and carebastine. Based on one dose-proportionality study (EBA 143) the sponsor concluded a lack of significant gender effect on the PK of ebastine and carebastine. However, the analysis included a small number of subjects (<15 per gender) and the results were not conclusive, since high variability on the data was observed. In addition, a study conducted to compare the PK in the elderly versus the young showed that young females have Cmax and AUCt values which are 31% and 35% higher, respectively than those observed in young males receiving the same dose of ebastine (20 mg for 5 days) (Clinical Pharmacology and Biopharmaceutics review).

The effect of race on pharmacokinetics of ebastine and carebastine has not been adequately addressed. Subsequent to submission of the complete response, the applicant submitted (on October 24, 2002) a re-analysis of EBA 136 by race. However, study EBA 136 was a high-dose cardiac safety study using two dosages of ebastine (60 and 100 mg QD), which are not clinically relevant. Dosages higher than 20 mg do not follow linear kinetics. In addition, the only races that the applicant tried to evaluate were Blacks and Caucasians. These subjects are not representative of the whole population. In fact, many of the other cardiac safety studies enrolled a large proportion of races other than Blacks and Caucasians (Clinical Pharmacology and Biopharmaceutics review).

In a study in 12 elderly subjects (EBA 112), there was no significant difference in carebastine exposure, but Cmax and AUC of ebastine were 1.55 and 2.3 times than that seen in younger subjects, suggesting that dose adjustment is needed in this population. (v 2.1, p 106-122; Clinical Pharmacology and Biopharmaceutics review)

In patients with mild and moderate liver impairment (Child Pugh A and B), the pharmacokinetics of ebastine are not affected. For patients with severe liver impairment (Child Pugh C), steady-state ebastine Tmax was delayed from 2 hours to 4 hours, and the carebastine free fraction was 2 to 3-fold higher, suggesting that dose adjustment is needed. (Clinical Pharmacology and Biopharmaceutics review)

The changes in total ebastine and carebastine systemic exposure observed (less than two-fold) due to renal impairment (mild, moderate or severe) may not be clinically significant. Although the $Cmax_f$ and AUC_f of carebastine increased about 3-fold in mild renally impaired subjects and about 4-fold in the moderate renally impaired subjects, these increments may not be clinically relevant due to the high variability of the data (90-200% CV) caused mainly by one subject which appears to be an outlier. There was no correlation of either ebastine or carebastine exposure to creatinine clearance. Therefore, dose-adjustment in renally impaired subjects may not be needed (v 2.1, p 106-122; Clinical Pharmacology and Biopharmaceutics review).

6. INTEGRATED REVIEW OF EFFICACY

6.1. Introduction to the Efficacy Review

This section will present an overview of the studies that tested the efficacy of ebastine in the treatment of SAR and PAR. The efficacy of ebastine for the treatment of SAR and PAR was studied in five pivotal studies, one onset of action study, and comparative efficacy and supporting studies. The five pivotal SAR and PAR studies (EBA 124, EBA 132, EBA 109, EBA 110, and CR 2714) and one SAR onset of action study (EBA 133) were submitted in the original NDA. The four supporting US comparative efficacy SAR studies (CM.030.ALGY, CM.031.ALGY, EBA.GMA.402, and M/EBS/28) were submitted as part of the complete response to the 'not approvable' letter. The concerns to be discussed at the December 20, 2002, PADAC meeting do not specifically relate to the efficacy of ebastine. Instead, they relate to the safety of ebastine (in particular, cardiac safety) and the risk/benefit ratio of the drug.

The duration of treatment in the pivotal SAR and PAR studies was 3 weeks for all of the pivotal studies except CR 2714 where the duration of treatment was 12 weeks. The goal of the pivotal efficacy studies was to show superiority of ebastine over placebo. Two doses of ebastine, 20 mg/day and 10 mg/day were used. The duration of treatment in the supporting comparative efficacy studies was 4 weeks for all of the studies. The primary goal of the comparative efficacy studies was to show superiority of ebastine over loratadine. Distribution of patients in the pivotal and comparative efficacy studies is shown in Table 14. In the subsequent sections, brief summaries of the 5 pivotal efficacy, 4 US comparative efficacy, and supporting studies are presented, followed by an integrated result of the primary efficacy variable with comparison across studies. Please note that the complete reviews of the major studies submitted to the NDA and the complete response may be found in the Individual Study Reviews section of this document starting on page 83.

6.2. Distribution of patients in the efficacy studies

Distribution of patients enrolled in the pivotal, comparative, and supportive studies is shown in Table 14 and Table 15. A total of 1394 patients were enrolled in the 5 pivotal studies (685 in the SAR studies, and 709 in the PAR studies). Of the 685 patients in the SAR studies, 678 had data available for efficacy analysis; 256 were treated with a total daily dose of 10 mg of ebastine, 249 were treated with a total daily dose of 20 mg of ebastine, and 173 were treated with placebo. Of the 709 patients in the PAR studies, 707 had data available for efficacy analysis; 88 were treated with a total daily dose of 10 mg of ebastine, 345 were treated with a total daily dose of 20 mg of ebastine, and 274 were treated with placebo.

A total of 2584 patients were enrolled in the 4 US comparative efficacy studies, of whom 2212 patients had data available for efficacy analysis. Of these, 396 patients were treated with 10 mg of ebastine once daily, 658 were treated with 20 mg of ebastine once daily, 515 were treated with placebo, and 643 were treated with the comparator drug loratadine 10 mg once daily.

A total of 2338 patients were enrolled in the 8 supportive studies submitted to the original NDA, 1860 in the SAR studies, and 478 in the PAR studies. Of the 1860 patients in the SAR studies, 1824 had data for efficacy analysis; 79 were treated with ebastine 1 mg/day, 76 were treated with ebastine 3 mg/day, 339 were treated with ebastine 10 mg/day, 339 were treated with ebastine 20 mg/day, 73 were treated with ebastine 30 mg/day, and 858 were treated with comparator drug (placebo, terfenadine, and cortisone). Of the 478 patients in the PAR studies, all had data available for efficacy analysis; 182 were treated with total daily dose of 10 mg of ebastine, 111 were treated with ebastine 20 mg/day, and 185 were treated with comparator drugs (placebo, and loratadine) (v 314, p 19, 20).

Table 14. Distribution of patients in pivotal and comparative efficacy studies

Population	Study	Location	Ebastine		Placebo	Loratadine	Total
			10 mg/d	20 mg/d		10 mg/d	
All patients enrolled and randomized:							
SAR studies	EBA 124	USA	161	78	157		396
	EBA 132	USA	98	96	95		289
PAR studies	EBA 109	USA	NA	73	151		224
	EBA 110	USA	NA	101	94		195
	CR 2714	Europe	88	100	102		290
Comparative	CM.030.ALGY	USA	142	143	142	140	567
SAR studies	CM.031.ALGY	USA	140	143	141	141	565
	EBA.GMA.402	USA	188	186	186	189	749
	M/EBS/28	USA	NA	282	142	279	703
Primary efficacy diary data available for analysis:							
SAR studies	EBA 124	USA	159	78	154		391
	EBA 132	USA	97	95	95		287
PAR studies	EBA 109	USA	NA	73	150		223
	EBA 110	USA	NA	101	93		194
	CR 2714	Europe	88	100	102		290
Comparative	CM.030.ALGY	USA	119	124	119	110	472
SAR studies	CM.031.ALGY	USA	119	118	116	120	473
	EBA.GMA.402	USA	158	167	161	163	649
	M/EBS/28	USA	NA	249	119	250	618
Source: v 314, p 36							

Table 15. Distribution of patients in supportive efficacy studies (original NDA only)

Population	Study	Location	Total daily dose of ebastine					Comparator*	Total
			1 mg	3 mg	10 mg	20 mg	30 mg		
All patients enrolled and randomized:									
SAR studies	EBA 133	USA	NA	NA	NA	53	NA	53	106
	EBA 102	USA	80	77	76	75	73	78	459
	CR 2747	Europe	NA	NA	NA	161	NA	311	472
	EBA 021	Europe	NA	NA	43	NA	NA	90	133
	EBA 028	Australia	NA	NA	115	NA	NA	232	347
	SI 01	Europe	NA	NA	116	111	NA	116	343
PAR studies	EBA 022	Europe	NA	NA	79	NA	NA	82	161
	CR 2715	Europe	NA	NA	103	111	NA	103	317
Primary efficacy diary data available for analysis:									
SAR studies	EBA 133	USA	NA	NA	NA	53	NA	53	106
	EBA 102	USA	79	76	74	74	73	78	454

Population	Study	Location	Total daily dose of ebastine					Comparator[*]	Total
			1 mg	3 mg	10 mg	20 mg	30 mg		
	CR 2747	Europe	NA	NA	NA	161	NA	311	472
	EBA 021	Europe	NA	NA	35	NA	NA	69	104
	EBA 028	Australia	NA	NA	114	NA	NA	231	345
	SI 01	Europe	NA	NA	116	111	NA	116	343
PAR studies	EBA 022	Europe	NA	NA	79	NA	NA	82	161
	CR 2715	Europe	NA	NA	103	111	NA	103	317
* Comparators include placebo, terfenadine, cetirizine, and loratadine									
Source: v 314, p 82									

6.3. Summary of the pivotal efficacy studies

Scoring for all efficacy studies was based on a composite of five symptoms (nasal discharge, nasal stuffiness, sneezing, itchy nose, itchy/watery eyes) on a 0-3 scale, called the total rhinitis symptom score.

6.3.1. SAR study EBA 124

The objective of this study was to compare the efficacy and safety of ebastine 20 mg and 10 mg administered once a day in the AM or PM, to placebo. A total of 396 SAR patients between the ages of 12 and 64 years were recruited from 16 sites in US, of which primary efficacy data were available from 391 patients. Based on the primary efficacy variable analysis (mean change from baseline in total rhinitis symptom score averaged over the double-blind treatment period for 24 hours), 10 mg dose taken in the morning, and the 20 mg dose taken either in the morning or in the evening, were effective in relieving the symptoms of SAR. Of the doses, 20 mg AM was most effective. The reduction in the symptom score was greater in the first 12 hours compared to the second 12 hours. The 20 mg AM dose significantly reduced symptoms by day 1, and the effect persisted at the end of each week of treatment. The efficacy of 20 mg AM dose was consistent in reducing the individual symptoms of SAR, patients' "snap-shot" global symptom scores, and global rating of efficacy by patients and physicians. The results of this study support 20 mg QD as the optimal dose for relief of symptoms of SAR, and 10 mg QD as a dose sufficient for some patients.

6.3.2. SAR study EBA 132

The objective of this study was to compare the efficacy and safety of ebastine 20 mg and 10 mg administered once a day in the AM to placebo. A total of 289 SAR patients between the ages of 12 and 68 years were recruited from 10 sites in US, of which primary efficacy data were available from 287 patients. Based on the primary efficacy variable analysis (mean change from baseline in total rhinitis symptom score averaged over the double-blind treatment period for 24 hours), 20 mg and 10 mg dose taken in the morning were both effective in relieving the symptoms of SAR. The reduction in the symptom score was greater in the first 12 hours as compared to the second 12 hours. Both doses significantly reduced symptoms by day 1, however, the effect did not persist to the end of dosing interval after the first dose. The reduction of symptoms persisted at the end of each week of treatment. The efficacy of both the doses were consistent in reducing the "snap-shot" scores, individual symptoms of SAR, and global rating of efficacy by patients and

physicians. The results of this study support 20 mg and 10 mg QD dose for relief of symptoms of SAR.

6.3.3. PAR study EBA 109

The objective of this study was to compare the efficacy and safety of ebastine 20 mg administered once a day in the AM, and 10 mg administered twice a day to placebo. A total of 224 PAR patients between the ages of 12 and 77 years were recruited from 8 sites in US, of which primary efficacy data were available from 223 patients. Based on the primary efficacy variable analysis (mean change from baseline in total perennial index score averaged over the double-blind treatment period for 24 hours), 20 mg QD dose taken in the morning and 10 mg BID dose were both effective in relieving the symptoms of PAR. The reduction in the symptom score was greater in the first 12 hours as compared to the second 12 hours. The reduction of symptoms persisted at the end of each week of treatment. The efficacy of both doses was consistent in reducing the individual symptoms of PAR. The results of this study support 20 mg QD and 10 mg BID dose for relief of symptoms of PAR.

6.3.4. PAR study EBA 110

The objective of this study was to compare the efficacy and safety of ebastine 20 mg administered once a day in the AM to placebo. A total of 195 PAR patients between the ages of 12 and 64 years were recruited from 8 sites in US, of which primary efficacy data were available from 194 patients. Based on the primary efficacy variable analysis (mean change from baseline in total perennial index score averaged over the double-blind treatment period for 24 hours), 20 mg dose taken in the morning was effective in relieving the symptoms of PAR. The reduction in the symptom score was greater in the first 12 hours as compared to the second 12 hours. The reduction of symptoms was seen at day 1, however, the effect did not persist through the next 2 days. The reduction of symptoms persisted at the end of each week of treatment. The efficacy of both the doses were consistent in reducing the "snap-shot" scores, individual symptoms of PAR, and global rating of efficacy by patients. On analysis of individual symptom scores, the favorable response was carried mainly by the sneezing and itchy nose scores. The results of this study support 20 mg QD dose for relief of symptoms of PAR.

6.3.5. PAR study CR 2714

The objective of this study was to compare the efficacy and safety of ebastine 10 mg and 20 mg administered once a day in the AM to placebo. A total of 290 PAR patients between the ages of 12 and 63 years were recruited from 37 sites in France, Spain, and Portugal. Primary efficacy data were available from all patients. Based on the primary efficacy variable analysis (mean change from baseline in total rhinitis symptom score averaged over the double-blind treatment period for 24 hours), 20 mg dose taken in the morning was effective in relieving the symptoms of PAR, and 10 mg dose taken in the morning had a favorable trend. The superiority of 20 mg dose over placebo was consistent for individual symptoms of PAR. The results of this study support 20 mg QD dose for relief of symptoms of PAR, and 10 mg QD as a dose sufficient for some patients.

6.4. Summary of the US comparative efficacy studies

The applicant submitted six comparative SAR efficacy studies. These studies were not submitted to the original NDA, but were submitted as part of the complete response. They were designed to compare ebastine against loratadine to show an efficacy advantage (and therefore a public health benefit) because of the safety burden of QT prolongation. Four were US comparative SAR efficacy studies (CM.030.ALGY, CM.031.ALGY, EBA.GMA.402, and M/EBS/28) and are reviewed in the sections that follow. Two non-US comparative studies were not reviewed because of lack of precision in defining the primary endpoint (CM.14.ALGY) and flexible dosing of ebastine according to symptom severity (CM.14.ALGY).

All four US studies were very similar in design. The first three used identical protocols, which are described within the first study, CM.030.ALGY. The fourth (M/EBS/28) used a variation of the same protocol. All four studies were four weeks in duration, but M/EBS/28 set the primary variable as the first two weeks of the four-week treatment period to conform to the suggestion in the Guidance for Industry entitled *Allergic Rhinitis: Clinical Programs for Drug Products* published by the FDA in April of 2000. All variations from the first protocol are reviewed at the beginning of each study review.

All four studies used the comparison between ebastine 20 mg with loratadine 10 mg as the primary efficacy variable. The first three also included a 10 mg ebastine arm as a secondary comparison against loratadine 10 mg. All were placebo controlled, with the comparison between active drugs and placebo as secondary efficacy variables. Of note, the effect sizes (Table 19) for all four studies were comparable, and the achievement of statistical significance in different studies reflected the powering of the studies. Two out of the four showed a statistically significant difference between ebastine 20 mg and loratadine 10 mg, but two did not. None showed significant statistical differences between ebastine 10 mg and loratadine 10 mg. All showed efficacy and significant statistical differences of both doses of ebastine against placebo. Two showed significant statistical differences between loratadine 10 mg and placebo, but two did not.

6.4.1. SAR study CM.030.ALGY

The objective of this study was to compare the efficacy and safety of ebastine 20 mg and 10 mg administered QAM to loratadine 10 mg QAM and placebo in patients with SAR. A total of 567 SAR patients between the ages of 12 and 70 years were recruited from 16 sites in the US (1 each in Nebraska, Colorado, Kansas, Illinois, New York, Massachusetts, and Connecticut, 2 each in Pennsylvania, Ohio, and North Carolina, and 3 in Georgia), of which primary efficacy data were available from 472 patients. The primary efficacy variable analysis (mean change from baseline in total rhinitis symptom score averaged over the 4-week double-blind treatment period for 24 hours) for the comparison between ebastine 20 mg and loratadine 10 mg, with step-down analyses between ebastine 10 mg and loratadine 10 mg and secondary analyses between all active drugs and placebo. The primary comparison between ebastine 20 mg and loratadine 10 mg was not significant. Ebastine 20 mg 10 mg QAM, and loratadine 10 mg QAM comparisons with placebo showed that all were effective in relieving the symptoms of SAR, both for composite and all individual scores except for loratadine in the treatment of nasal congestion. The ebastine 20 mg group

showed more improvement from baseline than either ebastine 10 mg or loratadine 10 mg in all composite and individual scores. There was a trend for ebastine 10 mg to show greater change from baseline than loratadine 10 mg in all composite and individual scores. The AM snap-shot scores were significant for both doses of ebastine, suggesting that the drug remains effective over the dosing interval. The results of this study support 20 mg and 10 mg QD dose for relief of symptoms of SAR.

6.4.2. SAR study CM.031.ALGY

The objective of this study was to compare the efficacy and safety of ebastine 20 mg and 10 mg administered QAM to loratadine 10 mg QAM and placebo in patients with SAR. Study design was identical to that of CM.030.ALGY. A total of 565 SAR patients between the ages of 12 and 70 years were recruited from 14 sites in the US (11 in Texas, 1 each in Tennessee, Louisiana, and Georgia), of which primary efficacy data were available from 473 patients. The primary and secondary variables and analyses were the same as for study CM.030.ALGY. Unlike study CM.030.ALGY, the primary comparison between ebastine 20 mg and loratadine 10 mg was significant for total rhinitis composite score and the individual scores of nasal discharge and sneezing. Ebastine 20 mg 10 mg QAM, and loratadine 10 mg QAM comparisons with placebo showed that all were effective in relieving the symptoms of SAR, both for composite and all individual scores. The ebastine 20 mg group showed more improvement from baseline than either ebastine 10 mg or loratadine 10 mg in all composite and individual scores. Ebastine 10 mg was roughly equal to loratadine 10 mg in all composite and individual scores. The AM snap-shot scores were significant for both doses of ebastine, suggesting that the drug remains effective over the dosing interval. The results of this study support 20 mg and 10 mg QD dose for relief of symptoms of SAR.

6.4.3. SAR study EBA.GMA.402

The objective of this study was to compare the efficacy and safety of ebastine 20 mg and 10 mg administered QAM to loratadine 10 mg QAM and placebo in patients with SAR. The study design was the same as for studies CM.030.ALGY and CM.031.ALGY except for a larger sample size per treatment arm (higher powering). Since many of the study sites were sites used in studies 030 or 031, the study excluded patients who had participated in the two previous comparative studies. A total of 749 SAR patients between the ages of 12 and 70 years were recruited from 18 sites in the US (1 each in Louisiana, South Carolina, and Tennessee, 3 in Georgia, and 12 in Texas), of which primary efficacy data were available from 649 patients. The primary and secondary variables and analyses were the same as for study CM.030.ALGY. Like study CM.030.ALGY, the primary comparison between ebastine 20 mg and loratadine 10 mg was not significant for total rhinitis composite score. However, the individual score comparisons between ebastine 20 mg and loratadine 10 mg for nasal discharge and sneezing were significant. Ebastine 20 mg QAM comparison with placebo showed effectiveness in relieving the symptoms of SAR, both for composite and all individual scores. Ebastine 10 mg versus placebo showed effectiveness for composite and individual scores except nasal discharge and nasal congestion. Loratadine 10 mg versus placebo did not show effectiveness for total rhinitis score or the individual scores of nasal discharge and nasal congestion. The ebastine 20 mg group showed more improvement from baseline than either ebastine 10 mg or loratadine 10 mg in all composite and individual

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Integrated Review of Efficacy

scores. There was a trend for ebastine 10 mg to show greater change from baseline than loratadine 10 mg in all composite and individual scores. The AM snap-shot scores were significant for both doses of ebastine, suggesting that the drug remains effective over the dosing interval. The results of this study support 20 mg and 10 mg QD dose for relief of symptoms of SAR.

6.4.4. SAR study M/EBS/28

The objective of this study was to compare the efficacy and safety of ebastine 20 mg (but not ebastine10 mg) administered QAM to loratadine 10 mg QAM and placebo in patients with SAR. The study design was the same as for studies CM.030.ALGY and CM.031.ALGY (and study EBA.GMA.402) except for a larger sample size per treatment arm (higher powering), a randomization ratio of 2:2:1 between the 2 active arms and placebo, and the elimination of the ebastine 10 mg arm. This resulted in significantly more patients per active treatment arm. Since many of the study sites were sites used in studies 030 or 031, the study excluded patients who had participated in the two previous comparative studies. A total of 703 SAR patients between the ages of 12 and 70 years were recruited from 21 sites in the US, of which primary efficacy data were available from 618 patients. The primary and secondary variables and analyses were the same as for the previous comparative efficacy studies, except that the primary endpoint was the first two weeks of the 4-week study, and there was no step-down comparison for ebastine 10 mg vs loratadine 10 mg (an ebastine 10 mg arm was not included). Like study CM.031.ALGY, the primary comparison between ebastine 20 mg and loratadine 10 mg was significant for total rhinitis composite score. All individual score comparisons were also significant. Ebastine 20 mg QAM comparison with placebo showed effectiveness in relieving the symptoms of SAR, both for composite and all individual scores. Loratadine 10 mg QAM comparison with placebo did not show effectiveness in relieving the symptoms of SAR, both for composite and all individual scores. The AM snap-shot scores were significant for both doses of ebastine, suggesting that the drug remains effective over the dosing interval. The results of this study support 20 mg QD dose for relief of symptoms of SAR.

6.5. Summary of the supportive studies (original NDA submission)

Supportive studies submitted to and reviewed for the original NDA submission are listed in Table 16, and the distribution of patients in the studies is shown in Table 15. Supportive studies submitted to the complete response were not reviewed. Overall, the supportive study results are in agreement with the pivotal studies.

Table 16. Supportive efficacy studies of ebastine (original NDA submission)

Protocol number	Location	Indication	Patient numbers and dose (mg and schedule)				Study duration
			Ebastine	Comparator	Placebo	Total	
EBA 133	USA	SAR	53 (20 mg QD)	x	53	106	1 day
EBA 102	USA & Canada	SAR	80 (1 mg QD) 77 (3 mg QD) 76 (10 mg QD) 75 (20 mg QD) 73 (30 mg QD)	x	78	459	2 weeks
CR 2747	Europe	SAR	161 (20 mg QD)	159 (Cetirizine)	152	472	3 weeks

Protocol number	Location	Indication	Patient numbers and dose (mg and schedule)				Study duration
			Ebastine	Comparator	Placebo	Total	
				10 mg QD)			
EBA 021	Europe	SAR	43 (10 mg QD)	45 (Terfenadine 60 mg BID)	45	133	2 weeks
EBA 028	Australia	SAR	115 (10 mg QD)	114 (Terfenadine 60 mg BD)	118	347	3 weeks
SI 01	Europe	SAR	116 (10 mg QD) 111 (20 mg QD)	116 (Cetirizine 10 mg QD)	x	343	2 weeks
EBA 022	Europe	PAR	79 (10 mg QD)	x	82	161	3 weeks
CR 2715	Europe	PAR	103 (10 mg QD) 111 (20 mg QD)	114 (Loratadine 10 mg QD)	x	317	4 weeks
Source: v 1, p 255-261							

6.5.1. SAR studies

EBA 133: This was a one day onset of action study comparing the efficacy of single dose of 20 mg ebastine with placebo (reviewed on page 130). All enrolled patients were evaluable for efficacy. The primary efficacy variable was the AUC_{0-10hr} after dosing of the mean change from baseline in total symptom score. The overall mean reduction of total symptom score for ebastine was better than the placebo.

EBA102: This was a parallel-group study comparing the efficacy of different doses of ebastine to placebo. Five patients could not be evaluated for efficacy. The primary efficacy variable was the mean change from baseline in total symptom score averaged over the double-blind period for the 24 hours score. A dose-related reduction of total symptom score for ebastine was seen (-1.7 for placebo, -1.9 for 1 mg, -2.2 for 3 mg, -2.2 for 10 mg, -2.6 for 20 mg, -2.4 for 30 mg), which was significant (p=0.026) for 20 mg. One patient (1793, a 53-year-old male) from ebastine 3 mg group was discontinued on day 4 of treatment for arrhythmia. On ECG, the baseline QTc was 404 msec, and QTc on day 4 was 431 msec. Follow-up Holter done 3 days later showed multiple PVCs. The consulting cardiologist's opinion was that the patient has "benign PVCs with labile hypertension." The event was considered to be remotely related to study drug.

CR2747: This was an active controlled study conducted in France, Scandinavia, and Eastern Europe. The primary efficacy measure was the mean change from baseline in total symptom score averaged over the double-blind period. Ebastine and cetirizine were both better than placebo in reducing total symptom score (p=0.002 and p=0.009, respectively); and the 2 drugs were not different from each other (p=0.681).

EBA 021: This was an active controlled study conducted in France, and Italy. The primary efficacy measure was the mean change from baseline in major rhinitis symptoms (nasal obstruction, rhinorrhea, and sneezing) recorded at weeks 1 and 2. Both the drugs were better than placebo, and significant improvement for ebastine was seen at week 1 for nasal obstruction, and at week 2 for nasal obstruction, and sneezing.

EBA 028: This was an active controlled study conducted in 8 centers in Australia. The primary efficacy measure was the mean change from baseline in major rhinitis symptoms (nasal obstruction, rhinorrhea, and sneezing) averaged over each week separately. Both the

drugs were better than placebo, and significant improvement for ebastine was seen for rhinorrhea, and sneezing at week 1 and overall.

EBA SI 01: This was an active controlled study conducted in 46 centers in France. The primary efficacy variables were the mean changes from baseline in total symptom score averaged over the double-blind period and by each week separately. There were no significant differences among the treatment groups in the efficacy measures. The mean reduction of symptom was greater for ebastine 20 mg compared to 10 mg (-10.6 and -9.8, respectively.

6.5.2. PAR studies

EBA 022: This was a placebo-controlled study conducted in France, Belgium, Netherlands, Denmark, and Sweden. The primary efficacy variable was the overall assessment of efficacy made by the patients on days 7 and 21 using a 4-point scale. At day 7, a significantly higher number of patients on 10 mg ebastine (37%) compared to placebo (21%) rated the overall efficacy of treatment as good or excellent (p=0.01). At day 21, 40% of patients on ebastine 10 mg and 32% of patients on placebo rated the overall efficacy of treatment as good or excellent, however, the difference was not statistically significant.

CR 2715: This was an active controlled study conducted in France, Germany, and Greece. The primary efficacy variable was the mean change from baseline in perennial index score averaged over the double-blind period. Pairwise comparisons showed that the scores were significantly improved in ebastine 10 mg and 20 mg group compared with loratadine (p=0.015 and p=0.003, respectively).

6.6. Subset efficacy analysis by age, gender, and race

The efficacy data for the pivotal and supportive studies were stratified based on age group (12-16 years, 17-59 years, and over 60 years), gender (male, and female), and race (Caucasian, and non-Caucasian), but this was not done for the comparative studies. The overall efficacy was consistent for these subsets analysis, although most of these did not reach statistical significance at 0.05 possibly because of small sample sizes in the subgroups (v 314, p 106-127).

6.7. Summary of efficacy results

The pivotal efficacy studies are adequate in showing that ebastine tablets at a dose of 20 mg QD is effective in providing relief of symptoms of SAR and PAR in patients 12 years of age and older. The results of the studies also show that for some patients ebastine at a dose of 10 mg QD may be adequate. Analysis of primary efficacy variable (mean change from baseline in total rhinitis symptom score averaged over the double-blind treatment period for 24 hours) (Table 17) was consistent across studies and was also consistent for the secondary efficacy variables (e.g., "snap-shot" rhinitis scores, individual rhinitis scores, AM and PM scores, global rating of efficacy by patient and physician, etc.). The consistent efficacy of ebastine 20 mg was also supported by global ratings of efficacy as rated by patients and physicians independently.

Scoring for all efficacy studies was based on a composite of five symptoms (nasal discharge, nasal stuffiness, sneezing, itchy nose, itchy/watery eyes) on a 0-3 scale, called the total rhinitis symptom score. The composite score in most studies was mainly carried by scores of sneezing, itchy nose, and nasal discharge, which is expected of an antihistamine. It was interesting to note that in the SAR pivotal efficacy studies, nasal stuffiness was also significantly controlled by ebastine when compared to placebo.

In 3 of the 4 US pivotal efficacy studies (EBA 124, EBA 132, and EBA 109), the reduction of symptom scores was greater in the first 12 hours as compared to the second 12 hours (Table 46, Table 59, and Table 71), although, in most of the studies reduction at both time points were statistically superior to placebo. This suggests a weaning of effect towards the end of dosing interval. In all the pivotal US studies, 20 mg/day of ebastine significantly reduced symptoms by day 1 of treatment. In study EBA 133, designed to study the onset of action of a single 20 dose of ebastine in SAR patients in a natural setting of exposure, significant symptom improvement was seen at 4 hours for total symptom score, and at 3 hours for total symptom score without nasal stuffiness (Table 97). Overall, the efficacy for ebastine for control of symptoms of SAR and PAR is adequately demonstrated in the pivotal studies.

The US comparative studies support the pivotal studies for the efficacy of ebastine in the treatment of seasonal allergic rhinitis. Statistically significant results against placebo were achieved in all four studies, even though the comparison with placebo was a secondary endpoint in the studies (Table 18). However, the magnitude of the statistical significance against placebo in these studies was affected by the powering, which was increased to allow the comparison against an active competitor. Therefore, the p-values are not helpful for the comparative studies, and a comparison of effect size (effect size = difference between treatment and placebo for change from baseline with treatment) is of more relevance.

Cross-study comparison of effect sizes is only made possible by the fact that for all the studies the efficacy evaluation used the same scoring system (reflective total rhinitis symptom score over the duration from baseline to endpoint) for the primary variable. Such a comparison is limited by the different study designs, the timing of endpoints, and the timing and location of the studies. With these limitations in mind, such a comparison, particularly when different dosages are used within multiple studies, can yield valuable information. Comparison of effect sizes in the pivotal SAR and PAR studies and US comparative SAR studies (Table 19) showed that, while the effect sizes varied somewhat, both the 10 mg and 20 mg doses of ebastine were effective. The effect sizes seen in US comparative SAR studies were generally comparable to the effect sizes seen in the pivotal SAR studies. As expected, dosing in the morning appears to be more effective for SAR. The 20 mg AM dosage (average = 1.27, range: 0.82 – 1.66) appears to be the most efficacious, followed by the 10 mg AM dosage (average = 1.12, range: 0.73 – 1.70) (Figure 3). Evening administration was less effective, with a 10 mg PM dosage the least effective (20 mg: 0.77; 10 mg 0.44). For PAR (Figure 4), the 10 mg BID and the 20 mg AM dosages were more effective than the 10 mg AM dosage (10 mg AM: 0.42, 20 mg AM: 0.57, 10 mg BID 0.70).

While 10 mg is an effective dose, the difference in exposure between 10 and 20 mg is small compared to the ~40- to 50-fold increase in exposure when ebastine is co-administered with

ketoconazole. Therefore, the ebastine 10 mg dose would not give a substantial safety margin over the ebastine 20 mg dose in situations where is taken concomitantly with drugs metabolized by the CYP3A4 pathway such as ketoconazole or erythromycin.

Table 17. Summary of primary efficacy variable* from pivotal efficacy studies

Study	Treatment	N	Baseline mean	Change from baseline, mean±SE	p-value vs. placebo[†]
SAR studies:					
EBA 124 (3 weeks)	10 mg AM	79	9.15	-3.47 ± 0.32	0.049
	20 mg AM	77	9.02	-3.90 ± 0.33	0.001
	10 mg PM	80	8.87	-3.05 ± 0.29	0.172
	20 mg PM	77	8.97	-3.38 ± 0.32	0.031
	Placebo	78	9.01	-2.61 ± 0.32	
EBA 132 (3 weeks)	10 mg AM	97	9.27	-3.76 ± 0.29	0.000
	20 mg AM	95	9.35	-3.53 ± 0.29	0.000
	Placebo	95	9.05	-2.06 ± 0.26	
PAR studies:					
EBA 109 (3 weeks)	10 mg BID	73	5.88	-2.40 ± 0.23	0.015
	20 mg AM	77	5.67	-2.23 ± 0.19	0.018
	Placebo	73	5.85	-1.70 ± 0.19	
EBA 110 (3 weeks)	20 mg QD	93	5.89	-2.06 ± 0.19	0.019
	Placebo	101	6.05	-1.51 ± 0.16	
CR 2714 (12 weeks)	10 mg QD	87	4.47	-1.66 ± 0.19	0.082
	20 mg QD	101	4.92	-1.87 ± 0.18	0.007
	Placebo	97	4.68	-1.24 ± 0.18	

* Primary efficacy variable for the SAR studies was the mean change from baseline in total reflective symptom score (sum of nasal discharge, nasal stuffiness, sneezing, itchy nose, and itchy/watery eyes) averaged over the double-blind treatment period for 24 hours; and for the PAR studies was the mean change from baseline in reflective perennial index score (sum of nasal discharge, sneezing, and itchy nose) averaged over the double-blind treatment period for 24 hours

[†] Based on t-test for a two-way main effects analysis of covariance with treatment and center as main effects and no interaction term

Source: This review: Table 46, Table 59, Table 71, Table 81, and Table 93.

Table 18. Summary of primary efficacy variable* from comparative US SAR efficacy studies**

Study	Treatment	N	Baseline mean	Change from baseline, LS mean±SE	p-value vs. loratadine[†]	p-value vs. placebo[†]
CM.030.ALGY (4 weeks)	E 10 mg QD	139	9.35	-3.66 ± 0.23	NS	0.0002
	E 20 mg QD	**141**	**9.17**	**-3.85 ± 0.23**	**0.1069**	**<0.0001**
	L 10 mg QD	**139**	**9.51**	**-3.33 ± 0.23**		**0.0070**
	Placebo	140	9.31	-2.47 ± 0.23		
CM.031.ALGY (4 weeks)	E 10 mg QD	137	9.90	-3.63 ± 0.23	0.7979	0.0006
	E 20 mg QD	**143**	**9.85**	**-4.18 ± 0.23**	**0.0454**	**<0.0001**
	L 10 mg QD	**140**	**9.76**	**-3.54 ± 0.23**		**0.0015**
	Placebo	139	9.71	-2.52 ± 0.23		
EBA.GMA.402 (4 weeks)	E 10 mg QD	185	10.21	-3.64 ± 0.20	NS	0.0083
	E 20 mg QD	**183**	**9.83**	**-3.92 ± 0.20**	**0.0614**	**0.0003**
	L 10 mg QD	**183**	**10.25**	**-3.40 ± 0.20**		**0.0785**
	Placebo	182	9.72	-2.91 ± 0.20		

Study	Treatment	N	Baseline mean	Change from baseline, LS mean±SE	p-value vs. loratadine[+]	p-value vs. placebo[+]
M/EBS/28 (first 2 weeks of 4-week study)	**E 20 mg QD**	282	**10.76**	**-3.46 ± 0.16**	**0.0018**	0.0024
	L 10 mg QD	278	**10.59**	**-2.77 ± 0.17**		0.6292
	Placebo	141	10.84	-2.64 ± 0.23		

* Primary efficacy variable for the comparative SAR studies was the mean change from baseline in total reflective symptom score (sum of nasal discharge, nasal stuffiness, sneezing, itchy nose, and itchy/watery eyes) averaged over the 4-week (except for study M/EBS/28, which used the first 2 weeks of the 4-week study as the primary endpoint) double-blind treatment period for 24 hours for the comparison between ebastine 20 mg and loratadine 10 mg. Step-down efficacy (except for M/EBS/28) was performed for ebastine 10 mg versus loratadine 10 mg when the primary comparison was significant. Secondary efficacy included individual symptom scores for all comparisons and for the comparison between active treatments and placebo. Primary comparisons are **bolded**.
** Two European comparative efficacy studies omitted because of study design flaws.
[+] Based on t-test for a two-way main effects analysis of covariance with treatment and center as main effects and no interaction term.

Source: This review: Table 101, Table 110, Table 119, and Table 129.

Table 19. Summary of effect size* from primary and US comparative efficacy studies

Dosage	Study	Effect size
SAR studies		
10 mg AM	EBA 124	0.86
	EBA 132	1.70
	CM.030.ALGY	1.19
	CM.031.ALGY	1.11
	EBA.GMA.402	0.73
10 mg PM	EBA 124	0.44
20 mg AM	EBA 124	1.29
	EBA 132	1.47
	CM.030.ALGY	1.38
	CM.031.ALGY	1.66
	EBA.GMA.402	1.01
	M/EBS/28	0.82
20 mg PM	EBA 124	0.77
PAR studies		
10 mg QD	CR 2714	0.42
10 mg BID	EBA 109	0.70
20 mg AM	EBA 109	0.53
	EBA 110	0.55
	CR 2714	0.63

* Effect size is difference between treatments for change from baseline in total reflective rhinitis symptom scores

Source: This review: Table 17, Table 18

Ebastine SAR studies

Effect Size (R-TRSS)

0.86	1.70	1.19	1.11	0.73	0.44	1.29	1.47	1.38	1.66	1.01	0.82	0.77

124 132 30 31 402 | 124 | 124 132 30 31 402 28 | 124
E10AM | E10PM | E20AM | E20PM
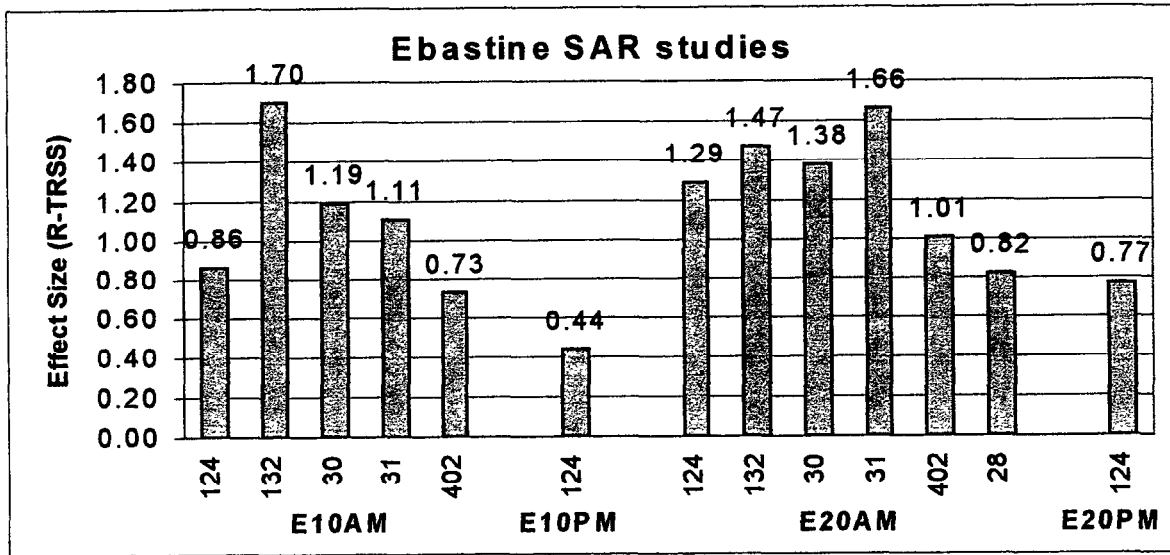
Figure 3. Effect size in ebastine SAR studies

* Effect size is difference between treatments for change from baseline in total reflective rhinitis symptom scores

Ebastine PAR studies

Effect Size (R-TRSS)

0.42	0.70	0.53	0.55	0.63

2714 | 109 | 109 110 2714
E10AM | E10BID | E20AM
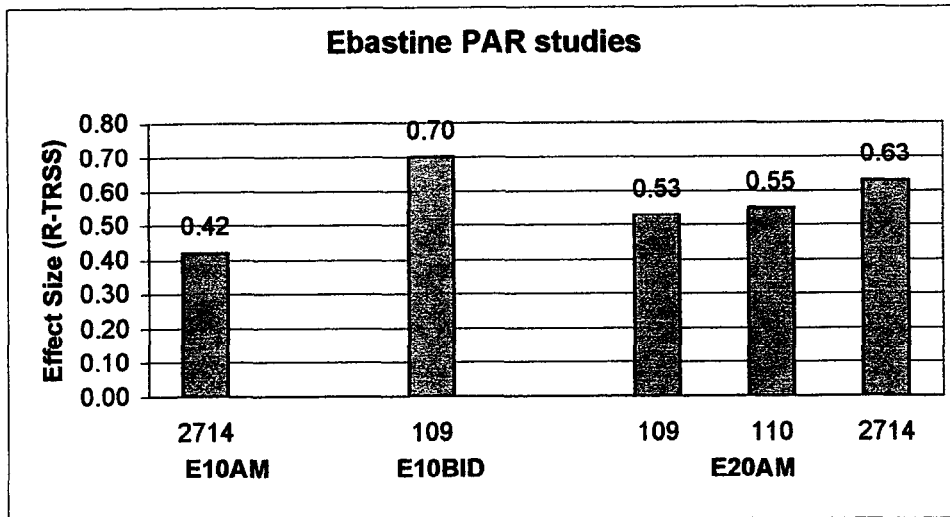
Figure 4. Effect size in ebastine SAR studies

* Effect size is difference between treatments for change from baseline in total reflective rhinitis symptom scores

7. INTEGRATED REVIEW OF SAFETY

This safety summary presents data from 9210 subjects enrolled in 35 efficacy and safety studies. This includes 7 non-cardiac clinical pharmacology studies (370 subjects), 16 placebo-controlled fixed-dose studies (6742 subjects, of whom 3657 received ebastine), 1 placebo-controlled flexible-dose study (309 subjects), 1 onset of action study (404 subjects), 8 cardiac safety studies (655 subjects), and 2 marketing support studies (730 subjects). Some of these studies evaluated ebastine against comparator drugs, so the actual number of subjects/patients exposed to ebastine or placebo is less. (v 2.203, p 11)

For the Summary of Safety presented in the original NDA submission, the applicant pooled data from 10 studies, 5 pivotal SAR and PAR efficacy studies (EBA 124, EBA 132, EBA 109, EBA 110, and CR 2714), and 5 supportive PAR and SAR efficacy studies (EBA 021, EBA 022, EBA 028, EBA 102, and CR 2747). These studies were placebo-controlled and were at least 2 weeks in duration. Study CR 2714 was 12 weeks in duration, and the other studies were 2-3 weeks in duration. In these 10 pooled placebo-controlled studies, 2966 patients were enrolled (Table 14, and Table 15), of which 1725 received ebastine, 923 received placebo, and 159 each received terfenadine or cetirizine. The majority of the patients in these studies were male (50% to 59%) and Caucasian (64% to 98%). Ages ranged from 12 to 77 years (mean ages were 30 to 35 years). The extent of exposure to ebastine in these studies is shown in Table 20. The 2 one-year open label safety studies (EBA 141 and CR 2713) were also pooled for some safety analysis. (v 21, p 20, 67, 110)

For the Summary of Safety presented in the complete response to the 'not approvable' letter, the applicant pooled data from 16 fixed-dose, placebo-controlled studies that evaluated more than one dose of ebastine in patients with SAR or PAR. One further flexible-dose study could not be pooled and was presented separately. This included safety information from 12 of studies that had previously been submitted with the original NDA and four new studies. The additional new studies were the 4 US comparative efficacy studies (CM.030.ALGY, CM.031.ALGY, EBA.GMA.402, and M/EBS/28). All four were 4-weeks in duration. Demographics of the 16 pooled studies is shown in Table 21. (v 2.203, p 13)

Cardiac safety was evaluated in eleven studies, of which seven had been submitted to the original NDA and four were new studies. Of these, M/EBS/25 was the key cardiac safety study, having been designed prospectively with FDA input to evaluate cardiac safety using a very large number of ECGs, far larger than any of the previous studies.

Table 20. Duration of exposure by days and dosage (original NDA submission)

Treatment		N	Days treated									Average
			1-3	4-7	8-14	15-22	23-30	31-60	61-90	91-120	>120	Days
Short-term placebo controlled studies*:												
Placebo		923	11	31	75	612	101	7	63	23	0	26
Ebastine	Overall	1725	24	38	231	1122	123	13	127	47	0	26
	1 mg QD	80	1	1	40	38	0	0	0	0	0	14
	3 mg QD	77	1	3	42	31	0	0	0	0	0	14
	10 mg QD	660	9	21	55	448	38	7	60	22	0	27
	20 mg QD	835	12	13	60	567	85	6	67	25	0	27
	30 mg QD	73	1	0	34	38	0	0	0	0	0	15
Cetirizine	10 mg QD	159	0	6	5	98	50	0	0	0	0	21
Terfenad.	60 mg BD	159	4	16	14	118	7	0	0	0	0	17
One-year open label studies†:												
			Days treated									
			1-7	8-60	61-120	121-180	181-240	241-300	301-350	351-364	>364	
Ebastine	20 mg QD	512	5	37	26	28	14	21	73	169	139	299

* Five pivotal SAR and PAR studies (EBA 124, EBA 132, EBA 109, EBA 110, and CR 2714), and 5 supportive PAR and SAR studies (EBA 021, EBA 022, EBA 028, EBA 102, and CR 2747).
† EBA 141, and CR 2713

Source: v 21, p 67, 69

Table 21. Demographic characteristics by treatment group (16 pooled studies in complete response)

Treatment		N	Sex		Age		Race		
			Male	Female	Mean	Range	Cauc	Black	Other
Placebo		1885	997	888	34	11 - 77	1587	80	218
Ebastine	Overall	3657	1893	1764	34	11 - 75	3098	166	393
	1 mg QD	80	47	33	33	18 - 63	76	3	1
	3 mg QD	77	45	32	34	19 - 57	71	1	5
	10 mg QD	1269	702	567	33	11 - 70	1082	54	133
	20 mg QD	2158	1062	1096	35	11 - 75	1806	103	249
	30 mg QD	73	37	36	35	20 - 65	63	5	5
Cetirizine	10 mg QD	159	80	79	31	11 - 63	155	2	2
Terfenad.	60 mg BD	159	93	66	35	17 - 65	102	1	56
Loratadine	10 mg QD	881	411	470	36	12 - 70	703	56	122

* Five pivotal SAR and PAR studies (124, 132, 109, 110, and 2714), 7 supportive PAR and SAR studies (014, 021, 022, 028, 102, 601, and 2747), and 4 comparative efficacy studies 030, 031, 402, .28)
† EBA 141, and CR 2713

Source: v 2.203, p 46

7.1. Adverse events

Adverse events reported by patients in the pivotal efficacy studies and comparative US efficacy studies, are tabulated within the individual reviews that follow this section (Pivotal studies: Table 52, Table 64, Table 75, Table 87, and Table 95; US Comparative studies: Table 103, Table 112, Table 121, and Table 132). When data from 6742 patients with SAR and PAR (3657 of whom received ebastine, and 1886 of whom received placebo) enrolled in the 16 placebo-controlled studies were pooled for analysis, the overall incidence of adverse

events were comparable between the ebastine (1 to 30 mg QD) and the placebo groups (35.1% and 35.4%, respectively). The most common adverse event in both groups was headache (9.2% and 11.1% for the ebastine and placebo groups, respectively). The most common drug-related adverse events for the ebastine group were dry mouth (2.7% ebastine, 1.6% placebo) and somnolence (2.4% ebastine, 1.4% placebo). The adverse events in the ebastine 10 mg and 20 mg QD groups (the recommended dose in the NDA) with an incidence of ≥0.5% and greater than the placebo group are listed in Table 22. Adverse events of specific concern for an antihistamine (dry mouth and somnolence) are shown in **bold**. The most common adverse events in this listing were dry mouth (4.8% ebastine 10mg, 2.6% ebastine 20 mg, 2.3% placebo) and somnolence (3.2% ebastine 10mg, 3.2% ebastine 20 mg, 2.2% placebo). When drug relationship was considered, the most commonly reported adverse events considered possibly or probably related to the study drug in the ebastine groups were dry mouth (2.7%, and 1.6%, respectively) and somnolence (2.4% and 1.4%, respectively). The majority of adverse events in each group were mild to moderate in intensity. The adverse events observed from other RPR and from non-RPR clinical studies are similar to the pooled placebo controlled studies reported to the original NDA. (v 21, p 22, 117-151; v 2.203, p 47)

Table 22. Adverse events with an incidence of ≥0.5% in the ebastine groups and greater than in placebo

	Ebastine 10 mg QD (n=1269)	Ebastine 20 mg QD (n=2158)	Placebo (n=1886)
Body as a whole:			
Abdominal pain	20 (1.6%)	14 (0.6%)	27 (1.4%)
Asthenia	22 (1.7%)	30 (1.4%)	25 (1.3%)
Back pain	19 (1.5%)	28 (1.3%)	22 (1.2%)
Flu syndrome	16 (1.3%)	20 (0.9%)	12 (0.6%)
Headache	147 (11.6%)	150 (7.0%)	210 (11.1%)
Infection	14 (1.1%)	18 (0.8%)	13 (0.7%)
Pain neck	9 (0.7%)	2 (0.1%)	4 (0.2%)
Pain	10 (0.8%)	25 (1.2%)	21 (1.1%)
Digestive system:			
Dyspepsia	18 (1.4%)	25 (1.2%)	19 (1.0%)
Flatulence	8 (0.6%)	3 (0.1%)	0 (0.0%)
Increased appetite	8 (0.6%)	8 (0.4%)	6 (0.3%)
Hemic and lymphatic system:			
Lymphadenopathy	7 (0.6%)	3 (0.1%)	4 (0.2%)
Musculoskeletal system:			
Arthralgia	4 (0.3%)	12 (0.6%)	4 (0.2%)
Myalgia	11 (0.9%)	19 (0.9%)	11 (0.6%)
Nervous system:			
Dizziness	15 (1.2%)	24 (1.1%)	19 (1.0 %)
Dry mouth	61 (**4.8%**)	56 (**2.6%**)	44 (**2.3 %**)
Somnolence	40 (**3.2%**)	69 (**3.2%**)	42 (**2.2 %**)
Respiratory system:			
Asthma	18 (1.4%)	14 (0.6%)	13 (0.7%)
Bronchitis	8 (0.6%)	15 (0.7%)	11 (0.6%)
Epistaxis	17 (1.3%)	33 (1.5%)	19 (1.0%)
Pharyngitis	49 (3.9%)	62 (2.9%)	70 (3.7%)
Sinusitis	18 (1.4%)	27 (1.3%)	25 (1.3%)

	Ebastine 10 mg QD (n=1269)	Ebastine 20 mg QD (n=2158)	Placebo (n=1886)
* Adverse Events in 16 pooled placebo-controlled studies. Subjects only counted once for multiple occurrences of the same event.			
Source: v 2.203, p 50			

7.2. Serious adverse events

Review of both the original NDA submission and the complete response to the 'not approvable' letter shows no trend toward significant adverse events in subjects treated with ebastine. In information reported in the complete response, a total of 8 patients (who were either on ebastine or placebo, since patients who experienced a serious adverse event on a comparator are omitted from this discussion) from the 16 pooled placebo-controlled studies reported serious adverse events, of whom 1 was an unintended pregnancy. The events were superficial phlebitis, cholecystitis, accidental knee injury, facial paralysis, kidney calculus, myocardial infarction, and accidental leg abrasion. Previously, in information submitted to the original NDA, the applicant had reported a total of 6 patients from the 10 placebo-controlled studies with serious adverse events. The events were facial paralysis, accidental knee injury, arrhythmia, elective abdominal liposuction, accidental leg abrasion, and urolithiasis. Several of these events were from patients/subjects who were on a comparator drug, accounting for why several different adverse events were reported previously.

However, the complete response submission did omit one serious adverse event of arrhythmia, which had been reported to the original NDA. This event occurred in a 53-year-old male in study EBA 102 (ebastine 3 mg group) on day 4 of treatment. Holter monitoring showed multiple benign PVCs. On ECG, the QTc was 404 msec at baseline and 431 msec on day 4 of study. The event was considered as remotely related to study drug. (v 21, p 151-154). Also, in information submitted to the original NDA but not to the complete response to the 'not approvable' letter, a total of 10 patients from the long-term studies (EBA 124 LT, EBA 141, and CR 2713) reported serious adverse events. The events were depression, hysterectomy, goiter, atrial fibrillation, basal cell skin cancer, hepatitis, ruptured ovarian cyst, femur fracture, and peritonitis. The adverse event of atrial fibrillation occurred in a 52-year-old female (study EBA 141, ebastine 20 mg group) on day 143 of the study. The patient's baseline QTc was 398 msec, and QTc the day after the event was 353 msec. The patient had a long history of hypertension. None of these adverse events were study drug related. (v 21, p 155-158)

7.3. Discontinuations due to adverse events

The incidence of discontinuations due to adverse events was similar for ebastine (2.8%) and placebo (3.0%) in the 16 pooled placebo-controlled studies. While there were no discontinuations due to adverse events in the 1- or 30-mg groups, discontinuations in the 3-, 10-, and 20-mg QD groups were 2.6%, 3.6%, and 2.6%, respectively. In the pooled placebo controlled studies, the most common adverse events (counted by number of subjects, rather than by number of occurrences of an adverse event) that led to discontinuation in the ebastine 10 mg group were headache (9), sinusitis (7), dizziness, bronchitis (4 each), and somnolence (3); in the ebastine 20 mg group were sinusitis (10), headache, somnolence (5 each), pharyngitis (4), rhinitis, and bronchitis (3 each); and in the placebo group were

rhinitis (11), sinusitis (9), headache (4), and abdominal pain (3). Tables for discontinuations due to adverse events in the pivotal efficacy studies and the US comparative efficacy studies may be found within the individual reviews that follow this section (Pivotal studies: Table 53,Table 65,Table 76,Table 88,and Table 96; US Comparative studies: Table 104, Table 113, Table 122, and Table 133). In the long-term studies (EBA 121 LT, EBA 124, and CR 2713) the most common adverse events that led to discontinuation were headache, asthenia, and dry mouth (5 occurrences each), and nervousness (2 occurrences each) (v 21, p 163-168; v 2.203, p 57).

7.4. Deaths

Almirall reported that there were no deaths reported in any of the clinical studies (v 21, p 163; v2.203, p 47) and five deaths reported as post-marketing spontaneous adverse events. However, one of the five deaths was in a patient enrolled in one of the clinical trials in Colombia, and is therefore reported here. All five deaths are discussed in the Postmarketing Safety section on page 72.

- EBST2000003. Male PAR patient, age 33, Colombia. This was a violent death in combat for a professional soldier who had been enrolled in a clinical trial (EBA-UY-501) with ebastine. He had been on ebastine 10 mg QD for 4-6 weeks. The patient had been lost to follow-up from within the trial, and afterwards the clinical investigator submitted a spontaneous adverse event report stating that the patient died in combat. Assessed by Almirall as unrelated causality. (Submission of 10/22/02, v 3, p 115-7)

7.5. Physical examination and laboratory evaluations

There were no clinically relevant changes in vitals signs, and physical examinations in the placebo-controlled studies, long-term safety studies, and other RPR and non-RPR studies (v 21, p 228; v 2.203, p 94), except for a small increase in body weight seen in the lung term studies. In CR 2714 the mean weight gain during the 4 months of treatment was 0.7 kg (page 129). In EBA 124 LT the weight gain was related to the duration of exposure and ranged from 0.45 to 1.42 kg during the 4 months of treatment. In EBA 141 the mean weight gain was 2 kg during the one year of treatment with ebastine. One patient in study CM.014.ALGY experienced chest pain on study day 5 and tachycardia on the final study visit (v 2.203, p 94).

Since several studies did not evaluate laboratory parameters, the complete response included pooled laboratory parameters from 12 pooled studies (EBA 021, EBA 022, M/EBS/028, CM.ALGY.030, CM.ALGY.031, EBA 102, EBA 109, EBA 124, EBA.GMA.402, RP-601). The incidence of clinically relevant changes in serum chemistry, hematology, and urinalysis parameters were low, 2.2% for placebo, and 2.8% overall for ebastine, with no dose-related trends noted within the ebastine-treated groups. Incidence of elevated SGOT was 0.3%, 0.5%, and 0.8% in the placebo, ebastine 10 mg, and ebastine 20 mg groups, respectively. Incidence of elevated SGPT was 0.6%, 0.6%, and 1.0% in the placebo, ebastine 10 mg, and ebastine 20 mg groups, respectively (v 2.203, p 62-4). In studies EBA 124, EBA 124 LT, and EBA 141, serum transaminase elevation was seen in the ebastine treated patients. The number of patients with the elevation was low, and the magnitude of elevation was also low. Elevated transaminase levels were more frequent in the long-term studies EBA 124 LT and

EBA 141 suggesting a cumulative dose effect. In two of the cardiac safety studies (EBA 136 and EBA 138) a trend was also noted in transaminase level elevation related to ebastine treatment (Table 141and Table 162).

Shift analysis of mean changes in laboratory values from pooled studies did not show any clinically relevant significant changes. The percent of subjects who experienced a shift up from low to normal, low to high, or normal to high for selected laboratory values are shown in Table 23. The percent of subjects with selected laboratory values that shifted from normal to high is shown in Table 24. The percent of subjects with laboratory values outside predefined limits in pooled studies is shown in Table 25. Differences between ebastine and placebo for effects on both SGOT and SGPT were seen, with a higher percent of subjects experiencing a shift up with ebastine treatment than with placebo, and with dose ordering between the ebastine 3 mg, 10 mg and the 20 mg doses (Table 24).

Table 23. Percent of subjects with shift up[†] from baseline for selected laboratory values in US pooled placebo-controlled studies*

Laboratory Parameter	Ebastine 10 mg		Ebastine 20 mg		Overall ebastine		Placebo	
	N	% with shift up[†]	N	% with shift up[†]	N	% with shift up[†]	N	% with shift up[†]
Bilirubin (mg/dl)	735	0.4%	1680	0.9%	2642	0.7%	1206	2.0%
Cholesterol (mg/dl)	787	7.0%	1307	6.0%	2321	6.5%	1021	4.2%
Creatinine (mg/dl)	786	0.9%	1735	0.8%	2748	0.8%	1236	1.1%
Glucose (mg/dl)	783	5.2%	1304	7.2%	2314	6.2%	1017	6.5%
SGOT (U/l)	785	3.2%	1732	4.7%	2744	4.2%	1235	3.3%
SGPT (U/l)	785	2.4%	1732	3.8%	2744	3.1%	1235	1.9%
Uric acid (mg/dl)	786	2.9%	1735	3.0%	2747	2.9%	1237	2.7%
Eosinophils (%)	449	5.6%	736	5.6%	1185	5.6%	587	5.3%
* Not all doses were administered, and not all tests were performed in all studies								
† % with shift up = % of subjects/patients who changed from low to normal, low to high, and normal to high								
Source: Submission of October 10, 2002, , p 72-85								

Table 24. Percent of subjects with selected laboratory values with N→H shifts in US pooled studies

Laboratory test	Ebastine (%)				Placebo (%)
	3 mg	10 mg	20 mg	Overall	
Cholesterol (mg/dl)	0	1.3	3.6	2.5	1.9
Creatinine (mg/dl)	0	0.9	0.7	0.7	1.1
Glucose (mg/dl)	0	4.0	6.4	5.1	6.3
SGOT (U/l)	0	2.3	3.6	3.0	1.8
SGPT (U/l)	2.6	3.2	4.7	4.2	3.3
Uric acid (mg/dl)	1.3	2.7	2.8	2.7	2.4
Source: Submission of October 10, 2002, , p 72-85					

Table 25. Percent of subjects with selected laboratory values outside predefined limits in US pooled studies

Laboratory test		Ebastine		Placebo
		10 mg	20 mg	
Glucose	>ULN (+30%)	2.8% (0.4%)	3.1% (0.2%)	3.4% (0.3%)
SGOT	>ULN (+50%)	1.4% (0.1%)	2.1% (0.1%)	0.8% (0.1%)
SGPT	>ULN (+50%)	2.0% (0.3%)	2.8% (0.2%)	2.1% (0.2%)
Uric acid	>ULN (+10%)	2.4% (0.3%)	2.7% (0.2%)	2.7% (0.2%)
Source: v 2.203, p 88-90				

7.6. Cardiac safety

Cardiac safety was specifically evaluated in 11 studies, of which 7 had been submitted to the original NDA and 4 were new studies. Study M/EBS/25 was the pivotal cardiac safety study, having been designed prospectively with FDA input to evaluate cardiac safety using a very large number of ECGs, far larger than any of the previous studies. The full review of the pivotal cardiac safety study, M/EBS/25, may be found starting on page 213 of this document.

Cardiac safety of ebastine from the placebo-controlled efficacy studies, US placebo-controlled comparative efficacy studies, open-label safety studies, high-dose cardiac safety studies, drug interaction cardiac safety studies, and from other studies and from postmarketing experience is summarized below.

7.6.1. Placebo-controlled US efficacy studies

ECGs were performed at baseline and weekly during the double-blind treatment periods at 3-5 hours after dosing, which approximated the T_{max} for ebastine. Holter monitoring was performed in a subset of patients in these studies. All ECGs were read in the central facility in Philadelphia. The results of these studies are pooled and presented here. The duration of the studies was 3 weeks (EBA 123, EBA 132, EBA 109, and EBA 110) or 2 weeks (EBA 102). A total of 1202 patients (842 on ebastine, and 360 on placebo) had both baseline and double-blind ECG evaluations. Holter monitoring was performed in 226 patients. Mean QTc changes at each week of treatment in the 4 pivotal efficacy studies are shown in Table 26, and summary of the QTc changes in the pooled studies is shown in Table 27. No changes in QTc were evident in these summary analyses. Changes in QTc over the duration of treatment in the pooled studies are shown in Table 28. More patients in the ebastine 20 mg/day group had longer QTc than patients in the placebo group. Summary results of QTc outliers (QTc >440 msec and an increase of $\geq 10\%$ above baseline) is shown in Table 29. A dose dependent increase of QTc outliers was seen, which was marked for the female patients. These analyses (Table 28, and Table 29) suggest that ebastine at the recommended therapeutic dose prolonged QTc in some patients. On Holter monitoring, no clinically relevant changes were seen (v 21, p 230, 260-269).

Table 26. Mean QTc changes by treatment weeks in pivotal US efficacy studies

Study	Treatment	N	Baseline (msec)	Increase from baseline (msec)		
				Week 1	Week 2	Week 3
EBA 124	Placebo	75-79	398	1	2	1
	Eba 10 mg AM	73-79	401	7	2	3
	Eba 10 mg PM	76-80	397	6	6	6
	Eba 20 mg AM	74-79	401	5	6	2
	Eba 20 mg PM	71-78	399	9	9	6
EBA 132	Placebo	90-95	388	-1	7	8
	Eba 10 mg AM	90-97	387	6	7	8
	Eba 20 mg AM	91-95	388	5	5	6
EBA 109	Placebo	68-73	401	1	-1	3
	Eba 10 mg BD	69-74	405	-1	-2	-1
	Eba 20 mg AM	74-76	400	5	2	1
EBA 110	Placebo	96-101	405	0	3	5
	Eba 20 mg AM	86-93	408	7	6	7

Source: Table 54, Table 66, Table 77, Table 89 of this review

Table 27. Summary QTc changes in pooled placebo-controlled US studies[*]

Treatment	N	Maximum observed QTc		QTc change from baseline	
		<444 msec n (%)	444-499 msec[†] n (%)	< 15% n (%)	15-24%[‡] n (%)
Placebo	360	339 (94 %)	21 (6 %)	355 (99 %)	5 (1 %)
Ebastine 10 mg/day	272	261 (96 %)	11 (4 %)	269 (99 %)	3 (1 %)
Ebastine 20 mg/day	518	474 (92 %)	44 (8 %)	506 (98 %)	12 (2 %)

[*] Includes studies EBA 124, EBA 132, EBA 109, EBA 110, EBA 102
[†] None had QTc ≥500 msec
[‡] None had QTc prolongation ≥25%

Source: v 21, p 261, tables merged and modified

Table 28. Summary QTc changes in pooled placebo-controlled pivotal US efficacy studies[*]

Treatment	N	Maximum observed QTc (msec)[†]				QTc change from baseline (msec)[†]			
		>430	>450	>470	>490[‡]	>15	>30	>45	>60[§]
Baseline:									
Placebo	344	24	1	0	0	na	na	na	na
Eba 10 mg/day	257	11	0	0	0	na	na	na	na
Eba 20 mg/day	503	40	3	0	0	na	na	na	na
Week 1:									
Placebo	330	37	3	0	0	86	32	9	0
Eba 10 mg/day	248	18	2	0	0	90	26	7	1
Eba 20 mg/day	488	62	5	0	0	138	54	12	1
Week 2:									
Placebo	320	24	3	0	0	89	29	7	1
Eba 10 mg/day	243	20	2	0	0	79	24	5	1
Eba 20 mg/day	477	50	13	2	0	130	49	14	3
Week 3:									
Placebo	339	45	6	0	0	97	30	6	1
Eba 10 mg/day	257	24	4	0	0	72	22	6	0
Eba 20 mg/day	501	60	13	2	0	146	45	12	1

6.4.2 CARDIAC EVENTS FROM POOLED PLACEBO-CONTROLLED TRIALS (Studies EBA 102, EBA 109, EBA 110, EBA 124, EBA 132, M/EBS/28)

6.4.2.1 QTc Intervals > 440 msec and a Change from Baseline ≥ 10 msec

The percentage of subjects with a QTcF interval > 440 mm <u>and</u> a change from baseline ≥ 10 msec was low and similar between treatment groups (0% - 4%). There were no relevant differences between any of the treatment groups by age subgroup, based on the categorical ECG changes. More female than male subjects in the ebastine 10- and 20-mg qd groups had categorical ECG changes (females, ≤ 5% and males, ≤ 1%). These results were similar when compared with the loratadine group (females, 4% and males, 2%). No subgroup analysis by race was performed due to the small number of the non-Caucasians in the studies. **Table 38** summarizes the number and percentages of subjects with QTcF intervals > 440 msec <u>and</u> change from baseline ≥ 10 msec.

Table 38   Number (Percent) of Subjects with QTcF Intervals > 440 msec and Change from Baseline ≥ 10 msec (US Pooled Placebo-Controlled Trials)

| Parameter | Placebo | Ebastine (mg/day) | | | | | Loratadine 10 mg |
		1 mg	3 mg	10 mg	20 mg	30 mg	
Patients with QTc Intervals > 440 msec and Change From Baseline >= 10 msec	36/1184 (3%)	0/24 (0%)	0/24 (0%)	23/734 (3%)	43/1683 (3%)	0/23 (0%)	20/737 (3%)
Male	16/619 (3%)	0/17 (0%)	0/12 (0%)	6/410 (1%)	11/827 (1%)	0/10 (0%)	5/331 (2%)
Female	20/565 (4%)	0/7 (0%)	0/12 (0%)	17/324 (5%)	32/856 (4%)	0/13 (0%)	15/406 (4%)
Age <= 16 years	4/121 (3%)	0	0	2/80 (3%)	2/154 (1%)	0	0/57 (0%)
Age > 16 < 60 years	30/1000 (3%)	0/24 (0%)	0/24 (0%)	19/630 (3%)	35/1436 (2%)	0/23 (0%)	14/627 (2%)
Age >= 60 years	2/63 (3%)	0	0	2/24 (8%)	6/93 (6%)	0	6/53 (11%)

Note: Includes data from studies 030, 031, 102, 109, 110, 124, 132, 402, 601, and CL28.

Note: QTcF = QT/ (60/VR)$^{1/3}$, corrected with Fridericia's formula.

Note: Ebastine 20 mg qd includes Ebastine 10 mg BID and 20 mg qd.

Appendix B, Table 21b.

In the gender analysis, the changes in QTcF interval > 440 mm <u>and</u> a change from baseline ≥ 10 msec **(Table 38)** observed in female subjects treated with ebastine 10 mg qd was higher than for female subjects in the loratadine and placebo groups. However, there appeared to be no difference between female subjects in the ebastine 10-mg group and the placebo group with respect to the mean change in maximum QTc interval compared with QTc baseline values. This lack of consistency across the two analyses suggests low specificity of the categorical ECG changes when evaluating gender. **Table 39** summarizes the change in QTcF from baseline by treatment group and gender.

Treatment	N	Maximum observed QTc (msec)[+]				QTc change from baseline (msec)[+]			
		>430	>450	>470	>490[‡]	>15	>30	>45	>60[§]

*Includes EBA 124, EBA 132, EBA 109, and EBA 110. Results are expressed as number (percentage).
[+] Normal QTc in adult males is <430 and in adult females is <450. QTc >450 in males and >470 in females is considered prolonged. Individual QTc change 30-60 msec are likely to represent drug effect, and >60 are risk for inducing arrhythmias including *Torsades de Pointes* (Ref. CPMP guideline, 1996).
[‡] None had QTc ≥500 msec.
[§] None had QTc prolongation ≥25%.

Source: Created from SAS data set of the studies

Table 29. Patients with QTc >440 msec and a change from baseline of ≥10% in pooled placebo-controlled US studies*

	Placebo n/N (%)	Ebastine 10 mg/day n/N (%)	Ebastine 20 mg/day n/N (%)
All patients	24/339 (7 %)	21/257 (8 %)	51/503 (10 %)
Male patients	12/192 (6 %)	5/161 (3 %)	15 (5 %)
Female patients	12/147 (8 %)	16/96 (17 %)	36/193 (19 %)

*Includes studies EBA 124, EBA 132, EBA 109, EBA 110

Source: v 21, p 269

7.6.2. Placebo-controlled US comparative efficacy studies

Unlike the primary efficacy studies, none of the four US comparative SAR efficacy studies included Holter monitoring. All were of four weeks in duration, with one ECG at baseline and one at the end of 28 days of treatment. All used QTcB for correction of QT for heart rate. A summary of heart rate changes in the US comparative efficacy studies is shown in Table 30. Subjects in all four studies experienced slight increases in heart rate over the course of the 4 weeks of treatment. The placebo, ebastine 10 mg, ebastine 20 mg groups had an increase of 2.1-4.3 msec, 3.3-4.6 msec, and 5.0 to 7.7 msec, respectively. A summary of QTcB changes in the US comparative efficacy studies is shown in Table 31. Mean change from baseline in QTcB for the placebo groups ranged from –1 to 1 msec, whereas the mean changes for ebastine 10 and 20 mg ranged from 1-5 and 1-3 msec, respectively. . A summary of outliers with a ≥30 msec prolongation in QTcB in the US comparative efficacy studies is shown in Table 32. In the outlier analyses, while numbers of patients who experienced an increase in QTcB of ≥ 30 msec from baseline were not significantly different between sets of treatment groups, both the Ebastine 10 mg and 20 mg groups each had 2 patients who had very large increases in QTcB from baseline. In the Ebastine 10 mg group in study CM.031.ALGY, one patient had an increase of 89 msec, and one an increase of 101 msec. In on Ebastine 20 mg group in study M/EBS/28, one patient had an increase on 60 msec, and one an increase of 55 msec. Except for these outliers, no definitive statements regarding cardiac safety may be made based on these studies.

Table 30. Summary of Heart Rate changes in placebo-controlled US comparative efficacy studies

Treatment	Study	N	Baseline mean (BPM)	Post-treatment mean	Mean change
E 10 mg	CM.030.ALGY	142	66.528	69.207	3.336
	CM.031.ALGY	140	66.093	69.794	4.000
	EBA.GMA.402	186	66.610	71.474	4.614
E 20 mg	CM.030.ALGY	143	65.350	70.612	5.065
	CM.031.ALGY	143	64.916	70.693	5.964
	EBA.GMA.402	188	64.697	72.178	7.708
	M/EBS/28	281	65.738	71.332	5.610
L 10 mg	CM.030.ALGY	140	65.471	70.723	5.350
	CM.031.ALGY	141	65.071	68.799	3.770
	EBA.GMA.402	189	66.283	71.011	4.927
	M/EBS/28	278	64.342	71.687	5.322
Placebo	CM.030.ALGY	142	65.275	67.364	2.171
	CM.031.ALGY	141	63.532	66.628	2.934
	EBA.GMA.402	186	65.670	69.769	4.325
	M/EBS/28	141	65.670	68.847	3.397
Source: Table 106, Table 115, Table 125, and Table 135					

Table 31. Summary of QTcB changes in placebo-controlled US comparative efficacy studies

Treatment	Study	N	Baseline mean (msec)	Post-treatment mean	Mean change
E 10 mg	CM.030.ALGY	142	404	405	1
	CM.031.ALGY	140	403	408	5
	EBA.GMA.402	186	405	407	2
E 20 mg	CM.030.ALGY	143	408	412	3
	CM.031.ALGY	143	405	407	3
	EBA.GMA.402	188	406	408	1
	M/EBS/28	281	407	409	2
L 10 mg	CM.030.ALGY	140	406	410	5
	CM.031.ALGY	141	407	406	-1
	EBA.GMA.402	189	408	407	-1
	M/EBS/28	278	408	408	0
Placebo	CM.030.ALGY	142	405	405	0
	CM.031.ALGY	141	406	406	0
	EBA.GMA.402	186	404	406	1
	M/EBS/28	141	410	410	-1
Source: Table 106, Table 115, Table 125, and Table 135					

Table 32. Summary of numbers of outliers with QTcB $\geq$ 30 msec in placebo-controlled US comparative efficacy studies

Study	Ebastine 10 mg (n = 468)	Ebastine 20 mg (n = 755)	Placebo (n = 610)
CM.030.ALGY	1	2	3
CM.031.ALGY	4*	2	0
EBA.GMA.402	2	2	0
M/EBS/28	–	2[†]	4

Study	Ebastine 10 mg (n = 468)	Ebastine 20 mg (n = 755)	Placebo (n = 610)
* One patient had an increase of 89 msec, and one an increase of 101 msec on Ebastine 10 mg. † One patient had an increase on 60 msec, and one an increase of 55 msec on Ebastine 20 mg.			
Source: Table 107, Table 116, Table 126, and Table 136			

7.6.3. Open-label safety studies

Cardiac safety was assessed in 2 US uncontrolled studies (EBA 124LT, and EBA 141) and one non-US uncontrolled study (CR 2713). Study EBA 124LT was 4 months in duration. Ebastine at 10 mg/day and 20 mg/day was used in this study. Mean QTc did not change during the study (Table 33), however, 7 patients had ≥15% prolongation of QTc over baseline (Table 34). The ranges of prolongation were 55-70 msec. Of these 7 patients, 4 were discontinued from the study for the protocol specified ECG discontinuation criteria of QTc prolongation of ≥15% over the final visit of study EBA 124. Two of these patients had ECG done after the study drug washout. In both, QTc returned towards baseline after discontinuation of ebastine (Table 34). In this study 6 more patients were discontinued for cardiac reasons, 3 for PVCs seen on ECG, and 3 for PVCs seen on Holter. The 3 patients discontinued for Holter findings were patients 00004 from the 20 mg PM group, 00421 from the 10 mg PM group, and 00503 from the 20 mg AM group. All were for ventricular ectopics - paired VPBs, and multiform VEs (v 165, p 53-54). The 3 patients discontinued for ECG changes were patients 00087 from the 10 mg PM group, 00406 from 20 mg PM group, and 00428 from the 20 mg AM group. These patients are described in below, since the individual study review is not included in this document. None of the arrhythmias were of nature typically associated with QTc prolongation, but it was of interest that 2 of these patients had QTc prolongation of 23 and 35 msec over baseline when they were discontinued.

- Patient 00087 (47 year old male on ebastine 10 mg PM) developed PVCs on day 28 of study drug. A repeat ECG was interpreted as normal. The adverse event was classified as mild and not related to the study drug (v 265, p 52). On review of line listing of ECG results of this patient, prolongation of QTc was observed (v 269, p 76). The baseline QTc was 377 msec. QTc on other study days were 391 msec (day 8), 397 msec (day 15), 392 msec (day 22), 400 msec (day 29), and 402 msec (day 35). PVCs were not seen on ECGs done at baseline, and on days 8, 15, 22, and 35.

- Patient 00406 (45 year old male on ebastine 20 mg PM) developed PVCs on day 50 of study drug. A repeat ECG was interpreted as normal. The adverse event was classified as mild and not related to the study drug (v 265, p 52). On review of line listing of ECG results of this patient, QTc prolongation was again observed (v 269, p 420). The baseline QTc was 431 msec. QTc on other study days were 450 msec (day 8), 395 msec (day 15), 417 msec (day 22), 421 msec (day 29), 466 msec (day 50), and 419 msec (day 63). PVCs were not seen on any study day other than day 50.

- Patient 00428 (58 year old female) developed PVCs every third beat on day 28 of the study. The patient reported lightheadedness, fluttering feeling in the mid-chest on exertion, and indigestion. Holter monitoring and repeat ECGs showed frequent PVCs, premature beats, and trigeminy. Study drug was discontinued and the patient was

referred to a cardiologist. After discontinuation of the drug the symptoms resolved and the PVCs decreased. A stress ECHO done a month later was negative. The patient later revealed a past history of rare palpitations and chest flutters that had not caused problems. This patient's baseline Holter showed PVCs. The investigator recorded the adverse event as moderate and not related to the study drug. The consulting cardiologist did not rule out a possible relationship to test drug considering the clinical symptoms and increase in PVCs. Further review revealed that the patient's screening QTc was 458 msec, which was above the exclusion limit of 444 msecs (v 165, p 30, 48-53). Line listing of ECG results of this patient could not be located at the appropriate place (v 269, p 305).

The studies EBA 141 and CR 2713 were one year in duration. Ebastine at 20 mg/day was used in these studies. In study EBA 141 the QTc calculations were from computer reading rather than the protocol specified manual reading by a qualified cardiologist. In this study a total of 25 patients (5.7%) had QTc values over 440 msec and with 10 msec prolongation over baseline. The maximum QTc prolongation was 93 msec and the highest recorded QTc was 483 msec. Study CR 2713 was a small study that enrolled 77 patients with PAR. No patient in this study had a QTc of over 440 msec and with 10 msec prolongation over baseline (v 21, p 231, 265).

Table 33. Study 124LT, Summary of QTc changes

Treatment Group	N	Baseline mean* in msec	On-treatment mean in msec	% change from baseline, mean (SE)
10 mg AM	53	400	403	0.021 (0.571)
10 mg PM	59	396	401	1.493 (0.574)
20 mg AM	54	403	403	0.141 (0.612)
20 mg PM	63	397	403	1.450 (0.500)
* Baseline refers to start of active treatment, double-blind EBA 124 or open-label 124LT				
Source: v 165, p 48				

Table 34. Study 124LT, Patients with ≥ 15% change from baseline in QTc

Patient	Treatment	Study day	Baseline QTc in msec	On treatment QTc in msec	Change in msec	QTc after washout[+]
00153*	10 mg AM	29	365	420	55	386
00292*	10 mg AM	45	363	422	59	Not reported
00430	10 mg PM	51	378	447	69	-
00059*	20 mg AM	20	355	425	70	Not reported
00317	20 mg PM	134	405	478	73	-
00397	20 mg PM	77	368	424	56	-
00402*	20 mg PM	77	386	455	69	389
* Patients discontinued due to QTc prolongation of at least 15% from the end of double-blind treatment [+] Washout period was 7 days for patient 00153, and 28 days for patient 00402						
Source: v 165, p 30, 51. Washout period data were obtained from line listing (v 268 p 437 for patient 00153, v 269 p 6 for patient 292, v 269 p 220 for patient 00059, and v 269 p 417 for patient 00402).						

7.6.4. Cardiac safety from other studies

Limited QTc data were obtained from PK studies in elderly (EBA 112), patients with renal insufficiency (EBA 113, EBA 128), and hepatic insufficiency (EBA 118) and PK/PD

studies in theophylline interaction (EBA 008), food effect (EBA 121, EBA 129), histamine skin response effect (EBA 101), and antimuscarinic effect (EBA 005). Single dose administration of ebastine 10 mg or 20 mg had no relevant effects on QTc in these studies (v 21, p 257).

7.6.5. High-dose cardiac safety studies

Three studies (EBA 136, EBA 126, and M/EBS/21) were done to evaluate the effect of high doses of ebastine on QTc. These studies were done in young (18 to 40 years of age) healthy male volunteers. All the cardiac safety studies were designed and powered based on Bazett's corrected QT. The applicant submitted results of some additional analyses of QT data for study EBA 136 in submission dated November 6, 1998, and December 29, 1998. The QT data from these studies were reanalyzed using Fridericia's correction for heart rate, and the reanalysis along with the uncorrected QT and heart rate were submitted. The analysis was done in a manner identical to the primary analysis using Bazett's correction and presented in the submissions in tabular form showing the mean, maximum, and AUC calculations for the data. The applicant's rationale for doing these additional analysis was that there is a debate regarding the appropriateness of the many formulas that correct the QT for heart rate, and a reference to the Committee for Proprietary Medicinal Products guidance (December 1997) that asks that applicants should provide an analysis of uncorrected QT and heart rate in addition to analysis of corrected QT.

EBA 136: Study EBA 136 compared the effects of placebo, ebastine 60 mg (3 times the therapeutic dose), ebastine 100 mg, and terfenadine 360 mg (3 times the therapeutic dose) administered QD for 7 days in a 4-way crossover design (n = 32). Serial baseline ECGs were done on study day 1 for comparison to steady-state serial ECG on days 5, 6, and 7. Results for all corrections are shown in Table 145. Analyses of the primary variables showed a dose-dependent prolongation of QTcB by ebastine as compared to placebo (3.7 msec by ebastine 60 mg, 10.3 msec by ebastine 100 mg, and 1.4 msec by placebo), which was less in magnitude than that of terfenadine (18.0 msec by terfenadine 360 mg). On the Bazett's corrected QT, the dose dependent prolongation of QTc was statistically significant for the 100 mg dose as compared to the placebo. On Fridericia's correction, the trend was in the same direction, although the differences were not statistical significant for ebastine. The uncorrected QT did not increase with ebastine. Subjects considered to be ECG outliers (QTcB above 440 msec and at least 10 msec prolongation over baseline) were more in the treated groups than the placebo group (6 in terfenadine 360 mg, 3 in the ebastine 100 mg, and 1 each in the ebastine 30 mg and in placebo) (Table 143).

EBA 126: Study EBA 126 compared the effects of 8 days of placebo, and ebastine at doses of 10, 20, 40, and 80 mg QD in a parallel group, two-period (the 80 mg dosage was given during the second period) design (n = 77). Serial baseline ECGs were done on study day 1 for comparison to steady-state serial ECG on days 5, 6, 7, and 8. Ebastine at higher doses tended to cause QTc prolongation, however, the effect was not dose-proportional, except between the 10, 20 and 40 mg doses administered within one treatment period (Table 147). The assessment of dose-response is difficult in this study because the doses were studied in 2 separate periods with different populations. A crossover study, such as EBA 136, is more appropriate since there is high inter-subject-variability of the QTc interval (v 21, 231-236).

M/EBS/21: Study M/EBS/21 compared the effects of placebo, and ebastine in ascending single doses of 80, 150, 300, and 500 mg in an open-label design with 5 days between successive doses (n = 6). This was considered a pilot study. Six subjects were recruited, and five completed the study, limiting interpretation of results. With incrementally higher single doses of ebastine, heart rate, QTcB, and QTcF are noted to increase incrementally (Table 150). No single QTcB or QTcF interval greater than 500 msec, and no intra-individual post-dose increase in mean QTcB or QTc F interval greater than 10% was found.

7.6.6. Drug-interaction cardiac safety studies

Eight drug-interaction cardiac safety studies were carried out, five for the original NDA (EBA 137, EBA 127, EBA 145, EBA 138, and EBA 130) and three for the complete response (EBA 148, M/EBS 24, and M/EBS 25). The studies were divided as shown below. Five studies listed in **bold** are discussed in this section. Four studies are not discussed in this section because they were judged non-informative. These included studies EBA 127, and EBA 130 that used single doses of ebastine, and study M/EBS/24 that enrolled only 6 subjects and had an unusual crossover design. M/EBS 25 was the pivotal drug-interaction cardiac safety study.

- 2 studies (**EBA 138**, and EBA 130) were done to evaluate the interaction of ebastine and erythromycin,

- 3 studies (**EBA 137**, and EBA 127, and **M/EBS 25**) were done to evaluate the interaction of ebastine and ketoconazole,

- 3 studies were focused on loratadine vs ebastine: 1 study (**EBA 145**) was done to study the interaction of loratadine and ketoconazole, and 2 studies (**EBA 148**, and M/EBS/24) were done to compare the interaction of loratadine and ketoconazole with the interaction of ebastine and ketoconazole.

In all the studies except study M/EBS/25, young (18 to 40 years of age) healthy male volunteers with an entry criterion of having a QTc under 444 msec were enrolled (except that the entry criterion for QTc in study M/EBS/24 was 430 msec, and in study EBS 148 was 440 msec). Therefore, study M/EBS/25 was the only study in females, and the only study with an unrestricted QTc entry criterion. In studies EBA 127 and EBA 130, single dose of ebastine was used, which was not suitable to study the interaction.

Having completed the first seven studies (and before study M/EBS/25 was designed), in which Bazett's correction for calculation of QTc was defined a priori, the applicant was unhappy with the analyses results and performed subsequent analyses. The QT data from these seven studies were reanalyzed using Fridericia's method of correction for heart rate. Uncorrected QT and heart rate were also submitted. The analyses were done in a manner identical to the primary analysis using Bazett's correction and presented in the submissions in tabular form showing the mean, maximum, and AUC calculations for the data. The applicant's rationale for doing these additional analysis was that there is a debate regarding the appropriateness of the many formulas that correct the QT for heart rate, and a reference to the Committee for Proprietary Medicinal Products guidance (December 1997) that asks that applicants should provide an analysis of uncorrected QT and heart rate in addition to analysis of corrected QT. In some instances, other methods of correction for heart rate,

including linear regression analysis and Malik's individual correction method (methodology is discussed in study M/EBS/25) were submitted. Where applicable, these *post hoc* analyses are also shown in the tables below.

EBA 138: Study EBA 138 was multiple dose ebastine and erythromycin interaction study. Ebastine 20 mg QD, erythromycin 800 mg TID, or combination of both were given for 10 days in a crossover design (n = 30). Serial ECGs were done at the end of treatment and compared to the baseline serial ECGs to study the interaction. Results are shown in Table 35 and Table 164. The co-administration of erythromycin with ebastine for 10 days caused a 2- and 3-fold increase in the Cmax and AUC_{0-24} of ebastine, respectively, and a 2-and 2.5 fold increase in the Cmax and AUC_{0-24} of carebastine, respectively, over the Cmax and AUC_{0-24} achieved with ebastine plus placebo. The administration of erythromycin with ebastine for 10 days caused a 19.6 msec prolongation in the mean QTcB compared to 6.1 msec prolongation by ebastine alone and 8.9 msec prolongation by erythromycin alone. The difference with treatment over baseline for ebastine plus erythromycin over placebo plus erythromycin for QTcB was 10.7 msec. The comparison for ebastine plus placebo and erythromycin and placebo for QTcB was –2.8 msec. As shown in Table 35 and Table 164, subsequent *post hoc* QT analyses using other methods of correction resulted in slightly different numbers, but did not change the overall findings.

Table 35. EBA 138, Difference in changes with treatment[†] for corrected and uncorrected mean QT results

	Treatment	N	Baseline mean	Adjusted[*] mean change from baseline (SEM)	Delta[†] against EES + Pbo
Mean Heart Rate (msec)	Eba+EES	25	67.2	7.6	4.8
	Eba+Pbo	27	65.0	5.6	2.8
	EES+Pbo	28	65.5	2.8	
Mean QT (msec)	Eba+EES	25	371.1	-2.8	-3.3
	Eba+Pbo	27	376.0	-10.2	-10.7
	EES+Pbo	28	377.3	0.5	
Mean QTcB (msec)	Eba+EES	25	389.8	**19.6**	**10.7**
	Eba+Pbo	27	387.9	**6.1**	-2.8
	EES+Pbo	28	391.6	8.9	
Mean QTcF (msec)	Eba+EES	25	383.2	11.7	7.3
	Eba+Pbo	27	383.6	2.4	-2.0
	EES+Pbo	28	386.5	4.4	
Mean QTcM (msec)	Eba+EES	25		9.3	5.0
	Eba+Pbo	27		-0.35	-4.65
	EES+Pbo	28		4.3	
Mean QTc Linear Regression	Eba+EES	25		12.0	9.2
	Eba+Pbo	27		4.6	1.8
	EES+Pbo	28		2.8	

[*] Adjusted for imbalance of primary population (subjects with at least placebo and ebastine 100 mg) in each treatment
[†] Delta = Difference between the ebastine treatment groups and the erythromycin plus placebo group in changes with treatment compared to baseline

Source: Table 164

EBA 137: Study EBA 137 was a multiple dose ebastine and ketoconazole interaction study. Ebastine 20 mg QD was given for 13 days and ketoconazole 400 mg QD was added to the last 8 days of ebastine treatment in a parallel group design (n = 55). Serial ECGs were done at the end of treatment and compared to the baseline serial ECGs to study the interaction. Results are shown in Table 36 and Table 156. The co-administration of ketoconazole with ebastine caused a 16- and 42-fold increase in the Cmax and AUC_{0-24} of ebastine, respectively. Pharmacokinetics of carebastine were less affected. The addition of 8 days of ketoconazole to ebastine at steady-state caused an 18.1 msec prolongation in the mean QTcB compared to an 8 msec prolongation for the placebo plus ketoconazole combination. The difference in QTcB between the two treatment groups was 10.1 msec. Results for prolongation in QTcB in the ebastine plus ketoconazole arm of 18.1 msec in this study was similar to that seen the ebastine plus ketoconazole arm in the comparative study EBA 148 (Table 37), where the prolongation was 16.5 msec. As shown in Table 36 and Table 156, subsequent *post hoc* QT analyses using other methods of correction resulted in slightly different numbers, but did not change the overall findings.

Table 36. EBA 137, Difference in changes with treatment[†] for corrected and uncorrected mean QT results

	Treatment	Baseline	Day 5 - Baseline	Delta[†] Day 5- base	Day 13 - 5 Change with keto	Delta[†] Day 13-5	Day 13- base	Delta[†] Day 13- base
Mean Heart Rate (bpm)	Ebastine	63.6	1.0	0.2	2.5	3.0	3.8	3.5
	Placebo	64.1	0.8		-0.5		0.3	
Mean QT (msec)	Ebastine	375.7	-4.4	-1.4	11.1	1.6	5.8	-0.7
	Placebo	373.3	-3.0		9.5		6.5	
Mean QTcB (msec)	Ebastine	383.8	-0.8	-0.3	**18.1**	**10.1**	17.4	10.0
	Placebo	384.0	-0.5		**8.0**		7.4	
Mean QTcF (msec)	Ebastine	380.8	-1.9	-0.6	15.6	7.2	13.4	6.3
	Placebo	380.2	-1.3		8.4		7.1	
Mean QTc Regression					15.4 8.5	6.9		
QTcM (msec)					13.0 7.1	5.9		
[†] Delta = Difference between the ebastine treatment groups and the erythromycin plus placebo group in changes with treatment compared to baseline								
Source: Table 156								

In both studies EBA 138 and EBA 137, pharmacokinetic analysis of ebastine and carebastine was also done. Both ketoconazole and erythromycin treatment altered ebastine kinetics, but the effect of ketoconazole was more pronounced. For example, administration of ebastine with ketoconazole for 8 days increased the ebastine Cmax by about 15 fold compared to ebastine alone, whereas administration of ebastine with erythromycin increased the ebastine Cmax by about 2 fold compared to ebastine alone (Table 152, and Table 161). Across the 2 studies, the QTc prolongation was not proportional to the systemic ebastine exposure. In both the studies, the QTc prolongation was comparable (18.1 msec for ketoconazole interaction, and 19.6 msec for erythromycin interaction), although the systemic exposure to ebastine was different (ebastine Cmax of 59.9 for ketoconazole interaction, and 18.6 or erythromycin interaction). This discrepancy is difficult to reconcile. Differences in

study design, duration of exposure, possible effect of the drugs on other unrecognized counter balancing cardiac ion channels, or presence of other unaccounted metabolites may be responsible for the discrepancy.

EBA 148: While EBA 148 was a comparative study between ebastine plus ketoconazole and loratadine plus ketoconazole. The 2-period crossover design allowed comparison between treatments in the same subjects (n = 43). Within each treatment period, the treatment design was similar to the other ebastine plus ketoconazole interaction studies, in which ebastine 20 mg QD or loratadine 10 mg QD was give alone for the first 5 days, followed by 8 days of co-administration with ketoconazole 400 mg QD. Unfortunately, there was no placebo control, as it was designed specifically for evaluation of the comparison with loratadine. Results are shown in Table 37. The co-administration of ketoconazole with ebastine caused a 6- and 16-fold increase in the Cmax and AUC_{0-24} of ebastine, respectively. Pharmacokinetics of carebastine were less affected. The addition of 8 days of ketoconazole to ebastine at steady-state caused an 16.5 msec prolongation in the mean QTcB, confirming the finding seen in study EBA 137 (parallel design against placebo), where the prolongation in QTcB was 18.1 msec. The magnitude of QTcB prolongation was larger than that seen by co-administration of loratadine plus ketoconazole. The findings did not change when other *post hoc* methods of QT correction for heart rate were used.

Table 37. EBA 148, Difference in changes with treatment[†] for corrected and uncorrected mean QT results

	Treatment	Baseline mean[*]	Day 5 Eba/Lora	Day 5 - Baseline	Day 13 Eba/Lora + Ketoconazole	Day 13 - 5 Change with ketoconazole
Mean Heart Rate (bpm)	Ebastine	63.5	65.2	1.7	67.4	2.2
	Loratadine	63.3	64.8	1.5	66.6	1.8
Mean QT[‡] (msec)	Ebastine	374.0	370.7	-3.3	380.4	9.7
	Loratadine	373.0	369.9	-3.1	375.5	5.7
Mean QTcB[‡] (msec)	Ebastine	383.2	384.7	1.5	401.2	**16.5**
	Loratadine	381.6	382.6	1.0	393.9	11.3
Mean QTcF[‡] (msec)	Ebastine	380.0	379.6	-0.4	394.0	14.1
	Loratadine	378.6	378.2	-0.4	387.5	9.3
QT regressn. (msec)	Ebastine					13.3
	Loratadine					8.6
QTcM (msec)	Ebastine					11.9
	Loratadine					7.8
[*] Results expressed as mean, n=30						
[†] Delta = Difference between the ebastine treatment groups and the erythromycin plus placebo group in changes with treatment compared to baseline						
Source: Table 171						

EBA 145: The study design of loratadine and ketoconazole multiple dose interaction study (EBA 145) was similar to the ebastine and ketoconazole interaction study (EBA 137). The administration of ketoconazole 400 mg QD with loratadine 10 mg QD for 8 days caused a 16.3 msec prolongation in the mean QTc compared to 9.6 msec prolongation for placebo plus ketoconazole (Table 38 and Table 159). On pharmacokinetic analysis, an interaction between loratadine and ketoconazole was also seen (Table 158). Although PK interaction

between loratadine and ketoconazole is reported (loratadine package insert), QTc prolongation by loratadine reported in this study contradicts the studies submitted in loratadine NDA, and difficult to reconcile with the in-vitro and cardiac potassium channel studies of loratadine (Section 4.8, page 30). Of note, this study was conducted in France, whereas all the other drug interaction cardiac safety studies were conducted in the United States.

Table 38. EBA 145, Difference in changes with treatment[†] for corrected and uncorrected mean QT results

	Treatment	Baseline mean[*]	Day 5 - base	Delta Day 5	Day 13 - 5 Change with keto	Delta Day 13-5
Mean Heart Rate (bpm)	Loratadine	57.1	1.1	1.1	3.4	2.0
	Placebo	56.6	0.0		1.4	
Mean QT (msec)	Loratadine	387.7	-4.4	-3.6	5.3	0.4
	Placebo	391.8	-0.8		4.9	
Mean QTcB (msec)	Loratadine	374.4	0.4	1.0	16.3	6.7
	Placebo	378.6	-0.6		9.6	
Mean QTcF (msec)	Loratadine	377.9	-0.7	-0.1	12.6	4.5
	Placebo	382.5	-0.6		8.1	

[*] Results expressed as mean (n) or mean ± sem, n=30
[†] Delta = Difference between the ebastine treatment groups and the erythromycin plus placebo group in changes with treatment compared to baseline
Source: Table 159

For the drug interaction cardiac safety studies with ebastine (studies EBA 138 and EBA 145) (Table 35 and Table 38), the Fridericia's corrected QT showed a numerically smaller but statistically significant difference between the ebastine and placebo groups than the Bazett's corrected QT. For the uncorrected QT, the ebastine groups tended to have longer QT than the placebo groups although the differences were not statistically significant. In all the studies, ebastine treated groups had an increase in heart rate that explains these observed numerical differences.

M/EBS/25: Having received the letter from the FDA stating that the NDA for ebastine was not approved on the basis of the cardiac safety concerns, the applicant designed one pivotal drug interaction cardiac safety study with FDA input. The applicant decided that due to the high inter- and intra- individual variability of QT, the only satisfactory QT correction methodology was a relatively new methodology based on individual variability of QT. For each subject, an individual correction factor would be determined at baseline, and used for the rest of the study. Determination of an individual correction factor would require multiple ECGs over 2 days of baseline, and multiple serial ECGs at specific timepoints during the study to reduce the effect of intra-subject variability. Study M/EBS/25 was designed with this in mind. In addition, as noted above, it was the only cardiac safety study conducted in women, and the only cardiac safety study that did not have an upper QTc limit at study entry. For this reason it is the pivotal drug-interaction cardiac safety study.

Study M/EBS/25 was a multiple dose ebastine and ketoconazole interaction study with a 2-period crossover design. All subjects were randomized to receive either ebastine 20 mg QD

for 13 days with ketoconazole 400 mg QD added during the last 8 days, or placebo and ketoconazole, in a crossover design (n = 24). Serial ECGs were done on day 1 after the first dose, day 5 at presumed steady-state, and days 12 and 13 with ketoconazole added. The crossover design allowed for minimization of inter-subject variability of QTc. Each subject had a 2-day baseline measurement before each treatment period, allowing not only the measurement of the individual correction factor but allowing direct comparison of treatment effects at each timepoint.

Results of this study are presented in depth in the individual review starting on page 213, and are only summarized here. Specifically, the Figures and Tables are not reproduced in this section, and references are made to the Figures and Tables within the primary multidisciplinary review. The addition of 400 mg QD of ketoconazole to a 20 mg QD regimen of ebastine caused a significant increase in Cmax, AUCt, and $AUC_{0\to\infty}$ of ebastine of about 16-, 44-, and 52-fold, respectively (Table 175). The Cmax of carebastine was about 6-10 times higher than the parent drug, and accumulated in the body due to its long half-life (24.6 hours at steady-state) compared with the dosing interval (Figure 9). Just as in other studies, co-administration of ketoconazole did not significantly alter Cmax or AUCt. However, the $AUC_{0\to\infty}$ of carebastine was found to be significantly affected, and carebastine levels remained constant throughout the dosing interval on day 12, and for 48 hours after dosing on day 13 (Figure 10).

The addition of 400 mg QD of ketoconazole to a 20 mg QD regimen of ebastine caused a statistically significant (+11.09 msec vs +0.38 msec; difference = 10.71 msec; p = 0.0000) mean QTcM interval prolongation when compared to placebo (Table 177). This effect was shown in all methods of QTc correction, and was present in both treatment groups regardless of treatment sequence (Figure 12). Fifteen days beyond co-administration of ebastine and ketoconazole (after the wash-out period), ebastine levels were still equivalent to the ebastine levels found at steady-state (Table 176), although there appeared to be no carryover effect on QTcM (Figure 12). While baseline varied slightly between the two baseline days and between the two treatment sequence groups, the baselines for each treatment sequence group remained quite similar between treatment sequences for both groups, implying that there was no regression to the mean for baseline QT interval over time. Previous studies employed an entry criteria limiting subjects to a QTc < 444 msec. The applicant has argued that the study entry criteria for ECG for the other cardiac safety studies predisposed to enrollment of individuals at the low end of natural rhythm of the individual QT variability, thus explaining the rise in QT over time for both the placebo and ebastine treatment groups in the other cardiac safety studies. However, since baseline did not change over the treatment sequences in this study (Figure 12), this argument for why QTc increased is no longer applicable.

The applicant has also argued that PK/PD regression analysis demonstrated a plateau effect for prolongation of QTc. They argue that even though a QTc difference of 10.71 msec was found in this study when ebastine was co-administered with ketoconazole, if exposure were to increase higher than those observed in this study the QTc would not prolong more. FDA's PK/PD modeling using individualized, group-wised, and mixed-effect methods with linear, exponential, and Emax models did not support this finding. The FDA PK/PD regression analysis demonstrated that there was a tendency toward increased QTc from

baseline with increasing ebastine and carebastine plasma concentrations or AUC. (For a brief review of the FDA PK/PD modeling analysis, please refer to separate document included in this Briefing Package.) Nevertheless, due to the limitations of inter- and intra-subject variability, goodness of fit analysis did not support any single exposure-response-QTc model. Therefore, the applicant's conclusion that there is a plateau of QTc changes with increasing doses, concentrations, or exposure (AUC) is not supported by PK/PD modeling.

The outlier analysis of QTcM results (Table 180) showed that 8 out of 23 the subjects had at least one (and often multiple) individual ECGs with an increase in QTcM of 30 msec or more from baseline during co-administration of ebastine and ketoconazole on either day 12 or 13 of treatment. This was not the case during placebo plus ketoconazole treatment, or during other days of treatment, implying that these results may be of clinical relevance.

Results of M/EBS/25 for QTcM (and also QTcB) substantiate the QTcB prolongation seen in previous, less rigorously designed studies such as EBA137 and EBA 148 (Table 39). Note that with ebastine plus ketoconazole treatment in M/EBS/25, heart rate was seen to increase 4.6 bpm at day 13 compared to placebo, slightly higher than the 3.0 bpm seen in EBA 137. The prolongation in QTcB of 21.49 msec with ebastine plus ketoconazole by day 13 in this study was also higher, compared to 18.1 msec in EBA 137 and 16.5 msec in EBA 148. While placebo plus ketoconazole prolonged QTcB by 8.0 msec in study EBA 137, the prolongation in QTcB in M/EBS/25 was 4.60 msec, compared to a 0.38 msec for QTcM. This points to a lack of prolongation in QTc by ketoconazole alone, and tends to substantiate the claim that QTcB overcorrects QT for heart rate when the heart rate is increased. The QT findings seen in study M/EBS/25 substantiate the findings seen in the other drug-interaction cardiac safety studies.

Table 39 Cross-study comparison of corrected and uncorrected mean QT results (multiple QTc analyses)

Variable	Study: Treatment (n = 23)	M/EBS/25 Baseline mean*	M/EBS/25 Day 13 - base*	M/EBS/25 Delta Day 13	EBA 137 Day 13 - 5 Change with keto	EBA 137 Delta Day 13-5	EBA 148 Day 13 - 5 Change with keto
Heart Rate (bpm)	Ebastine	70.01	7.53	4.60	2.5	3.0	2.2
	Placebo	70.10	2.93		-0.5		1.8
QT (msec)	Ebastine	393.60	-1.03	2.93	11.1	1.6	9.7
	Placebo	393.01	-3.96		9.5		
Mean QTcB (msec)	Ebastine	423.21	21.49	16.88	18.1	10.1	16.5
	Placebo	422.94	4.60		8.0		
Mean QTcF (msec)	Ebastine	412.92	13.53	11.92	15.6	7.2	14.1
	Placebo	412.53	1.61		8.4		
Mean QTcM (msec)	Ebastine	410.01	11.09	10.71			
	Placebo	410.17	0.38				

* Results expressed as mean (SD) in milliseconds. For HR, QT, QTcB, and QTcF, the baseline pooled values were derived from baseline data of each subject separately. Delta = comparison between ebastine and placebo change from baseline.
† Delta = Difference between the ebastine treatment groups and the erythromycin plus placebo group in changes with treatment compared to baseline

Source: Table 156, Table 171, and Table 179

7.7. Effects on pregnancy

Two patients in the reported pooled US clinical studies became pregnant, one on placebo and one on loratadine 10 mg QD, both in study M/EBS/28 (discussed within the study review on page 165). The patient on loratadine had a miscarriage, and the patient on placebo is being followed for the outcome of the pregnancy. The In the European positive controlled study CR 2715, one patient became pregnancy while on ebastine 20 mg/day. The outcome of the pregnancy is not known (v 21, p 154).

7.8. Withdrawal effects and abuse potential

Withdrawal effects were not specifically studied in the clinical program of ebastine. Based on experience with other antihistamines, withdrawal or drug abuse is not anticipated for ebastine (v 21, p 295).

7.9. Drug-drug interaction

Drug interactions with ebastine were studied for ketoconazole (EBA 127, EBA 137, EBA 148, M/EBS/24, and M/EBS/25), erythromycin (EBA 130, EBA 138), cimetidine (EBA 017), diazepam (EBA 006), theophylline (EBA 008), warfarin (EBA 011), and ethanol (EBA 004). Other than interaction with ketoconazole and erythromycin (Drug Interaction Cardiac Safety Studies, page 186), no interaction with other drugs was seen (v 21, p 289).

7.10. Drug-disease interaction

Drug-disease interaction with ebastine was studied in patients with renal insufficiency (EBA 113, EBA 128, and EBA 147), and in patients with hepatic insufficiency (EBA 118, EBA 146), and in an elderly population (EBA 112, EBA 151). Please refer to page 35 for a discussion of the effects of ebastine and the major metabolite carebastine in these populations.

7.11. Adverse event sub-analysis by race, age, and gender

The complete response included four large US comparative efficacy studies in which the effects of race, age and gender were not evaluated. Therefore, a reanalysis of safety by race, age and gender was not carried out or submitted as part of the complete response. However, the complete response did include the results of study M/EBS/25 (page 213), the cardiac safety and pharmacokinetic drug interaction study of multiple doses of ebastine and ketoconazole in healthy female volunteers. This study was the most carefully performed cardiac safety study, and was designed with FDA input. The study was designed to take into account the applicant's concerns regarding possible flaws in previous cardiac safety studies, and was the only cardiac safety study performed in females.

Subsequent to submission of the complete response, the applicant submitted (on October 24, 2002) a pharmacokinetic re-analysis of EBA 136 by race. However, study EBA 136 was a high-dose cardiac safety study using two dosages of ebastine (60 and 100 mg QD), which are not clinically relevant. Dosages higher than 20 mg do not follow linear kinetics. In addition, the only races that the applicant tried to evaluate were Caucasians and Blacks.

These subjects are not representative of the whole population. In fact, many of the other cardiac safety studies enrolled a large proportion of races other than Caucasians and Blacks.

Of the 2966 patients in the 10 pooled placebo controlled studies submitted to the original NDA (Table 1, Table 14, and Table 15), the majority of the patients (96%) were Caucasian, and majority (88%) were between 16 and 60 years of age. Only 2% of patients were over 60 years of age, and 11% were below 16 years of age. Due to small number of patients in the non-Caucasian racial groups, and in the ages of below 16 and over 60, meaningful comparisons could not be made about the relationship between age and race and the occurrence of adverse events to ebastine. The study population were reasonably well represented by the genders (56% were male, and 44% were female). Overall the incidence of adverse events was higher in the females compared to the males (47.2% vs 39.6% for ebastine, and 54.0% vs 39.5% for ebastine). There were no unique adverse events seen in either gender (v 21, p 290).

7.12. Postmarketing Safety

Ebastine was first marketed in Spain in 1990, and since 1995 the drug has been marketed in 78 countries. The majority of countries have approved the 10 mg dosage, and only 8 or 9 countries have approved the 20 mg dosage. A discussion of Foreign Marketing History will be found on page 19.

This section contains information regarding significant adverse events that were reported to Almirall (or RPR), and were reported by Almirall to the NDA or complete response. In addition to the spontaneous adverse events reported in the complete response of August, 2002, a Safety Update Report for the period of January 1, 2002 through June 30, 2002 and was submitted on October 22, 2002. Finally, the Division of Drug Risk Evaluation, Office of Drug Safety, CDER reviewed the above information as well as all adverse event reports submitted to the IND (See attached Consult).

7.12.1. Placing Adverse Events into context

Before discussing the postmarketing information available for review, it is well to discuss how to interpret the events that have been reported. There are several difficulties inherent in evaluating postmarketing safety of a drug, and in particular, a drug that has not yet been marketed in the United States. Among them are developing adequate estimates of both the numerator and denominator for any adverse events of concern. The major difficulty with defining a numerator for an event is the lack of reporting. This certainly varies from country to country. Other difficulties include differences in prescribing habits from country to country, and ability to collect and collate adverse events in different countries. In particular, co-administration of ebastine with other drugs known to affect CYP3A4 (i.e. ketoconazole or erythromycin) is likely to vary significantly from country to country. In some countries, ketoconazole is not marketed. In others, the prescribing patterns differ than in the US. The patient may be well-known to the physician prescribing a drug, and the patient-physician relationship may be more highly established than the often transient relationship common in the United States. This is known to affect prescribing habits and prevent inadvertent co-administration of drugs that may induce an undesired adverse event, especially a cardiac adverse event in the case of ebastine. In addition, since ebastine is not marketed in the US,

there is no regulatory authority to have adverse events that have occurred in other countries reported to the FDA. While an attempt was made to review all adverse events reported to the INDs and NDAs, the Office of Drug Safety at the FDA was not able to provide information from the US database to evaluate ebastine safety.

Defining a denominator of use for the numbers that are presented below is even more problematic. While information regarding the amount of drug sold is available, it is difficult to translate this into actual use. There are several reasons for this, including inadequate estimation of new versus renewed prescriptions, different prescription and renewal practices in different countries, and an inability to estimate how much drug is either not used or thrown away after expiry. Nevertheless, the safety update report for the period of January 1, 2002 through June 30, 2002 submitted on October 22, 2002 provides information on the amount o ebastine sold worldwide. Between January 1 and June 30, 2002, 1,537.71 kg of ebastine were sold worldwide. Since the typical world-wide daily dose (as defined by the applicant) is 10 mg, the Almirall estimates that this translates to 153,770,888 daily doses of 10 mg sold during the period. The cumulative worldwide exposure as of December 31, 2001 was 929,345,290.8 daily 10 mg doses, and as of June 30, 2002 was 1,083,116,178.8 daily 10 mg doses (v 2.203, p 144; Submission of October 22, 2002, v 1, p 85-6). Based on estimates like this, the applicant has tried to estimate a denominator for certain countries. However, the estimates are likely to be so inaccurate that they will not be presented here. Because of the difficulties outlined above, no attempt was made to place reported spontaneous adverse events into the perspective of an incidence for that event.

7.12.2. Spontaneous adverse events reported by Almirall

The distribution of reported spontaneous adverse event (SAE) (or adverse drug reaction, ADR) reports by country is shown in Table 40, and the distribution of reported spontaneous adverse event reports by sex is shown in Table 41. It will be seen that Japan and Spain make up the vast majority of reported spontaneous adverse events, of which Japan far surpasses any other country. Note that the dosage of ebastine approved in Japan and Spain is 10 mg where most of these occurred.

The total number of ADR reports submitted as part of the complete response, by body system, was 621, divided between ebastine in 612 and ebastine-pseudoephedrine in 9 cases. Other reports were submitted as part of the Safety Update Report (SUR) on October 22, 2002. Table 42 shows selected ADR reports of interest for an antihistamine. Where appropriate, the numbers have been updated with information from the SUR. Unfortunately, ADRs for some patients were placed in multiple categories, making interpretation of the table difficult. For example, one patient who had jaundice also had elevated liver enzymes, and many of the patients who had an elevation of SGOT also had an elevation of SGPT. Of interest, there were 67 reports of somnolence, and 11 reports of dry mouth.

Of the reported events, there were five death of the patients while taking ebastine, one during a clinical trial and four reported post-marketing. All five deaths are shown in section 7.12.3 on page 76.

Of specific interest are the cardiac and hepato-biliary adverse events. To evaluate these events, FDA requested the latest Safety Update Report (SUR) as well as copies of the actual

Integrated Review of Safety

hepatic or cardiac adverse event reports. All reports were reviewed (Submission of October 22, 2002, v 2, 3). For many patients, comorbid conditions and co-administration with other medications make interpretation of the relative contribution of ebastine to any outcome difficult to interpret, even when there was a temporal relationship to the use of ebastine. Some reports contain too little information to make any inferences, and therefore are not presented. However, there are a few cases in which no comorbid condition or co-administration of other medication was present that might confound the clinical picture, or a strong temporal relationship to the use of ebastine was present, or the event was significant enough to warrant description. Selected cases and a discussion of heart rhythm disturbances are presented in section 7.12.4 on page 77, and selected cases and a discussion of hepato-biliary disturbances are presented in section 7.12.5 on page 79.

Table 40. Distribution of reported spontaneous adverse event reports by country

Country	Accumulated cases
Belgium	2
Brazil	3
Colombia	5
Finland	1
France	2
Japan	409
Mexico	1
The Netherlands	3
Norway	2
Pakistan	1
Russian Federation	2
South Africa	8
Spain	20
Sweden	1
USA	1
Zimbabwe	1
Source: v 2.203, p 145	

Table 41. Distribution of reported spontaneous adverse event reports by sex

Sex	Accumulated cases
Female	298
Male	163
Unknown	1
Total	462
Source: v 2.203, p 145	

Table 42. Selected reported spontaneous adverse event reports of interest for an antihistamine* (partially updated from SUR for 1/1/02-6/30/02[†])

Body System	Accumulated cases
Central and Peripheral Nervous System	
Convulsions	2
Dizziness	15
Headache	20
Hypoaesthesia	13
Paresthesia	2
Stupor	3
Taste Perversion	8
Tinnitus	2
Vertigo	2
Psychiatric Disorders	
Anxiety	2
Hallucination	2
Insomnia	6
Nervousness	2
Somnolence	67
Gastrointestinal System	
Abdominal Pain	5
Dyspepsia	15
Dry Mouth	11
Nausea	7
Vomiting	5
Liver and Biliary System [†]	
GGT increased	4
Hepatic coma	1
Hepatic enzymes increased	2
Hepatic function abnormal	13
Hepatocellular damage	4
SGOT increased	4
SGPT increased	6
Heart Rate and Rhythm Disorders [†]	
Arrhythmia	4
Arrhythmia atrial	6
Arrhythmia ventricular	1
AV block	2
Cardiac arrest	2
Extrasystoles	4
Fibrillation atrial	4
Palpitation	23
QT prolonged	4
Tachycardia	10
Tachycardia ventricular	3
[†] Hepato-biliary and cardiac ADRs represent updated figures including the SUR of 1/1/02-6/30/02 submitted 10/22/02. Some patients experienced more than one ADR.	
* Note that only reported events of interest for an antihistamine, and not all reported events, are listed on this table.	
Source: v 2.203, p 145	

7.12.3. Deaths

Almirall reported that there were **five deaths** in patients taking ebastine; three from Japan, and one each from Colombia and Spain. However, the death of the patient in Colombia actually occurred during a clinical trial, and therefore is discussed both in this section and in section 7.4 on page 55. Two of the deaths could have been related to ventricular arrhythmias (EBS980001 and EBST 2002006). However, the relationship of ebastine to the deaths is difficult to establish from the reports. For patient report EBS980001, multiple medical problems and concomitant drugs confounds the evaluation of any relationship of the ventricular tachycardia to ebastine. Patient report EBST 2002006 is consistent with a sudden cardiac arrhythmia as a potential cause of sudden death, but there is no ECG to substantiate this possibility. The cases are presented in temporal order, with Almirall's assessment of causality at the end of each presentation.

- EBS 960077. Male patient, age 69, Japan. The patient was on ebastine 10 mg/day for acute eczema for 15 days. Ten days after ending treatment, he was diagnosed with pancytopenia. He died due to cerebral hemorrhage probably related and thrombocytopenia. Prior to death, a CBC showed a hemoglobin of 4.3 g/dl, WBC count of 2,900/cmm, and platelet count of 14,000/cmm. Hematological data prior to starting of ebastine were not available. Assessed by Almirall as unlikely causality due to the onset and level of anemia relative to the timing of ebastine use. (Submission of 10/22/02, v 3, p 150-2)

- EBS980001. Female patient, age 51, Japan. The cause of death was ventricular tachycardia. The patient had history of coronary artery disease, prolonged QTc (472-548 msec), angina pectoris, end stage renal disease, epilepsy, gastritis, arthritis, and pruritic skin eruptions. The patient was on multiple drugs that included ebastine, rebamipide, nicorandilranitidine, cisapride, Bufferin, propranolol, isorbide mononitrate, bifemelane hydrochloride, clonazepam, and mequitazine. Four months after starting ebastine, after a hemodialysis session, she was found unconscious. An ECG revealed ventricular tachycardia. She recovered after initial CPR, but ventricular tachycardia reappeared 12 hours later, treated with counter shocks and pharmacotherapy. She returned to sinus rhythm, but required respirator support and "continuous hemodiafiltration" for 5 days, and recovered. Two days later she experienced a sudden cardiac arrest and died. Assessed by Almirall as unlikely causality due to the use of other medications and the underlying heart disease. (v 21, p 282-284; Submission of 10/22/02, v 3, p 118-149)

- EBST 2002035. Male patient, age 69, Spain. The patient had a history of alcohol dependence, and hypercholesterolemia. Shortly after starting treatment with atorvastatin, he developed dermatitis, which was treated with ebastine and hydroxyzine. Two months after starting treatment with ebastine, when the dermatitis did not improve, he was admitted to the hospital by the dermatologist, and subsequently diagnosed with severe cholestatic hepatitis and acute renal insufficiency. Death was due to hepatic failure and hepatic encephalopathy. He was also being treated with ranitidine (timing and duration unknown). Assessed by Almirall as possible causality. (Submission of 10/22/02, v 3, p 110-4)

- EBST 2002006. Male patient, age 33, Japan. The patient was a musician on tour who died suddenly three weeks after starting ebastine for allergic rhinitis. He had a medical history of high blood pressure treated with nifedipine and losartan for >1 year. He was eating and drinking with his family after a performance when he suddenly fell down and experienced a cardiopulmonary arrest. Death was said to be due to cardiac arrest, cerebral edema, and brainstem hernia. There were no cardiac anomalies at autopsy, but the full the autopsy report was not available. Assessed by reporting agency as possible, and by Almirall as not assessable causality. (Submission of 10/22/02, v 3, p 107-9)

- EBST2000003. Male PAR patient, age 33, Colombia. This was a violent death in combat for a professional soldier who had been enrolled in a clinical trial (EBA-UY-501) with ebastine. He had been on ebastine 10 mg QD for 4-6 weeks. The patient had been lost to follow-up from within the trial, and afterwards the clinical investigator submitted a spontaneous adverse event report stating that the patient died in combat. Assessed by Almirall as unrelated causality. (Submission of 10/22/02, v 3, p 115-7)

7.12.4. Spontaneous adverse events of cardiac rhythm disturbances

There were 62 patient notifications with a total of 66 adverse events related to heart rhythm disturbances, of which 4 events were related to the use of the combination product. The majority of the reports were cases of palpitations, with no ECG findings. There were 4 cases of QT prolongation, and 3 cases of ventricular tachycardia (one patient had both QT prolongation and ventricular tachycardia). Almirall states that 15 of the heart rhythm disorder adverse events were considered as serious events. Since *Torsades de Pointes* may lead to death, or may be missed if an ECG is not done at the appropriate time, the numbers of patients who were actually reported to have developed *Torsades* may be misleading. Nevertheless, two patients (EBST2002015 and EBST2002043) with *Torsades de Pointes* was reported, and two patients who died are suspect cases (EBS980001 and EBST 2002006). One case of irregular heart rate fulfilled Koch's postulates for recurrence with repeated ebastine exposure (EBS980048). In addition, there are a number of cases of QTc prolongation that are highly suspect as related to ebastine use. One case of QT prolongation (EBS960244) was discovered during a routine examination of an otherwise healthy, asymptomatic 12-year old. This leads to the suspicion that QT prolongation may be significantly underdiagnosed and underreported, and that there may be many more cases of asymptomatic QT for which physicians are not evaluating patients despite the label warnings. The patients listed below are representative examples of these reports. (v 2.203, p 144-9; Submission of October 22, 2002, v 1, p 10-19)

- EBST2002015. A 69 yo female from Japan was treated with ebastine 5 mg for chronic urticaria. She developed a ventricular arrhythmia initially diagnosed as *Torsades de Pointes* 3.5 years into therapy with ebastine. She was treated with propranolol hydrochloride, and the ebastine and mequitazine were discontinued. A subsequent ECG was normal. Co-morbid conditions: Asthma, cholelithiasis. Concurrent medications: Ursodeoxycholic acid and flopropione x 4years, mequitazine x8 months, meloxicam x3 months. (10/22/02, v 2, p 296-306)

- EBST2002043. A 70 yo female from Finland was treated with ebastine 10 mg for itching developed prolonged QT and *Torsades de Pointes*. She had a medical history of

sick sinus syndrome (treated with a pacemaker since 1977), paroxysmal atrial fibrillation, gout, cardiac insufficiency, sleep apnea, depression, osteoporosis, and subclinical hypothyroidism. She underwent a scheduled cardioversion for atrial fibrillation (present x 1-2 months), after which her pacemaker was set to 50/minute and hysteresis 30. That evening, her ECG revealed a prolonged QTc of 563 msec, HR 42, atrial fibrillation with slow ventricular response, and frequent ventricular extrasystoles. Overnight, her heart rate reduced to 35/min, she had short spells of ventricular tachycardia, and felt unwell. Her pacemaker rate was increased to 55/min, hysteresis 10. No more ventricular extrasystoles and spells were seen after the adjustment. Cardiologist records from the following morning describe that the bradycardia after the adjustment to 50/min provoked ventricular arrhythmia, first ventricular extrasystoles, then *Torsades de Pointes* type ventricular tachycardia. Concurrent medications: Nitrosid (isosorbide dinitrate) 5 mg x1, Zyloric (allopurinol) 100 mg x1, Losec (omeprazole) 20 mg x1, Emgesan (magnesium hydroxide) 250 mg x1, Furosis (furosemide) 40 mg 2+1, Doxal (doxapine) 25 mg x2, Primaspan (acetylsalicylic acid) 250 mg x1, Emconcor (bisoprolol fumerate) 2.5 mg x1, Digoxin Semi (digoxin) x1, Marevan (warfarin sodium) 3-6 mg/day, and Cohemin inj. (hydroxycobolamin acetate) at intervals of every 2 months. Subsequent to the event, the patient was placed on thyroxin. (11/7/02)

- EBS960244. A 12 yo female from Japan was treated with ebastine 10 mg for allergic rhinitis. Ten weeks into treatment she had a routine physical examination including ECG for high school, at which time QTc prolongation was noted (QT/QTc = 416/454 msec, RR – 0.74 sec). One month later the ebastine was stopped because her allergic rhinitis was improved. One month after stopping ebastine, her ECG showed a QT/QTc of 380/414 msec, and a RR of 0.76 sec. The difference in QTc on-treatment and post-treatment was 40 msec. An ECG in elementary school had been normal. Co-morbid conditions: None stated. Concurrent medications: None. (10/22/02, v 2, p 183)

- EBS980048. A 75 yo female from Norway was treated with ebastine 10 mg for 11 days for allergies, during which time she experienced an irregular heart rate, which abated after stopping ebastine and started again when ebastine was reintroduced. No ECG was done. Co-morbid conditions: None stated. Concurrent medications: Atenolol, ASA. (10/22/02, v 2, p 3)

- EBS990095. A 23 yo female nursing school student from Japan was treated with ebastine 10 mg for allergic rhinitis. Three weeks into treatment, she noted her own irregular pulse. When ebastine was discontinued, the irregular pulse disappeared. ECG after stopping ebastine was considered normal. Co-morbid conditions: None stated. Concurrent medications: None. (10/22/02, v 2, p 5)

- EBS960236. A 44 yo female nurse from Japan was treated with ebastine 10 mg for chronic urticaria. Eleven days into treatment she experienced palpitations all day long. BP 110/60, pulse 90, and arrhythmia noted on PE. ECG showed frequent supraventricular extrasystoles (5 times/20 seconds). Symptoms stopped two days after ebastine was stopped. Co-morbid conditions: None stated. Concurrent medications: Isothipendyl hydrochloride. (10/22/02, v 2, p 29)

- EBS960167. A 70 yo female from Japan was treated with ebastine 10 mg for chronic urticaria. Heart pounding and light-headed feeling appeared on the same day. Ebastine

was discontinued and the symptoms resolved and did not return. Co-morbid conditions: None stated. Concurrent medications: None. (10/22/02, v 2, p 163)

- EBS990031. A 37 yo female from Japan was treated with ebastine 10 mg for allergic rhinitis. Heart pounding appeared on the second day of treatment. Ebastine was discontinued and the symptoms resolved and did not return. Co-morbid conditions: None stated. Concurrent medications: None. (10/22/02, v 2, p 175)

- EBS960078. A 42 yo female from Japan was treated with ebastine 10 mg for allergic rhinitis. She developed dizziness and heart pounding about two months into treatment. Ventricular tachycardia was found on ECG, with a run of 15 consecutive VT in the ambulance. Ebastine was discontinued and she was treated with IV xylocaine, then oral mexiletine hydrochloride. Arrhythmias did not appear thereafter. Cardiac catheterization results unknown. Co-morbid conditions: History of premature ventricular contractions during pregnancy. Concurrent medications: None. (10/22/02, v 2, p 241-251)

- EBS990065. A 25 yo male from Japan was treated with ebastine 10 mg for allergic rhinitis. He had a history of schizophrenic psychosis, but the report states that his symptoms of psychosis were well-controlled and his neuroleptics were being decreased. Four weeks after staring ebastine, he became ill with fever, dizziness, nausea and vomiting. QT prolongation was noted ("QTc 0.60"). His BP became undetectable, and he experienced a cardio-respiratory arrest. Lidocaine was injected, and the patient recovered. FU revealed that ECGs 10 months previous to the event and again on the day of or the day after starting ebastine both had abnormal QTc intervals of "0.50" and "0.60". Co-morbid conditions: History of schizophrenic psychosis. Concurrent medications: Biperiden, bromazepam, distigmine bromide, oxatomide, brotizolam, perixiazine, pimozide (ORAP) 9 mg for 4 months, tiapride hydrochloride. (10/22/02, v 2, p 252-275)

7.12.5. Spontaneous adverse events of hepato-biliary dysfunction

There were 28 patient notifications with a total of 37 adverse events related to the hepato-biliary system, of which 18 events were considered serious in nature, and 15 were sufficiently severe to require hospitalization. In most of the cases, patients experienced increases in more than one liver enzyme. Reports of histopathological examination of liver tissue were not included. Biochemically (when the results of biochemical tests of the liver were available), the type of hepatic injury observed in the case series was cholestatic; however, marked elevations in liver transaminases were present in some of the cases. Most cases were in Japan, although there were several from Spain, one from Pakistan (in the mother of a US physician), and one from Sweden. One patient (EBST 2002035) with a history of alcohol dependence died of liver failure two months after starting ebastine (see section 7.12.3 on page 76). Most patients who had elevations of SGOT, SGPT, or GGT had elevations in other enzymes. There were a number of cases that appeared temporally related to ebastine use, but in many cases other causes of hepatitis were not ruled out. The patients listed below are representative examples of these reports.

- EBS990006. A 57 yo female from Pakistan (reported by son, who is a US physician) was treated with ebastine 10 mg for vertigo following a tympanostomy. One month into

treatment, she experienced onset of jaundice, elevated liver enzymes (SGOT 1500 U/L, SGPT 1500 U/L) and elevated bilirubin (5 mg/ml). She had also been treated with cephradine (Velosef), which was discontinued 5 days prior to onset of the jaundice. Ebastine was discontinued, and one week later the SGOT was 1160 U/L, SGPT was1160 U/L. The patient recovered uneventfully. There was no evaluation for other forms of hepatitis. (10/22/02, v 3, p 2-4)

- EBS990107. A 21 yo female from Japan was treated with ebastine 10 mg for SAR. Two weeks into treatment both SPGT and gamma-GT were increased. No other drugs or diagnoses listed, and no further information was given. (10/22/02, v 3, p 10)

- EBS990125. A 78 yo female from Japan was treated with ebastine 10 mg for senile cutaneous pruritus. Lab values at the start of treatment were normal. Seven weeks into treatment, SGOT was 218, SGPT was 422, ALP was 1610, gamma-GT was 526, and CPK was 214 U/L. She was also being treated with biperiden hydrochloride x9 weeks and haloperidol x9 weeks. All drugs were stopped, and one month later her liver functions were SGOT 14, SGPT 17, ALP 547, gamma-GT 329, and CPK 134 U/L. There was no evaluation for other forms of hepatitis. (10/22/02, v 3, p 12-3)

- EBS960083. A 24 yo female from Japan was treated with ebastine 10 mg for atopic dermatitis. She had a history of fever and elevation in SGOT and SGPT after treatment with cefpoxime proxetil and plaunotol one year previously, but had normal liver enzymes 10 months previous to ebastine treatment. She also had a history of a positive ANA. Two days after starting ebastine, she developed epigastric pain and fever, SGOT 83, SGPT 91. On the third day, SGOT was 234 U, SGPT was 279 U, and bilirubin was 4.07 mg/dl. After 5 days on ebastine, liver enlargement was confirmed by sonogram, SGOT was 287 U, SGPT was 644 U, and bilirubin was 1.65 mg/dl. One month later, liver functions were normal. There was no evaluation for other forms of hepatitis. (10/22/02, v 3, p 24-6)

7.12.6. Spontaneous adverse events of overdose

There was one spontaneous adverse event report of overdose.

- EBS990062. A 23-month-old boy in Japan ingested approximately 80-100 mg of ebastine. Facial hot flushes were observed after 2 hours. He was treated with a gastrolavage and drip infusion (3-4 hours after the drug intake). Drug levels of ebastine and carebastine four hours after intake were <10 ng/mL (under the assay limit) and 1507 ng/mL, respectively. The original adverse event report noted a lengthened corrected AT more than 20% and supraventricular extra systoles on ECG (14-15 hours after the drug intake). The patient recovered without treatment except monitoring. Because of the initial report, Almirall sought expert opinions from three cardiologists, all of whom read the ECGs as supraventricular extra systoles without prolongation of QTc.

7.13. Summary of safety

In the clinical studies, ebastine was well tolerated by the patients with a safety profile consistent with other currently marketed second generation H_1 antihistamines, except the cardiac safety. In the short-term placebo controlled studies, the incidence of adverse events

was comparable between the ebastine and the placebo groups. The most common adverse event was headache in both groups, which is not unexpected because headache is a common symptom of allergic rhinitis. Somnolence and dry mouth was slightly more common in the ebastine treated patients than placebo treated patients. Serum transaminase elevation above the normal level was seen in some patients in the short-term efficacy studies, drug interaction cardiac safety studies, and in the long-term safety studies.

In the spontaneous reports of adverse events submitted, there were 5 reports of deaths in patients on ebastine, 28 reports of patients with liver injury and/or abnormal liver function, and 62 reports of patients with a cardiac rhythm disturbance. For most of these cases, patients were taking 10 mg of ebastine daily, so no dose-response relationship could be determined. Of these, there were two cases of *Torsades de Pointes* diagnosed, and a number of cases of QT prolongation were reported. The cases include a 12 year-old asymptomatic female who experienced a 40 msec QTc prolongation while being treated with ebastine 10 mg QD, which resolved after stopping ebastine. This finding was noted on a routine ECG for high school entry. This leads to the suspicion that QT prolongation may be significantly underdiagnosed and underreported, and that there may be many more cases of asymptomatic QT for which physicians are not evaluating patients despite the label warnings. The liver case series indicates that ebastine could cause liver injury in some patients. Some patients experienced a marked increase in liver transaminases, and 15 cases were severe enough to require hospitalization. While the efficacy studies revealed a tendency for transaminases to increase during the course of the study, there were no cases of a rise in transaminases of 2x or more in any of the efficacy studies. Three spontaneous adverse event cases of pancytopenia and/or thrombocytopenia were reported in the original NDA submission, but not in the complete response. Of the five deaths in patients treated with ebastine, one was from cerebral hemorrhage related to thrombocytopenia, two were from events that could be associated with prolonged QTc, one was from hepatic and renal failure, and one was from trauma.

Considering the clinical studies and spontaneous adverse event reporting ebastine appears to be causally associated with serum transaminase elevation in some subjects. An association with pancytopenia and/or thrombocytopenia remains unclear but appears unlikely. An association with asymptomatic QT prolongation and symptomatic palpitations is likely.

In the pivotal efficacy and open-label safety studies ebastine did not consistently prolong the mean QTc, although more patients on ebastine tended to have longer QTc compared to placebo. In the pivotal efficacy studies, females were more susceptible than males to QTc prolongation by ebastine. None of the patients in the clinical studies had *Torsades de Pointes*, QTc dispersion, and T-U wave morphological changes that were seen in the terfenadine post-marketing experience. This is not unexpected because in the whole clinical program the exclusion criteria including ECG criteria were strict and any high-risk patients would have been excluded.

In the high-dose cardiac safety studies, ebastine caused a small but dose-dependent prolongation of QTcB. In the drug-interaction cardiac safety studies, administration of ketoconazole or erythromycin with ebastine prolonged QTcB. Of the high dose and the drug-interaction cardiac safety studies, only one study (M/EBS/25) evaluated females, who are known to be more susceptible to QTc prolongation. Study M/EBS/25 was the "pivotal"

drug-interaction cardiac safety study. This study was the most carefully performed cardiac safety study, and was designed with FDA input. The study was designed to take into account the applicant's concerns regarding possible flaws in previous studies. To take into account the individual variability of QT interval and the effect of heart rate changes on corrected QT, the applicant used the QTcM method of QTc calculation. The QTcM method was declared *a priori* to be the primary QT correction method. To obtain individual correction factors, a large number of ECGs were performed on each of the subjects on two baseline days (day −1 and day −2). This was also the only cardiac safety study that did not have a limiting study entry criterion for QTc interval, and the only cardiac safety study performed in females.

Results of study M/EBS/25 confirmed that, when ketoconazole (400 mg QD) is added to ebastine (20 mg QD) at steady-state, there is a prolongation in QTcM of 11.09 msec from baseline compared with a prolongation of 0.38 msec from baseline for placebo plus ketoconazole. The difference, 10.71 msec was statistically significant (p = 0.0000). This effect was shown in all methods of QT correction, for heart rate and was present in both treatment groups regardless of treatment sequence. The PK parameters of ebastine were also significantly altered (AUC_{0-24} increased 44 fold) when ketoconazole was added. Fifteen days following co-administration of ebastine and ketoconazole (after the wash-out period), ebastine levels were still equivalent to steady-state ebastine levels, although there appeared to be no carryover effect on QTcM.

The FDA PK/PD regression analysis demonstrated that there was a tendency toward increased QTc from baseline with increasing ebastine and carebastine plasma concentrations or AUC. Multiple modeling of the PKPD relationship was attempted, but due to the limitations of inter- and intra-subject variability, no exposure-response-QTc model could be defined to explain these relationships. Therefore, the applicant's conclusion that there is a plateau of QTc prolongation with increasing doses, concentrations, or exposure (AUC) of ebastine is not supported by PK/PD modeling.

The outlier analysis of QTcM results showed that 8 out of 23 the subjects had at least one (and often multiple) individual ECGs with an increase in QTcM of 30 msec or more from baseline during co-administration of ebastine and ketoconazole on either day 12 or 13 of treatment. This was not the case during placebo plus ketoconazole treatment, or during other days of treatment, implying that these results may be of clinical relevance.

The results of study M/EBS/25, that demonstrated both a QTc prolongation and a tendency to create QTc prolongation outliers of ≥ 30 msec when ebastine was co-administered with ketoconazole, is consistent with the results seen in the previous cardiac safety and clinical studies.

INDIVIDUAL STUDY REVIEWS

8. PIVOTAL SEASONAL ALLERGIC RHINITIS (SAR) EFFICACY STUDIES

The applicant submitted 2 studies (EBA 124, and EBA 132) supporting the efficacy of ebastine for SAR. Ebastine was given as a single oral dose of 10 mg or 20 mg in the morning or in the evening and compared to placebo. The efficacy measures were based on patient recording of SAR symptoms in diary cards. In both the studies ebastine 20 mg was statistically superior to placebo, and for some measures ebastine 10 mg was also statistically superior to placebo. The 2 studies are reviewed in the following sections. Note that efficacy was also shown in the four US comparative SAR efficacy studies presented in Section 11.

8.1. EBA 124: Multicenter, double-blind, parallel-group, randomized comparison of ebastine and placebo in patients with seasonal allergic rhinitis.

8.1.1. Investigators and centers

The study was conducted in 16 sites in US. The principal investigators, study sites, and number of patients enrolled are listed below (v 183, p 116-118).

Charles H. Banov, MD, Charleston, South Carolina.	26 patients
Wilfred N. Beaucher, MD, Chelmsford, Massachusetts	24 patients
Paul Chervinsky, MD, N. Dartmouth, Massachusetts	23 patients
Elliot J. Ginchansky, MD, Dallas, Texas	24 patients
Michael J, Kraemer, MD, Spokane, Washington	26 patients
Richard J. Morris, MD, Minneapolis, Minnesota	27 patients
Zev M. Munk, MD, Houston, Texas	6 patients
Michael J. Noonan, MD, Portland, Oregon	27 patients
David Pearlman, MD, Aurora, Colorado	25 patients
Warren W. Pleskow, MD, Encinitas, California	25 patients
James P. Rosen, MD, West Hartford, Connecticut	20 patients
Michael S. Rowe, MD, Novi, Michigan	24 patients
William Silvers, MD, Englewood, Colorado	25 patients
Sheryl Talbot, MD, Philadelphia, Pennsylvania	17 patients
Julius H. Van Bavel, MD Austin, Texas	29 patients
Michael J. Welch, MD, San Diego, California	28 patients

8.1.2. Objective

The objective of this study was to compare the efficacy and safety of ebastine 20 mg and 10 mg administered once a day in the AM or PM, to placebo in patients with SAR (v 183, p 115).

8.1.3. Study population

Patients with SAR meeting the following criteria were selected for participation.

8.1.3.1. Inclusion criteria (v 183, p 165):

1. Male or females 12 years of age and above. Female were to be nonpregnant, or without childbearing potential, or using an accepted method of contraception.
2. Diagnosis of SAR to grass and/or trees for at least 2 consecutive years, and positive skin test to a seasonal allergen present in the patient's environment during the study.
3. Minimum total rhinitis symptom score of 42 (out of 105) over the last 3 days of screening period plus the morning of the baseline visit (described below).
4. Meet the screening criteria (described below) for ECG with/without Holter monitoring, and for Holter monitoring.

8.1.3.2. Exclusion criteria (v 183, p 167):

1. Acute upper respiratory tract infection, sinusitis, otitis media, nasal polyp, acute asthma. History of chronic sinusitis in the past 6 months.
2. Significant acute or chronic disease, or clinically relevant screening laboratory values outside the normal range.
3. History of hypersensitivity to antihistamines.
4. Use of any of the following: H_1-antagonist (except astemizole) within 7 days, astemizole within 6 months, depot corticosteroids within 2 months, short acting systemic or topical (inhaled, intranasal, and ocular) corticosteroids and topical cromolyn within 21 days, and ketoconazole or erythromycin (oral or topical) within 2 weeks or randomization.
5. Currently on medication which may suppress or exacerbate symptoms of SAR (e.g., centrally acting cardiovascular drugs, neuroleptic drugs, etc.,)
6. Stabilized on immunotherapy for less than one month prior to randomization.
7. Investigational treatment within 30 days prior to randomization.
8. Night shift (11 PM to 8 AM) workers.

8.1.3.3. ECG exclusion criteria at screening without Holter monitoring (v 183, p 214):

1. QTc >0.444 seconds.
2. Second or third degree AV block.
3. Bradycardia <45 bpm, as determined from the 30 sec. rhythm strip.
4. Ventricular dysrhythmia (ventricular tachycardia, *Torsades de Pointes,* ventricular flutter, ventricular fibrillation).
5. High grade ventricular ectopy (paired VE, R on T phenomenon, multiform VE).
6. Premature ventricular beats (2 or more PVB on a 3 minute rhythm strip).

8.1.3.4. ECG exclusion criteria at screening with Holter monitoring (v 183, p 214)

1. QTc >0.444 seconds.
2. Second or third degree AV block.

8.1.3.5. Holter monitoring exclusion criteria at screening (v 183, p 216)

1. Ventricular ectopics ≥30/hr in any single hour.

2. Presence of any multiform ventricular ectopics (VE), or any paired VE, or isolated VE's showing the R on T phenomenon.
3. Ventricular run of 3 or more - regardless of rate.
4. *Torsades de Pointes,* or ventricular flutter and/or fibrillation, or atrial fibrillation.
5. Average heart rate ≤40 bpm for any one hour.
6. Transient or fixed second or third degree AV block.
7. Ventricular asystole ≥2 sec.

8.1.3.6. ECG criteria for patient discontinuation at visits 3 and 4 (v 183, p 217)

1. QTc prolonged >15% over baseline.
2. Ventricular dysrhythmia or high grade ventricular ectopy
3. Ventricular ectopy (2 or more PVBs on 3 minute rhythm strip.
4. Bradycardia <45 bpm, as determined from the 30 sec. rhythm strip.
5. Second or third degree AV block.
6. By request of physician.

8.1.4. Study design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study (v 183, p 112).

8.1.5. Study procedures

The study was conducted between May and July, 1992, depending on time of pollination at the different study sites. All patients were enrolled within a 7-14 day period, when in the judgment of the investigator the patients were symptomatic with the seasonal allergens present in the environment. The study procedures are outlined in Table 43. The study had a day of screening, a 4-13 day baseline lead-in period, followed by 3 weeks of double-blind treatment. Patients satisfying the inclusion/exclusion and ECG/Holter criteria (described above) were dispensed with diary cards (visit 1) and asked to record severity of 5 rhinitis symptoms (nasal discharge, nasal stuffiness, sneezing, itchy nose, itchy/watery eyes) on a 4-point scale (0 = absent, no symptoms; 1 = mild, symptoms present but not annoying to self; 2 = moderate, symptoms present and annoying to self; 3 = severe, symptoms interfere with activities of daily living) twice a day - upon arising in the morning, and in the evening before dinner. Scoring was to reflect symptom severity over the previous 12 hours. In addition, at the same time twice a day, patients were to rate in a general sense how s/he felt at the time of recording ("snap-shot" global symptom score) on the same 4-point scale described above. To be eligible for randomization (visit 2), patients were required to have an aggregated sum of rhinitis symptom score over the last 3 days of lead-in period plus the morning of the visit (total of 7 readings) of at least 42 points out of a maximum possible of 105. This was the baseline score.

Eligible patients were randomized into 5 study groups (ebastine 20 mg QDAM, ebastine 20 mg QDPM, ebastine 10 mg QDAM, ebastine 10 mg QDPM, and placebo), with a separate randomization schedule for patients 12-17 years of age and for patients 18 years and older. Study medications were administered in the morning immediately after breakfast or in the

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Pivotal Seasonal Allergic Rhinitis (SAR) Efficacy Studies, EBA 124

evening immediately after dinner with 8 ounces of water. Both meals were to contain solids. No study medication was administered in the morning of visit 5. During the study, patients were instructed to refrain from using any over the counter or prescription medication for alleviating the symptoms of rhinitis, cold, or cough, or any medication for another indication that could relieve or produce symptoms of allergic rhinitis. Throughout the study patients continued recording rhinitis symptom scores (reflective scores for the previous 12 hours, and a global snap-shot score at the time of recording) daily in the morning and in the evening before study medication administration. In addition, at the end of the study (visit 5), patients and physicians separately recorded the global evaluation of efficacy on a 5 point scale (0 = greatly improved, 1 = somewhat improved, 2 = no change, 3 = somewhat worsened, 4 = greatly worsened) relative to the baseline. During the study, ECG and Holter monitoring were done at time points shown in Table 43, and patients were discontinued based on criteria described above. The examining physician at the study site read the ECGs for implementing the discontinuation criteria. All ECG tracings were finally interpreted in the central facility in Philadelphia. Patients discontinued for ECG abnormalities were immediately followed-up with a Holter recording, and close-out procedures (as in visit 5) were done including a blood draw for ebastine/carebastine analysis. A repeat ECG and Holter were performed after a wash-out period of at least 5 days (v 183, p 118-126, 161, 168-178).

Table 43. EBA 124, Schedules of observations

Procedures	Visit 1 Screening/Lead in Day -14 to -1	Visit 2 Baseline Day 1	Visit 3 Day 8 ± 1	Visit 4 Day 15 ± 1	Visit 5 Day 22 ± 1
Informed consent	x				
Medical history and skin test*	x				
Fasting, midnight to clinic visit	x				x
Physical exam, laboratory tests†	x				x
Dispense medication		x			
Collect medication					x
Dispense diary	x	x	x	x	
Collect and review diary		x	x	x	x
ECG‡	x		x	x	x
24-hour Holter (optional)§	x			x	x
Symptom evaluation	x	x	x	x	x
Physician global assessment					x
Patient global assessment					x
Adverse events		x	x	x	x

* Skin test done within one year was acceptable.
† Pregnancy test, urinalysis (ketones, protein, glucose, and microscopic exam), hematology (hemoglobin, hematocrit, WBC count, RBC count, and platelet count), and serum chemistry (creatinine, BUN, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT calcium, phosphorus, magnesium, electrolytes: sodium, potassium, chloride, bicarbonate) (v 183, p 182).
‡ Obtained on any screening day from day -14 to -5 (v 183, p 169), on visits 3 and 4 at 3-5 hours after medication, and at anytime during close-out procedures at visit 5.
§ Performed on any screening day from day -14 to -5 (v 183, p 169), and at anytime between visits 4 and 5.

Source: v 183, p 213

8.1.6. Efficacy parameters

The primary efficacy variable was the mean change from baseline in the total rhinitis symptom score (the sum of scores for nasal discharge, nasal stuffiness, sneezing, itchy nose, and itchy/watery eyes) averaged over the double-blind treatment period for the 24-hour score. The 24-hour score on a day for the AM dosing groups was the average of the evening measurement on that day and the morning measurement on the next day, and the 24-hour score on a day for PM dosing group was the average of the morning and evening measurement the next day. For the placebo group, the 24-hour score was defined to be the same as the AM dosing groups. The results of this placebo group was the same when the 24-hour score was defined to be the same as the PM dosing groups. The mean change from baseline in the total symptom score was also averaged separately for the first and second 12 hours as well as for the 24-hour scores. Secondary variables were the mean changes from baseline for each symptom, nasal index (sum of the scores for nasal discharge, nasal stuffiness, sneezing, and itchy nose), and global perception of efficacy by the patient and the physician (v 183, p 112, 128).

8.1.7. Safety analysis

Safety analysis included laboratory values, ECG, Holter monitoring, physical examination, and adverse events (v 183, p 178-184).

8.1.8. Statistical considerations

8.1.8.1. Sample size

A sample size of 70 patients per group was calculated to detect a mean change of one in total symptom score from baseline between ebastine and placebo group with a power of 90 at a one-sided α level of 0.05. The projected standard deviation used in the calculation was 2. In the actual analysis, the standard deviation was 2.2 (v 183, p 131).

8.1.8.2. Statistical analysis

The primary efficacy variable was analyzed sequentially in two stages using a two-way analysis of covariance (ANCOVA) with treatment and center as fixed effect and no interaction term. The baseline score was included in the model as the covariate. Two trend tests were first performed, which included placebo and either the AM or the PM doses. If the maximum of two p-values was significant at <0.05, the 20 mg AM and PM doses were considered to be different than placebo. Second, if the 20 mg AM and PM doses were significant, the 20 mg doses were dropped and two trend tests were performed which included placebo and either the 10 mg AM or 10 mg PM dose. Again, if the maximum of the two p-values was significant at <0.05, the 10 mg doses were considered to be different than placebo. If in the two stages, no difference was identified and the minimum of the p-value was less than 0.025, it was concluded that only that dose regimen corresponding to the minimum p-value was different from placebo. If a higher dose was not significant from placebo, the lower dose was considered not different from placebo. The patients' and physicians' global assessment of efficacy was analyzed by the Cochran-Mantel-Haenszel test (v 183, p 18, 21, 128-131).

8.1.9. Results

8.1.9.1. Patients enrolled/analyzed

A total of 625 patients were screened, 229 failed the screening, and 396 were randomized. Of the randomized patients, 5 patients (0263, and 0388 from the 10 mg AM group, 0224, and 0491 in the 20 mg AM group, and 0189 in the 20 mg PM group) had no recorded diary efficacy data, and 4 patients (0077, 0263, and 0388 in the 10 mg AM group, and 0491 in the 20 mg AM group) had no patient and physician efficacy evaluations. Therefore, 391 patients were included in the primary efficacy analysis, and 392 patients were included in the patient and physician analysis of efficacy. Disposition of the randomized patients and reasons for discontinuation are shown in Table 44 (v 183, p 15, 131).

Table 44. EBA 124, Disposition of study patients

	Placebo	10 mg AM	20 mg AM	10 mg PM	20 mg PM	Total
Enrolled	78	81	79	80	78	396
Completed	74	74	75	77	72	372
Discontinued:	4	7	4	3	6	24
Reasons for discontinuation:						
Drug ineffective	1	0	0	0	1	2
Adverse event	0	2	2	1	3	8
Protocol deviation	0	2	2	2	1	7
Lost to follow-up	0	2	0	0	0	2
Others	3	1	0	0	1	5
Source: v 183, p 132						

8.1.9.2. Subject demographics

Demographics of the enrolled patients is shown in Table 45. The groups were comparable.

Table 45. EBA 124, Demographic summary

	Placebo	10 mg AM	20 mg AM	10 mg PM	20 mg PM	Total
Number	78	81	79	80	78	396
Sex: male/female	53/25	52/29	47/32	60/20	56/22	268/128
Age: years (range)	27 (12-58)	29 (12-63)	28 (12-58)	27 (12-63)	29 (12-64)	28 (12-64)
Race: Cauc/others	74/4	77/4	74/5	76/4	74/4	375/21
Source: v 183, p 132						

8.1.9.3. Protocol deviations

There were no significant deviations from the protocol in this study.

8.1.9.4. Efficacy endpoint outcomes

Results of the rhinitis symptom scores during the double-blind treatment period for 24 hours (protocol specified primary efficacy variable), 1st and 2nd 12 hours, and snap-shot global symptom scores are shown in Table 46. Based on the primary efficacy variable analysis, the 10 mg dose taken in the morning, and the 20 mg dose taken either in the morning or evening, were effective in relieving the symptoms of SAR as compared to placebo. Of the doses, 20 mg AM dose was most effective. The reduction in the symptom scores was

greater in the first 12 hours as compared to the second 12 hours. The 20 mg AM dose significantly reduced symptoms by day 1 (Table 47), and the effect persisted at the end of each week of treatment (Table 48, Table 49). The efficacy of 20 mg AM dose was consistent in reducing all five individual symptoms of SAR (Table 50), patients' "snap-shot" global symptom scores (Table 46), and global rating of efficacy by patients and physicians (Table 51). The overall efficacy of the 20 mg dose was consistent when the data were stratified based on gender (male, female), race (Caucasian, non-Caucasian), and age groups (12-16 years, 17-59 years, over 60 years), although for some analysis the differences did not reach statistical significance at 0.05 (v 183, p 8-48, 134-144).

Table 46. EBA 124, Reflective and snap-shot rhinitis symptom scores[*] for the three week treatment period

Time	Treatment	N	Baseline mean	Change from baseline, mean±SE	p-value vs. placebo[†]
Reflective total symptom scores:					
24 hours	10 mg AM	79	9.15	-3.47 ± 0.32	0.049
	20 mg AM	77	9.02	-3.90 ± 0.33	0.001
	10 mg PM	80	8.87	-3.05 ± 0.29	0.172
	20 mg PM	77	8.97	-3.38 ± 0.32	0.031
	Placebo	78	9.01	-2.61 ± 0.32	
1st 12 hours	10 mg AM	79	8.89	-3.49 ± 0.28	0.064
	20 mg AM	77	9.16	-4.18 ± 0.29	0.001
	10 mg PM	80	8.77	-2.81 ± 0.28	0.654
	20 mg PM	77	9.15	-3.36 ± 0.29	0.164
	Placebo	78	8.88	-2.71 ± 0.29	
2nd 12 hours	10 mg AM	79	9.42	-3.47 ± 0.34	0.047
	20 mg AM	77	9.00	-3.76 ± 0.33	0.001
	10 mg PM	80	8.87	-3.14 ± 0.30	0.040
	20 mg PM	77	8.88	-3.42 ± 0.33	0.005
	Placebo	78	9.15	-2.51 ± 0.30	
Snap-shot global symptom scores:					
24 hours	10 mg AM	79	2.03	-0.66 ± 0.07	0.076
	20 mg AM	77	2.05	-0.79 ± 0.07	0.001
	10 mg PM	80	2.03	-0.54 ± 0.07	0.625
	20 mg PM	77	2.03	-0.66 ± 0.07	0.057
	Placebo	78	2.06	-0.52 ± 0.07	
1st 12 hours	10 mg AM	79	1.96	-0.66 ± 0.07	0.094
	20 mg AM	77	2.04	-0.85 ± 0.08	0.001
	10 mg PM	80	2.03	-0.50 ± 0.07	0.529
	20 mg PM	77	2.08	-0.65 ± 0.07	0.355
	Placebo	78	2.05	-0.57 ± 0.08	
2nd 12 hours	10 mg AM	79	2.10	-0.65 ± 0.07	0.064
	20 mg AM	77	2.08	-0.75 ± 0.07	0.001
	10 mg PM	80	2.01	-0.56 ± 0.08	0.134
	20 mg PM	77	2.01	-0.68 ± 0.07	0.005
	Placebo	78	2.07	-0.48 ± 0.07	

[*] Symptom score is the sum of nasal discharge, nasal stuffiness, sneezing, itchy nose, and itchy/watery eyes
[†] Based on t-test for a two-way main effects analysis of covariance with treatment and center as main effects and no interaction term

Source: volume 183, p 84, 85, 88, 89

Table 47. EBA 124, Total rhinitis symptom scores* for days 1 to 3 for 24-hour period

Treatment	Day 1		Day 2		Day 3	
	Change from baseline[†], mean ± SE (n)	p-value[‡]	Change from baseline[†], mean ± SE (n)	p-value[‡]	Change from baseline[†], mean ± SE (n)	p-value[‡]
10 mg AM	-2.33 ± 0.31 (77)	0.106	-2.63 ± 0.33 (77)	0.121	-3.17 ± 0.33 (77)	0.076
20 mg AM	-3.10 ± 0.31 (76)	0.001	-3.69 ± 0.34 (75)	0.000	-3.71 ± 0.34 (76)	0.005
10 mg PM	-2.47 ± 0.31 (79)	0.057	-2.81 ± 0.33 (79)	0.060	-2.91 ± 0.33 (79)	0.192
20 mg PM	-2.70 ± 0.31 (76)	0.019	-2.58 ± 0.34 (74)	0.144	-2.74 ± 0.33 (76)	0.311
Placebo	-1.78 ± 0.31 (77)		-2.07 ± 0.34 (76)		-2.51 ± 0.33 (77)	

* Symptom score is the sum of nasal discharge, nasal stuffiness, sneezing, itchy nose, and itchy/watery eyes
[†] Adjusted for imbalance among investigators
[‡] vs. placebo, based on a one-tailed test

Source: v 183, p 139

Table 48. EBA 124, Total rhinitis symptom scores* by treatment weeks

Treatment	Week 1		Week 2		Week 3	
	Change from baseline, mean ± SE (n)	p-value[†]	Change from baseline, mean ± SE (n)	p-value[†]	Change from baseline, mean ± SE (n)	p-value[†]
10 mg AM	-3.12 ± 0.29 (79)	0.015	-3.57 ± 0.34 (76)	0.104	-3.84 ± 0.38 (75)	0.069
20 mg AM	-3.65 ± 0.30 (77)	0.000	-3.72 ± 0.36 (75)	0.029	-4.44 ± 0.37 (75)	0.001
10 mg PM	-2.59 ± 0.24 (80)	0.149	-2.90 ± 0.35 (78)	0.604	-3.41 ± 0.32 (78)	0.216
20 mg PM	-2.44 ± 0.30 (77)	0.348	-3.67 ± 0.32 (75)	0.033	-3.80 ± 0.39 (72)	0.045
Placebo	-2.16 ± 0.29 (78)		-2.80 ± 0.34 (78)		-2.95 ± 0.39 (77)	

* Symptom score is the sum of nasal discharge, nasal stuffiness, sneezing, itchy nose, and itchy/watery eyes
[†] Based on a t-test for a two-way main effects analysis of covariance with treatment and center as main effects and no interaction term

Source: v 184, p 139

Table 49. EBA 124, Snap shot global symptom scores* by treatment weeks

Treatment	Week 1		Week 2		Week 3	
	Change from baseline, mean ± SE (n)	p-value[†]	Change from baseline, mean ± SE (n)	p-value[†]	Change from baseline, mean ± SE (n)	p-value[†]
24 hours:						
10 mg AM	-0.59 ± 0.06 (79)	0.022	-0.68 ± 0.08 (76)	0.130	-0.75 ± 0.08 (75)	0.133
20 mg AM	-0.73 ± 0.07 (77)	0.000	-0.74 ± 0.08 (75)	0.043	-0.93 ± 0.08 (74)	0.003
10 mg PM	-0.45 ± 0.06 (80)	0.456	-0.51 ± 0.08 (78)	0.907	-0.61 ± 0.05 (78)	0.905
20 mg PM	-0.48 ± 0.06 (77)	0.327	-0.74 ± 0.07 (75)	0.028	-0.73 ± 0.08 (72)	0.163
Placebo	-0.42 ± 0.06 (78)		-0.55 ± 0.08 (78)		-0.62 ± 0.08 (77)	
1st 12 hours:						
10 mg AM	-0.57 ± 0.07 (79)	0.057	-0.68 ± 0.09 (76)	0.157	-0.77 ± 0.09 (75)	0.117
20 mg AM	-0.79 ± 0.08 (77)	0.000	-0.77 ± 0.09 (75)	0.081	-1.01 ± 0.09 (74)	0.001
10 mg PM	-0.46 ± 0.06 (80)	0.910	-0.48 ± 0.08 (80)	0.287	-0.56 ± 0.08 (78)	0.369
20 mg PM	-0.54 ± 0.08 (77)	0.439	-0.71 ± 0.07 (77)	0.282	-0.70 ± 0.09 (74)	0.755
Placebo	-0.46 ± 0.07 (78)		-0.60 ± 0.08 (78)		-0.66 ± 0.10 (77)	
2nd 12 hours:						
10 mg AM	-0.57 ± 0.07 (79)	0.024	-0.67 ± 0.09 (78)	0.084	-0.72 ± 0.09 (76)	0.199
20 mg AM	-0.69 ± 0.07 (77)	0.000	-0.68 ± 0.08 (76)	0.040	-0.90 ± 0.08 (75)	0.003
10 mg PM	-0.49 ± 0.07 (80)	0.044	-0.54 ± 0.09 (78)	0.229	-0.65 ± 0.09 (78)	0.267

Treatment	Week 1		Week 2		Week 3	
	Change from baseline, mean ± SE (n)	p-value[†]	Change from baseline, mean ± SE (n)	p-value[†]	Change from baseline, mean ± SE (n)	p-value[†]
20 mg PM	-0.52 ± 0.07 (77)	0.019	-0.77 ± 0.08 (75)	0.001	-0.76 ± 0.09 (72)	0.026
Placebo	-0.36 ± 0.07 (78)		-0.47 ± 0.08 (78)		-0.58 ± 0.08 (77)	
[*] Symptom score reflect in a general sense how the patients felt at the time of recording [†] Based on a t-test for a two-way main effects analysis of covariance with treatment and center as main effects and no interaction term						
Source: v 184, p 88, 89						

Table 50. EBA 124, Summary of individual rhinitis symptom variables for the three weeks of treatment

Treatment	N	First 12-hour		Second 12-hour		24-hour	
		Change from baseline	p-value vs. Placebo*	Change from baseline	p-value vs. Placebo*	Change from baseline	p-value vs. Placebo*
Nasal discharge:							
10 mg AM	79	-0.66	0.234	-0.65	0.121	-0.64	0.148
20 mg AM	77	-0.80	0.008	-0.62	0.009	-0.75	0.010
10 mg PM	80	-0.54	0.702	-0.57	0.120	-0.57	0.474
20 mg PM	77	-0.63	0.725	-0.69	0.009	-0.66	0.112
Placebo	78	-0.55		-0.44		-0.51	
Nasal stuffiness:							
10 mg AM	79	-0.63	0.081	-0.59	0.198	-0.61	0.0130
20 mg AM	77	-0.73	0.015	-0.68	0.022	-0.69	0.019
10 mg PM	80	-0.47	0.467	-0.52	0.216	-0.50	0.770
20 mg PM	77	-0.58	0.702	-0.62	0.015	-0.59	0.159
Placebo	78	-0.47		-0.46		-0.47	
Sneezing:							
10 mg AM	79	-0.71	0.039	-0.75	0.029	-0.72	0.028
20 mg AM	77	-0.91	0.000	-0.80	0.001	-0.85	0.000
10 mg PM	80	-0.64	0.072	-0.72	0.039	-0.71	0.030
20 mg PM	77	-0.69	0.048	-0.64	0.068	-0.67	0.045
Placebo	78	-0.55		-0.57		-0.55	
Itchy nose:							
10 mg AM	79	-0.76	0.109	-0.75	0.123	-0.76	0.101
20 mg AM	77	-0.88	0.004	-0.83	0.003	-0.83	0.004
10 mg PM	80	-0.51	0.797	-0.59	0.416	-0.56	0.733
20 mg PM	77	-0.69	0.160	-0.66	0.069	-0.68	0.091
Placebo	78	-0.61		-0.60		-0.60	
Itchy eyes:							
10 mg AM	79	-0.72	0.173	-0.73	0.067	-0.71	0.114
20 mg AM	77	-0.90	0.004	-0.83	0.001	-0.86	0.001
10 mg PM	80	-0.65	0.155	-0.74	0.003	-0.70	0.024
20 mg PM	77	-0.78	0.072	-0.81	0.002	-0.78	0.011
Placebo	78	-0.54		-0.46		-0.51	
[*] Based on a t-test for a two-way main effects analysis of covariance with treatment and center as main effects and no interaction term							
Source: volume 183, p 70-83							

Table 51. EBA 124, Summary of patients' and physicians' evaluation of efficacy

Treatment	N	Improved		No	Worsened		p-value*
		Greatly	Somewhat	Change	Somewhat	Greatly	
Patients' evaluation		N (%)	N (%)	N (%)	N (%)	N (%)	
10 mg AM	78	14 (18)	44 (56)	18 (32)	1 (1)	1 (1)	0.14
20 mg AM	78	22 (28)	36 (46)	18 (23)	2 (3)	0 (0)	0.02
10 mg PM	80	16 (20)	41 (51)	22 (28)	0 (0)	1 (1)	0.09
20 mg PM	78	22 (28)	39 (50)	13 (17)	3 (4)	1 (1)	0.04
Placebo	78	12 (15)	40 (51)	22 (28)	3 (4)	1 (1)	
Physicians' evaluation		N (%)	N (%)	N (%)	N (%)	N (%)	
10 mg AM	78	12 (15)	42 (54)	19 (24)	3 (4)	2 (3)	0.40
20 mg AM	78	24 (31)	33 (42)	19 (24)	2 (3)	0 (0)	0.01
10 mg PM	80	12 (15)	41 (51)	25 (31)	2 (3)	0 (0)	0.14
20 mg PM	78	14 (18)	43 (55)	17 (22)	3 (4)	1 (1)	0.17
Placebo	78	12 (15)	37 (47)	25 (32)	4 (5)	0 (0)	
* One-sided p-value calculated using Cochran-Mantel Hazel test adjusting for investigator and AM and PM scores compared to placebo and correcting for multiple comparison using the Hochberg procedure							
Source: volume 183, p 144							

8.1.10. Safety outcomes

8.1.10.1. Total drug exposure

All patients enrolled in the study were included in the safety analysis. The mean duration of exposure was 20.1 days for the 10 mg AM group, 20.2 days for the 20 mg AM group, 20.5 days for the 10 mg PM group, 19.7 days for the 20 mg PM group, and 20.6 days for the placebo group (v 183, p 145).

8.1.10.2. Adverse events

Adverse events reported by at least 3% of patients in any treatment group are presented in Table 52. The majority of the adverse effects were mild to moderate and not related to the study medication. Headache, dry mouth, and somnolence were commonly reported and the frequency was higher in the 20 mg ebastine groups (v 183, p 145).

Table 52. EBA 124, Common adverse experience reported by patients*

	Placebo (n=78)	10 mg AM (n=81)	10 mg PM (n=80)	20 mg AM (n=79)	20 mg PM (n=78)
Total with adverse experience	33 (42.3 %)	37 (45.7 %)	28 (35.0 %)	30 (38.0 %)	41 (52.6 %)
Body as a whole					
Headache	10 (12.8 %)	9 (11.1 %)	11 (13.8 %)	9 (11.4 %)	16 (20.5 %)
Pain abdomen	0 (0.0 %)	4 (4.9 %)	1 (1.3 %)	0 (0.0 %)	0 (0.0 %)
Digestive system					
Dyspepsia	1 (1.3 %)	4 (4.9 %)	1 (1.3 %)	0 (0.0 %)	0 (0.0 %)
Nausea	1 (1.3 %)	5 (6.2 %)	1 (1.3 %)	2 (2.5 %)	2 (2.6 %)
Nervous system					
Dizziness	1 (1.3 %)	4 (4.9 %)	0 (0.0 %)	1 (1.3 %)	1 (1.3 %)
Dry mouth	2 (2.6 %)	3 (3.7 %)	3 (3.8 %)	5 (6.3 %)	5 (6.4 %)
Nervousness	4 (5.1 %)	3 (3.7 %)	0 (0.0 %)	1 (1.3 %)	1 (1.3 %)
Somnolence	1 (1.3 %)	3 (3.7 %)	0 (0.0 %)	4 (5.1 %)	3 (3.8 %)
Respiratory system					

	Placebo (n=78)	10 mg AM (n=81)	10 mg PM (n=80)	20 mg AM (n=79)	20 mg PM (n=78)
Cough	0 (0.0 %)	2 (2.5 %)	4 (5.0 %)	1 (1.3 %)	0 (0.0 %)
Epistaxis	1 (1.3 %)	2 (2.5 %)	3 (3.8 %)	2 (2.5 %)	2 (2.6 %)
Pharyngitis	4 (5.1 %)	4 (4.9 %)	5 (6.3 %)	2 (2.5 %)	3 (3.8 %)
* Events reported by ≥3% of patients in any group is listed (number and %) as Costart preferred term.					
Source: v 187, p 275-282					

8.1.10.3. Premature withdrawals due to adverse events

A total of 8 patients were withdrawn due to adverse events (Table 44). The events are summarized in Table 53. All patients recovered (v 183, p 146).

Table 53. EBA 124, Discontinued patients due to adverse events

Group	Patient	Event	Days on study medication	Severity	Relationship to study med.
10 mg AM	0144	Pharyngitis	6	Moderate	None
	0230	Dizziness, headache	1	Moderate	Probable
10 mg PM	0191	Rash	5	Moderate	Possible
20 mg AM	0148	Anxiety, somnolence	1	Mild	Probable
	0224	Dizziness	1	Severe	Probable
20 mg PM	0046	Exfoliative dermatitis	8	Moderate	Possible
	0466	Sinusitis	15	Moderate	None
	0498	Constipation, nausea	4	Moderate	Remote
Source: v 183, p 146					

8.1.10.4. Physical examination, ECG, and laboratory measures

There were no clinically significant changes in physical examination or vital signs in any of the patients. Of the 396 patients in the study, all but 2 patients who discontinued (0388 in the 10 mg AM, 0491 in the 20 mg AM groups) had ECG at baseline and after drug administration. No patient was discontinued from the study for ECG abnormality. The results of the QTc data analysis is shown in Table 54. There was a small but statistically significant prolongation of QTc in the 20 mg PM group compared to placebo at weeks 1 and 2. There were a total of 32 patients who had QTc ≥ 440 msec at some point during the 3 weeks of treatment, of which 17 were from the 20 mg group, 11 were from the 10 mg group, and 4 were from the placebo group. Three patients, all from 20 mg group, had QTc prolongation over 15% from baseline. Patients 0203, 0059, and 0395, had 17.4, 21.4, and 16.8 msec QTc prolongation at week 1, week 2, and week 3 respectively. A total of 74 patients had 24-hour Holter monitoring done at baseline and at the end of the study. There were no clinically relevant findings in any Holter data collected. For the laboratory values, there were no clinically relevant changes for any parameters. On review of the individual patient values, serum transaminase levels were more frequently elevated in the ebastine groups as shown in Table 55 (v 183, p 148-153).

Table 54. EBA 124, Summary of QTc changes

Treatment week	Treatment group	N	Baseline mean in msec	Post-treatment mean in msec	Mean raw % change	p-value s. placebo
Week 1	10 mg AM	79	401	408	1.66	0.167
	20 mg AM	79	401	406	1.36	0.311
	10 mg PM	80	397	403	1.80	0.117
	20 mg PM	78	399	408	2.77	0.033
	Placebo	78	398	399	0.54	
Week 2	10 mg AM	77	400	402	0.45	0.797
	20 mg AM	74	401	407	1.73	0.216
	10 mg PM	79	397	403	1.74	0.203
	20 mg PM	76	399	408	2.45	0.037
	Placebo	79	398	400	0.67	
Week 3	10 mg AM	73	401	404	0.90	0.678
	20 mg AM	74	402	404	0.69	0.869
	10 mg PM	76	397	403	1.56	0.218
	20 mg PM	71	399	405	1.47	0.271
	Placebo	75	398	399	0.55	
* Based on a two-tailed t-test for comparisons of each ebastine dose to placebo						
Source: v 183, p 149						

Table 55. EBA 124, Number of patients with elevation of liver function tests above baseline

Group	Total bilirubin		SGOT (AST)		SGPT (ALT)		Alk. phosphatase	
	> basal	> 2x	> basal	> 2x	> basal	> 2x	> basal	> 2x
10 mg AM	4	1	1	1	5	1	0	0
20 mg AM	3	1	5	2	5	1	1	0
10 mg PM	3	1	0	0	3	1	2	0
20 mg PM	1	0	4	3	4	3	0	0
Placebo	2	0	3	1	1	1	1	0
Source: v 183, p 154								

8.1.11. Conclusion from EBA 124 study results

This study evaluates the efficacy and safety of ebastine 20 mg/day and 10 mg/day administered in the AM and PM in patients with SAR. The results show that ebastine 20 mg/day taken in the morning was effective in relieving the symptoms of SAR. The improvement in total symptom score relative to placebo occurred as early as day 1 for the 20 mg/day AM group and persisted at the end of each treatment week for the 3-week duration of treatment. The other doses (20 mg PM, 10 mg AM, and 10 mg PM) failed to show convincing efficacy in this study. The 10 mg doses did not work at the end of dosing interval and the efficacy did not persist at weeks 2 and 3. The 20 mg PM dose did not work at week 1. The results of this study support 20 mg QD AM as the optimal dose of ebastine for relief of symptoms of SAR, and 10 mg QD as a dose sufficient for some patients. Clinical, ECG, and laboratory safety parameters collected during the study show that ebastine was well tolerated in this study group. In the ebastine treated groups, particularly in the 20 mg/day group, dry mouth, somnolence, QTc prolongation, and elevation of serum transaminase levels were more frequently seen.

8.2. EBA 132: Multicenter, double-blind, parallel group, randomized comparison of ebastine 10 mg and 20 mg versus placebo in patients with seasonal allergic rhinitis.

8.2.1. Investigators and centers

The study was conducted in 10 sites in US. The principal investigators, study sites, and number of patients enrolled are listed below (v 193, p 112-113).

Paul Chervinsky, MD, N. Dartmouth, Massachusetts	30 patients
Kraig W. Jacobson, MD, Eugene, Oregon	28 patients
Michael J, Kraemer, MD, Spokane, Washington	25 patients
Craig LaForce, MD, Raleigh, North Carolina	30 patients
John Norton, MD, Colorado Springs, Colorado	30 patients
Warren W. Pleskow, MD, Encinitas, California	30 patients
Sheryl Talbot, MD, Philadelphia, Pennsylvania	29 patients
Alan Wanderer, MD, Engelwood, Colorado	30 patients
Suzanne Weakley, MD, Bryan, Texas	29 patients
Michael J. Welch, MD, San Diego, California	28 patients

8.2.2. Objective

The objective of this study was to compare the efficacy and safety of ebastine 20 mg and 10 mg administered once a day to placebo in patients with SAR (v 193, p 174).

8.2.3. Study population

Patients 12 years of age and above with a 2 year history of SAR were selected for participation in the study. The inclusion and exclusion criteria were similar to the previous SAR study (EBA 124), except that the drug exclusion list was expanded to include itraconazole and any macrolide antibiotics (v 196, p 175-178). The ECG and Holter criteria were slightly different and is given below.

8.2.3.1. ECG exclusion criteria at screening without Holter monitoring (v 193, p 220)

7. QTc >0.444 seconds.
8. Fixed second or transient or fixed third degree AV block.
9. Atrial fibrillation
10. Ventricular dysrhythmia (sustained ventricular tachycardia i.e. >30 sec., *Torsade de Pointes*, ventricular flutter, ventricular fibrillation).
11. High grade ventricular ectopy (R on T phenomenon).
12. If ventricular ectopy (3 or more ventricular ectopics on a 3-minute rhythm strip) is present, the patient may enter the study provided they wear a Holter at screening and end of the study.

8.2.3.2. ECG exclusion criteria at screening with Holter monitoring (v 183, p 214)

1. QTc >0.444 seconds.
2. Fixed second or transient or fixed third degree AV block.

8.2.3.3. Holter monitoring exclusion criteria at screening and post visit 4-5 (v 193, p 222)

1. Ventricular ectopics ≥30/hr in any single hour.
2. Isolated VE's showing the R on T phenomenon
3. Ventricular run of 3 or more - regardless of rate.
4. *Torsade de Pointes*, or ventricular flutter and/or fibrillation, or atrial fibrillation.
5. Fixed second or transient or fixed third degree AV block.
6. Ventricular asystole ≥2 sec.

8.2.3.4. ECG criteria for patient discontinuation at visits 3 and 4 (v 193, p 223)

1. QTc prolonged >520 msec or >30% over baseline.
2. Ventricular dysrhythmia (sustained ventricular tachycardia, i.e., >30 seconds, *Torsade de Pointes*, ventricular flutter, ventricular fibrillation).
3. High grade of ventricular ectopy (R on T phenomenon), or ventricular ectopy (3 or more ventricular ectopic beats on 2 successive 3 minute rhythm strips).
4. Fixed second or transient or fixed third degree AV block.
5. By request of physician.

8.2.4. Study design

This was a multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group study (v 193, p 107).

8.2.5. Study procedures

The study was conducted between May and July, 1993, depending on time of pollination at the different study sites. All patients were enrolled within a 7-14 day period, when in the judgment of the investigator the patients were symptomatic with the seasonal allergens present in the environment. The study procedures are outlined in Table 56. The study had a day of screening, a 4-13 day baseline lead-in period, followed by 3 weeks of double-blind treatment. Patients satisfying the inclusion/exclusion and ECG/Holter criteria (described above) were dispensed with diary cards and asked to record severity of 5 rhinitis symptoms (nasal discharge, nasal stuffiness, sneezing, itchy nose, itchy/watery eyes) on a 4-point scale (0 = absent, no symptoms; 1 = mild, symptoms present but not annoying to self; 2 = moderate, symptoms present and annoying to self; 3 = severe, symptoms interfere with activities of daily living) twice a day - upon arising in the morning, and in the evening before dinner. Scoring were based on symptom severity over the previous 12 hours (reflective symptom assessment) and at the time of recording ("snap-shot" symptom assessment). To be eligible for randomization (visit 2), patients were required to have an aggregated sum of reflective rhinitis symptom score over the last 3 days of lead-in period

plus the morning of the visit (total of 7 readings) of at least 42 points out of a maximum possible of 105 with at least one of the symptoms present at a moderate or severe level. This was the baseline score.

Eligible patients were randomized into 3 study groups (ebastine 10 mg, ebastine 20 mg, or placebo). Study medications were administered in the morning immediately after breakfast (containing solids) with 8 ounces of water. No study medication was administered in the morning of visit 5. During the study, patients were instructed to refrain from using any over the counter or prescription medication for alleviating the symptoms of rhinitis, cold, or cough, or any medication for another indication that could relieve or produce symptoms of allergic rhinitis. Throughout the study patients continued recording rhinitis symptom scores (reflective scores for the previous 12 hours, and a snap-shot scores at the time of recording) daily in the morning and in the evening before study medication administration. In addition, at the end of the study (visit 5), patients and physicians separately recorded the global evaluation of efficacy on a 5 point scale (0 = greatly improved, 1 = somewhat improved, 2 = no change, 3 = somewhat worsened, 4 = greatly worsened) relative to the baseline. During the study, ECG and Holter monitoring were done at time points shown in Table 56, and patients were discontinued based on criteria mentioned above. The examining physician at the study site read the ECGs for implementing the discontinuation criteria. All ECG tracings were finally interpreted in the central facility in Philadelphia. Patients discontinued for ECG abnormalities were immediately followed-up with a Holter recording, and close-out procedures (as in visit 5) were done. A repeat ECG and Holter were performed after a wash-out period of at least 5 days (v 193, p 114-123, 171, 179-187).

Table 56. EBA 132, Schedules of observations

Procedures	Visit 1 Screening/Lead in Day -14 to -1	Visit 2 Baseline Day 1	Visit 3 Day 8 ± 1	Visit 4 Day 15 ± 1	Visit 5 Day 22 ± 1
Informed consent	x				
Medical history and skin test[*]	x				
Fasting, midnight to clinic visit	x				x
Physical exam, laboratory tests[†]	x				x
Dispense medication		x			
Collect medication					x
Dispense diary	x	x	x	x	
Collect and review diary		x	x	x	x
ECG[‡]	x		x	x	x
24-hour Holter (optional)[§]	x			x	x
Symptom evaluation	x	x	x	x	x
Physician global assessment					x
Patient global assessment					x
Adverse events		x	x	x	x

[*] Skin test done within one year was acceptable.
[†] Same as study EBA 124, listed in Table 43 footnote (v 193, p 190).
[‡] Obtained on visit 1, on visits 3 and 4 at 3-5 hours after medication, and at anytime during close-out procedures at visit 5 (v 193, p 192).
[§] Performed on any screening day from day -14 to -5, and at anytime between visits 4 and 5 (v 193, p 193).
Source: v 193, p 219

8.2.6. Efficacy parameters

The primary efficacy variable was the mean change from baseline in the total reflective rhinitis symptom score averaged over the double-blind treatment period for 24 hours. Secondary variables were the mean changes from baseline in the reflective score for each symptom, nasal index (sum of the scores for nasal discharge, nasal stuffiness, sneezing, and itchy nose), and global perception of efficacy by the patient and the physician for each week separately, and on days 1 through 4 for the 24 hours, first 12 hours, and second 12 hours. Additional secondary variables were mean changes from baseline in the "snap-shot" scores of the variables listed above for reflective scores (v 193, p 107, 125, 126).

8.2.7. Safety analysis

Safety analysis included laboratory values, ECG, Holter monitoring, physical examination, and adverse events (v 193, p 189-194).

8.2.8. Statistical considerations

8.2.8.1. Sample size

A sample size of 86 patients per group was calculated to detect a mean change of one in symptom score from baseline between ebastine and placebo group with a power of 90 at a two-sided α level of 0.05. The projected standard deviation used in the calculation was 2. In the actual analysis, the standard deviation was 2.2 (v 193, p 129).

8.2.8.2. Statistical analysis

The primary efficacy variable was analyzed using a two-way ANCOVA with treatment group and investigator as main effects and no interaction term. The baseline score was included in the model as the covariate. The test was two-sided without adjustment for two dose comparisons. For multiple dose comparison a step-down process as in study EBA 124 was used. The patients' and physicians' global assessment of efficacy was analyzed by the Cochran-Mantel-Haenszel test (v 193, p 19, 125-129).

8.2.9. Results

8.2.9.1. Patients enrolled/analyzed

A total of 447 patients were screened, 158 failed the screening, and 289 were randomized. Of the randomized patients, 16 patients discontinued from the study during double blind treatment period. Disposition of the randomized patients and reasons for discontinuation is shown in Table 57. In the placebo and ebastine 10 mg groups, one patient each (00024, 00286), respectively, did not have any efficacy data and therefore were not included in the efficacy analysis. Eight patients (00050, and 00057 in the placebo group, 00044, and 00071 in the 10 mg group, and 0043, 00049, 00056, and 00149 in the 20 mg group) were missing snap shot AM or PM or both scores and were excluded form those analyses (v 193, p 15, 129).

Table 57. EBA 132, Disposition of study patients

	Placebo	Ebastine 10 mg	Ebastine 20 mg	Total
Enrolled	96	98	95	289
Completed	91	91	91	273
Discontinued	5	7	4	16
Reasons for discontinuation:				
Drug ineffective	2	2	0	4
Adverse event	2	3	2	7
Consent withdrawn	0	1	0	1
Lost to follow-up	1	0	1	2
Others	0	1	1	2
Source: v 193, p 130, 131, merged tables				

8.2.9.2. Subject demographics

Demographic data by treatment group are summarized in Table 58. There were no important differences between the treatment groups.

Table 58. EBA 132, Demographic summary

	Placebo	10 mg AM	20 mg AM	Total
Number	96	98	95	289
Sex: male/female %	61/39	51/49	57/43	
Age: years (range)	27 (12-58)	29 (12-63)	28 (12-58)	31 (12-68)
Race: Cauc/others %	86/14	83/17	81/19	
Source: v 193, p 14, 132				

8.2.9.3. Protocol deviations

There were no significant deviations from the protocol in this study.

8.2.9.4. Efficacy endpoint outcomes

Results of the rhinitis symptom scores during the double-blind treatment period for 24 hours (protocol specified primary efficacy variable), 1st and 2nd 12 hours, and snap-shot symptom scores are shown in Table 59. Ebastine at a daily dose of 10 mg and 20 mg given in the morning were both effective in controlling the symptoms of SAR as compared to placebo. The reduction of symptom score tended to be greater in the first 12 hours as compared to the second 12 hours, although both were statistically superior to placebo. This suggests a weaning of effect towards the end of the dosing interval. Both the doses significantly reduced symptoms by day 1, however, the effect did not persist to the end of dosing interval after the first dose (Table 60). The reduction of symptom score persisted at the end of each week of treatment (Table 61). The efficacy of both doses were consistent in reducing all five individual symptoms of SAR (Table 62), and global rating of efficacy by patients' and physicians' (Table 63). The overall efficacy was consistent when the data were stratified based on gender (male, female), race (Caucasian, non-Caucasian), and age groups (12-16 years, 17-59 years, over 60 years), although for some analysis the differences did not reach statistical significance at 0.05 (v 193, p 16-78, 135-152). In this study, both 10 mg and 20 mg doses were better than placebo, and for most of the measures the 10 mg dose was as good as or even better than the 20 mg dose.

Pivotal Seasonal Allergic Rhinitis (SAR) Efficacy Studies, EBA 132

Table 59. EBA 132, Reflective and snap-shot rhinitis symptom scores[*] for the three week treatment period

Time	Treatment	N	Baseline mean	Change from baseline, mean±SE	p-value vs. placebo[+]
Reflective total symptom scores:					
24 hours	10 mg AM	97	9.27	-3.76 ± 0.29	0.000
	20 mg AM	95	9.35	-3.53 ± 0.29	0.000
	Placebo	95	9.05	-2.06 ± 0.26	
1st 12 hours (PM scores)	10 mg AM	97	9.43	-4.05 ± 0.33	0.000
	20 mg AM	95	9.47	-3.82 ± 0.31	0.000
	Placebo	95	9.24	-2.22 ± 0.26	
2nd 12 hours (AM scores)	10 mg AM	97	9.14	-3.48 ± 0.29	0.000
	20 mg AM	95	9.16	-3.18 ± 0.30	0.002
	Placebo	95	8.79	-1.84 ± 0.25	
Snap-shot symptom scores:					
24 hours	10 mg AM	95	8.72	-3.55 ± 0.32	0.000
	20 mg AM	91	8.87	-3.32 ± 0.30	0.001
	Placebo	93	8.41	-1.90 ± 0.25	
1st 12 hours (PM scores)	10 mg AM	96	8.56	-3.68 ± 0.37	0.000
	20 mg AM	92	8.74	-3.46 ± 0.31	0.001
	Placebo	93	8.30	-1.98 ± 0.26	
2nd 12 hours (AM scores)	10 mg AM	96	8.76	-3.33 ± 0.31	0.000
	20 mg AM	92	8.87	-2.99 ± 0.31	0.008
	Placebo	94	8.53	-1.83 ± 0.25	

[*] Symptom score is the sum of nasal discharge, nasal stuffiness, sneezing, itchy nose, and itchy/watery eyes
[+] Based on t-test for a two-way main effects analysis of covariance with treatment and center as main effects and no interaction term

Source: volume 193, p 67, 77

Table 60. EBA 132, Total rhinitis symptom scores[*] for days 1 to 3

Treatment	Day 1 Change from baseline[+], mean ± SE (n)	Day 1 p-value[‡]	Day 2 Change from baseline[+], mean ± SE (n)	Day 2 p-value[‡]	Day 3 Change from baseline[+], mean ± SE (n)	Day 3 p-value[‡]
24 hours:						
10 mg AM	-3.39 ± 0.29 (94)	0.000	-3.74 ± 0.31 (96)	0.000	-3.69 ± 0.35 (94)	0.000
20 mg AM	-2.80 ± 0.29 (94)	0.000	-3.25 ± 0.31 (94)	0.000	-3.22 ± 0.35 (94)	0.002
Placebo	-1.27 ± 0.28 (95)		-1.65 ± 0.31 (95)		-1.68 ± 0.34 (95)	
1st 12 hours (PM scores):						
10 mg AM	-3.46 ± 0.35 (94)	0.000	-3.93 ± 0.34 (96)	0.000	-3.82 ± 0.38 (95)	0.000
20 mg AM	-3.08 ± 0.35 (94)	0.000	-3.41 ± 0.34 (95)	0.001	-3.54 ± 0.38 (94)	0.000
Placebo	-1.32 ± 0.35 (95)		-1.72 ± 0.34 (95)		-1.52 ± 0.38 (94)	
2nd 12 hours (AM scores):						
10 mg AM	-0.25 ± 0.18 (96)	0.727	-3.54 ± 0.32 (96)	0.000	-3.54 ± 0.33 (95)	0.000
20 mg AM	-0.37 ± 0.18 (95)	0.427	-2.74 ± 0.32 (95)	0.012	-3.11 ± 0.33 (94)	0.001
Placebo	-0.16 ± 0.18 (95)		-1.61 ± 0.32 (95)		-1.57 ± 0.33 (95)	

[*] Symptom score is the sum of nasal discharge, nasal stuffiness, sneezing, itchy nose, and itchy/watery eyes
[+] Adjusted for imbalance among investigators
[‡] vs. placebo, based on a two-tailed test

Source: v 193, p 147

Table 61. EBA 132, Total reflective rhinitis symptom scores* by treatment weeks

Treatment	Week 1		Week 2		Week 3	
	Change from baseline[†], mean ± SE (n)	p-value[‡]	Change from baseline[†], mean ± SE (n)	p-value[‡]	Change from baseline[†], mean ± SE (n)	p-value[‡]
24 hours:						
10 mg AM	-3.45 ± 0.29 (96)	0.000	-3.83 ± 0.32 (94)	0.000	-4.12 ± 0.33 (92)	0.000
20 mg AM	-3.21 ± 0.28 (95)	0.000	-3.57 ± 0.32 (93)	0.003	-3.95 ± 0.37 (91)	0.000
Placebo	-1.77 ± 0.26 (95)		-2.23 ± 0.28 (92)		-2.28 ± 0.32 (92)	
1st 12 hours (PM scores):						
10 mg AM	-3.74 ± 0.35 (96)	0.000	-4.19 ± 0.37 (95)	0.000	-4.43 ± 0.35 (92)	0.000
20 mg AM	-3.53 ± 0.30 (95)	0.000	-3.86 ± 0.34 (93)	0.002	-4.22 ± 0.38 (91)	0.000
Placebo	-1.89 ± 0.26 (95)		-2.42 ± 0.29 (92)		-2.42 ± 0.33 (92)	
2nd 12 hours (AM scores):						
10 mg AM	-3.18 ± 0.29 (96)	0.000	-3.49 ± 0.32 (96)	0.000	-3.83 ± 0.33 (92)	0.000
20 mg AM	-2.74 ± 0.28 (95)	0.004	-3.20 ± 0.32 (95)	0.004	-3.56 ± 0.37 (92)	0.001
Placebo	-1.51 ± 0.26 (95)		-1.88 ± 0.27 (93)		-2.09 ± 0.29 (92)	

* Symptom score is the sum of nasal discharge, nasal stuffiness, sneezing, itchy nose, and itchy/watery eyes
† Based on t-test for a two-way main effects analysis of covariance with treatment and center as main effects and no interaction term

Source: v 193, p 67

Table 62. EBA 132, Summary of individual reflective rhinitis symptom scores for the three weeks of treatment

Treatment	N	First 12-hour		Second 12-hour		24-hour	
		Change from baseline	p-value vs. Placebo*	Change from baseline	p-value vs. Placebo*	Change from baseline	p-value vs. Placebo*
Nasal discharge:							
10 mg AM	97	-0.83	0.000	-0.69	0.000	-0.75	0.000
20 mg AM	95	-0.70	0.001	-0.57	0.005	-0.63	0.002
Placebo	95	-0.39		-0.30		-0.35	
Nasal stuffiness:							
10 mg AM	97	-0.65	0.014	-0.56	0.019	-0.59	0.014
20 mg AM	95	-0.74	0.004	-0.60	0.011	-0.67	0.003
Placebo	95	-0.43		-0.32		-0.37	
Sneezing:							
10 mg AM	97	-0.87	0.000	-0.70	0.000	-0.78	0.000
20 mg AM	95	-0.74	0.000	-0.65	0.002	-0.70	0.000
Placebo	95	-0.48		-0.39		-0.44	
Itchy nose:							
10 mg AM	97	-0.90	0.000	-0.79	0.000	-0.87	0.000
20 mg AM	95	-0.81	0.000	-0.70	0.005	-0.76	0.001
Placebo	95	-0.41		-0.40		-0.42	
Itchy eyes:							
10 mg AM	97	-0.80	0.001	-0.74	0.001	-0.77	0.001
20 mg AM	95	-0.83	0.002	-0.67	0.020	-0.76	0.004
Placebo	95	-0.51		-0.44		-0.48	

* Based on two-tailed t-test on t-test for a two-way main effects analysis of covariance with treatment and center as main effects and no interaction term

Source: volume 193, p 61-66

Table 63. EBA 132, Summary of patients' and physicians' evaluation of efficacy

| Treatment | N | Improved | | No | Worsened | | p-value* |
		Greatly	Somewhat	Change	Somewhat	Greatly	
Patients' evaluation		N (%)	N (%)	N (%)	N (%)	N (%)	
10 mg AM	97	28 (27)	44 (43)	22 (21)	2 (2)	4 (4)	0.003
20 mg AM	95	31 (29)	36 (34)	27 (26)	6 (6)	0 (0)	0.002
Placebo	95	14 (13)	40 (38)	33 (31)	8 (8)	5 (5)	
Physicians' evaluation		N (%)	N (%)	N (%)	N (%)	N (%)	
10 mg AM	97	27 (26)	41 (40)	25 (24)	4 (4)	3 (3)	0.012
20 mg AM	95	33 (31)	34 (32)	27 (26)	6 (6)	0 (0)	0.001
Placebo	95	12 (11)	39 (37)	40 (38)	10 (9)	0 (0)	
* One-sided p-value calculated using Cochran-Mantel Hazel test adjusting for investigator and AM and PM scores compared to placebo and correcting for multiple comparison using the Hochberg procedure							
Source: volume 193, p 151, 152							

8.2.10. Safety outcomes

8.2.10.1. Total drug exposure

All patients enrolled in the study were included in the safety analysis. The mean duration of exposure was 20.1 days for the 10 mg ebastine group, 20.7 days for the 20 mg ebastine group, and 20.3 days for the placebo group (v 193, p 153).

8.2.10.2. Adverse events

Adverse events reported by at least 3% of patients in any treatment group are presented in Table 64. The majority of the adverse events were mild to moderate and not reported by the investigators to be related to the study medication. Headache, and dry mouth were more frequent in the ebastine treated groups. There was one serious adverse event in this study. The event was facial paralysis in a 42-year old male patient (00008) in the ebastine 10 mg group. The event was considered not to be related to the study medication (v 193, p 153, 154).

Table 64. EBA 132, Common adverse experience reported by patients*

	Placebo (n=96)	Ebastine 10 mg (n=98)	Ebastine 20 mg (n=95)
Total with adverse experience	35 (36.5 %)	38 (38.8 %)	41 (43.2 %)
Body as a whole			
Headache	9 (9.4 %)	11 (11.2 %)	12 (12.6 %)
Pain abdomen	4 (4.2 %)	0 (0.0 %)	2 (2.1 %)
Digestive system			
Diarrhea	3 (3.1 %)	1 (1.0 %)	1 (1.1 %)
Tooth disease	1 (1.0 %)	3 (3.1 %)	2 (2.1 %)
Nervous system			
Dry mouth	0 (0.0 %)	0 (0.0 %)	3 (3.2 %)
Somnolence	1 (1.0 %)	0 (0.0 %)	2 (2.1 %)
Respiratory system			
Cough	3 (3.1 %)	0 (0.0 %)	3 (3.2 %)
Pharyngitis	5 (5.2 %)	4 (4.1 %)	4 (4.2 %)
Sinusitis	1 (1.0 %)	0 (0.0 %)	3 (3.2 %)

*Events reported by ≥3% of patients in any group is listed (number and %) as Costart preferred term. Somnolence is included because of the relevance of this adverse event to this application.

Source: v 199, p 55-58

8.2.10.3. Premature withdrawals due to adverse events

A total of 7 patients were withdrawn due to adverse events (Table 57). The events are summarized in Table 65 (v 183, p 146).

Table 65. EBA 132, Discontinued patients due to adverse events

Group	Patient	Event	Days on study medication	Severity	Relationship to study med.
Placebo	00067	Dizziness, malaise, chest pain	1	Moderate	Possible
	00294	Pain abdomen, rash, tinnitus	15	Moderate	Remote
10 mg	00008	Facial paralysis	8	Severe	None
	00085	Urticaria	14	Moderate	Possible
	00230	Flu syndrome	8	Moderate	None
20 mg	00178	Sinusitis	10	Moderate	None
	00340	Ear disorder	6	Severe	Possible

Source: v 193, p 154

8.2.10.4. Physical examination, ECG, and laboratory measures

There were no clinically significant changes in physical examination or vital signs in any of the patients. No patient was discontinued from the study for ECG abnormality. The results of the QTc data analysis is shown in Table 66 and patients with a ≥ 15% increase from baseline in QTc interval are shown in Table 67. There was a small but statistically significant mean percentage change from baseline in QTc in the ebastine groups compared to placebo at week 1, and the trend persisted at later time points. There were a total of 13 patients who had QTc ≥ 444 msec at some point during the 3 weeks of treatment, of which 6 were from the 20 mg group, and 7 were from the 10 mg group. A total of 57 patients had 24-hour Holter monitoring done at baseline and at the end of the study. There were no clinically relevant findings in the Holter data. Two patients, 1 from placebo group, and 1

from 20 mg ebastine group, had 2°AV block at the final visit. For the laboratory values, there were no clinically relevant changes for any parameters including serum transaminase levels (v 193, p 156-163).

Table 66. EBA 132, Summary of QTc changes

Treatment week	Treatment group	N	Baseline mean in msec	Post-treatment mean in msec	Mean raw % change	p-value s. placebo
Week 1	10 mg AM	94	387	393	1.595	0.021
	20 mg AM	94	388	393	1.535	0.032
	Placebo	92	388	387	-0.326	
Week 2	10 mg AM	90	387	394	1.775	0.111
	20 mg AM	91	388	393	1.441	0.281
	Placebo	90	388	389	0.448	
Week 3	10 mg AM	97	387	395	1.823	0.362
	20 mg AM	95	388	394	1.780	0.421
	Placebo	95	388	392	1.111	
* Based on a two-tailed t-test for comparisons of each ebastine dose to placebo						
Source: v 193, p 158						

Table 67. EBA 132, Patients with ≥ 15% change from baseline in QTc

Patient	Treatment	Study day	Baseline QTc	On treatment QTc	Change from baseline in msec
00310	Placebo	15	350	406	56
00018	10 mg	8	387	457	70
00346	10 mg	13	400	463	63
00020	20 mg	8	371	430	59
00135	20 mg	15	347	402	55
00165	20 mg	15	359	421	62
00219	20 mg	21	343	401	58
00226	20 mg	7	354	410	56
00263	20 mg	22	356	415	59
Source: v 193, p 159					

8.2.11. Conclusion from EBA 132 study results

This study evaluates the efficacy and safety of ebastine 20 mg/day and 10 mg/day administered in the AM in patients with SAR. The results show that ebastine 10 mg/day and 20 mg/day were both effective in relieving symptoms of SAR. The improvement in total symptom score relative to placebo occurred as early as day 1 for both the groups and persisted at the end of each treatment week for the 3-week duration of treatment. However, the effect did not persist at the end of dosing interval after the first dose, and the reduction of symptom scores tended to be greater in the first 12 hours as compared to the second 12 hours. This suggests a weaning of the effective towards the end of dosing interval. The results of this study support the efficacy of ebastine 20 mg QD and 10 mg QD for relief of SAR symptoms. Safety parameters collected during the study show that ebastine was well tolerated in this study group, however, in the ebastine treated groups, dry mouth, and QTc prolongation were more frequently seen.

9. PIVOTAL PERENNIAL ALLERGIC RHINITIS (PAR) EFFICACY STUDIES

The applicant submitted 2 US studies (EBA 109, and EBA 110) and 1 European study (CR 2714) supporting the efficacy of ebastine for PAR. Ebastine was given at a daily dose of 10 mg or 20 mg and compared to placebo. The efficacy measures were based on patient recording of PAR symptoms in diary cards. In all 3 studies ebastine 20 mg was statistically superior to placebo, and for some measures ebastine 10 mg was also statistically superior to placebo. The 3 studies are reviewed in the following sections.

9.1. EBA 109: Multicenter, double-blind, parallel group, randomized comparison of ebastine and placebo in patients with perennial allergic rhinitis.

9.1.1. Investigators and centers

The study was conducted in 8 sites in the US. The principal investigators, study sites, and number of patients enrolled are listed below (v 204, p 57).

Wilfred N. Beaucher, MD, Chelmsford, Massachusetts	31 patients
Andrew W. Green, MD, Buffalo, New York	26 patients
Jay Grossman, MD, Albany, New York	36 patients
Louis M. Mendelson, MD, West Hartford, Connecticut	19 patients
Richard J. Morris, MD, Minneapolis, Minnesota	20 patients
Andrew J. Pedinoff, MD, Princeton, New Jersey	33 patients
Michael S. Rowe, MD, Novi, Michigan	30 patients
Howard Schwartz, MD, Cleveland, Ohio	29 patients

9.1.2. Objective

The objective of this study was to compare the efficacy and safety of ebastine 20 mg administered once a day in the AM, and 10 mg twice a day in the AM or PM, to placebo in patients with PAR (v 204, p 99).

9.1.3. Study population

Patients with PAR meeting the following criteria were selected for participation.

9.1.3.1. Inclusion criteria (v 204, p 101)

1. Male or females 12 years of age and above. Female were to be nonpregnant, or without childbearing potential, or using an accepted method of contraception.
2. Diagnosis of PAR for at least 2 consecutive years, and positive skin test to a perennial allergen, e.g. dust mites, molds, cockroaches, and/or animal dander.
3. Positive nasal smear for eosinophils.
4. Minimum total rhinitis symptom score (for nasal discharge, sneezing, and itchy nose) of 32 (out of 63) over the last 3 days of screening period plus the morning of the baseline visit (scoring described below).

5. Normal ECG at screening without prolonged QTc (i.e., >0.44 seconds). For 3 selected centers, normal Holter monitoring. ECG and Holter criteria described below.

9.1.3.2. Exclusion criteria (v 204, p 103)

1. History of non-allergic rhinitis, e.g., infectious, vasomotor, rhinitis medicamentosa, etc. Acute upper respiratory tract infection, sinusitis, otitis media, nasal polyps, acute asthma. History of chronic sinusitis in the past 6 months.

2. Significant acute or chronic disease, or clinically relevant screening laboratory values outside the normal range.

3. History of hypersensitivity to antihistamines.

4. Use of any of the following: H_1-antagonist (except astemizole) within 7 days, astemizole within 6 months, depot corticosteroids within 2 months, short acting systemic or topical (inhaled, intranasal, and ocular) corticosteroids and topical cromolyn within 21 days, and ketoconazole or erythromycin (oral or topical) within 2 weeks or randomization.

5. Currently on medication which may suppress or exacerbate symptoms of PAR (e.g., centrally acting cardiovascular drugs, neuroleptic drugs, etc.,)

6. Stabilized on immunotherapy for less than one month prior to randomization.

7. Investigational treatment within 30 days prior to randomization.

8. History of alcohol or drug abuse within the past 2 years.

9. Night shift (11 PM to 8 AM) workers.

9.1.3.3. ECG exclusion criteria at screening (v 204, p 131)

1. QTc >0.444 seconds.

2. Ventricular ectopy.

3. Bradycardia <50 bpm.

4. Second or third degree AV block.

9.1.3.4. Holter monitoring exclusion criteria at screening (for the 3 centers) (v 204, p 132)

1. Ventricular ectopics ≥30/hr during one reading.

2. Presence of any multiform ventricular ectopics (VE), or any paired VE, or isolated VE's showing the R on T phenomenon.

3. Ventricular run of 3 or more - regardless of rate.

4. Ventricular flutter and/or fibrillation, or atrial fibrillation.

5. Average heart rate ≤40 bpm for any one hour.

6. Transient or fixed second or third degree AV block.

7. Ventricular asystole ≥2 sec.

9.1.3.5. ECG criteria for patient discontinuation at visits 3, 4, and 5 (v 204, p 133)

1. QTc prolonged >15% over baseline.

2. Ventricular dysrhythmia or ventricular ectopy

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3. Bradycardia <50 bpm.
4. Second or third degree AV block.
5. By request of physician.

9.1.4. Study design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study.

9.1.5. Study procedures

The study was conducted between January and April, 1992. The study procedures are outlined in Table 68. The study had a day of pre-screening, a day of screening, 4 days baseline lead-in period, followed by 3 weeks of double-blind treatment. Patients satisfying the inclusion/exclusion and ECG/Holter criteria (described above) were dispensed with diary cards and asked to record severity of 4 rhinitis symptoms (nasal discharge, nasal stuffiness, sneezing, itchy nose) on a 4-point scale (0 = absent, no symptoms; 1 = mild, symptoms present but not annoying to self; 2 = moderate, symptoms present and annoying to self; 3 = severe, symptoms interfere with activities of daily living) twice a day - upon arising in the morning, and in the evening before dinner. Scoring were to reflect symptom severity over the previous 12 hours. To be eligible for randomization (visit 3), patients were required to have an aggregated sum of 3 primary rhinitis symptom (nasal discharge, sneezing, and itchy nose) score over the last 3 days of lead-in period plus the morning of the visit (total of 7 readings) of at least 32 points out of a maximum possible of 63. This was the baseline score.

Eligible patients were randomized into 3 study groups (ebastine 20 mg QD, ebastine 10 mg BID, and placebo). Study medications were administered in the morning immediately after breakfast or in the evening immediately after dinner. No study medication was administered in the morning of visit 6. During the study, patients were instructed to refrain from using any other medication for alleviating symptoms of rhinitis. Throughout the study patients continued recording rhinitis symptom scores (reflective scores for the previous 12 hours) daily in the morning and in the evening before study medication administration. In addition, at the end of the study (visit 6), patients recorded the global evaluation of efficacy on a 5 point scale (0 = greatly improved, 1 = somewhat improved, 2 = no change, 3 = somewhat worsened, 4 = greatly worsened) relative to the baseline. During the study, ECG and Holter monitoring were done at time points shown in Table 68, and patients were discontinued based on criteria mentioned above. The examining physician at the study site read the ECGs for implementing the discontinuation criteria. All ECG tracings were finally interpreted in the central facility in Philadelphia. Patients discontinued for ECG abnormalities were immediately followed-up with a Holter recording, and close-out procedures (as in visit 6) were done. A repeat ECG was done after a wash-out period of >5 days. (v 204, p 58-68, 99-110)

Table 68. EBA 109, Schedules of observations

Procedures	Visit 1 Pre-Screening	Visit 2 Screening/ Lead in Day -11 to -1	Visit 3 Baseline Day 1	Visit 4 Day 8 ± 1	Visit 5 Day 15 ± 1	Visit 6 Day 22 ± 1
Informed consent	x					
Nasal smear & skin test[*]	x					
Medical history		x				
Physical exam		x				x
Fasting, midnight to visit		x				x
Laboratory tests[†]		x				x
Dispense medication			x			
Collect medication						x
Dispense diary		x	x	x	x	
Collect and review diary			x	x	x	x
ECG[‡]		x		x	x	x
24-hour Holter (optional)[§]		x				x
Symptom evaluation			x	x	x	x
Patient global assessment						x
Adverse events			x	x	x	x

[*] Skin test done within one year was acceptable.
[†] Same as study EBA 124, listed in Table 43 footnote (v 204, p 115).
[‡] Obtained on screening day and on visits 4, 5, and 6 at 3-4 hours after medication
[§] For centers performing Holter, patients to report to clinic 24-hours prior to the visit.

Source: v 204, p 130

9.1.6. Efficacy parameters

The primary efficacy variable was the mean change from baseline in the reflective perennial index score (the sum of the scores for nasal discharge, sneezing, and itchy nose) averaged over the double-blind treatment period for 24 hours. The 24-hour score was the average of the evening measurement on that day and the morning measurement of the following day. Secondary variables were the mean changes from baseline for each symptom, nasal index (sum of the scores for nasal discharge, nasal stuffiness, sneezing, and itchy nose), and global perception of efficacy by the patient for each week separately, and over the double-blind period for the first 12 hours, second 12 hours, and 24 hours (v 204, p 53, 69).

9.1.7. Safety analysis

Safety analysis included laboratory values, ECG, Holter monitoring, physical examination, and adverse events (v 204, p 4).

9.1.8. Statistical considerations

9.1.8.1. Sample size

A sample size of 70 patients per group was calculated to detect a mean change of one in symptom score from baseline between ebastine and placebo group with a power of 90 at a one-sided α level of 0.05. The projected standard deviation used in the calculation was 1.7. In the actual analysis, the standard deviation was 1.7 (v 204, p 70).

9.1.8.2. Statistical analysis

The primary efficacy variable was analyzed using a two-way ANCOVA with center and treatment as fixed effect with no interaction term. The baseline score was included in the model as the covariate. For the primary and secondary diary variables, a two-sided test was done on the primary comparison, ebastine 20 mg QD versus placebo, and then on the secondary comparison, ebastine 10 mg BID versus placebo. For the patients' evaluation of efficacy, the Cochran-Mantel-Haenszel test was used to compare each treatment group to placebo (v 204, p 16, 69-70).

9.1.9. Results

9.1.9.1. Patients enrolled/analyzed

A total of 431 patients were screened, 207 failed the screening, and 224 were randomized. Of the randomized patients, 18 patients discontinued from the study during double blind treatment period. Disposition of the randomized patients and reasons for discontinuation is shown in Table 69. One patient (4208) in the ebastine 10 mg BID group had no recorded diary efficacy data and, therefore, was not included in the primary efficacy analysis (v 204, p 13, 71).

Table 69. EBA 109, Disposition of study patients

	Placebo	10 mg BID	20 mg QD	Total
Enrolled	73	74	77	224
Completed	67	71	70	206
Discontinued	6	5	7	18
Reasons for discontinuation:				
Drug ineffective	1	0	1	2
Adverse event	3	0	2	5
Deviation from protocol	2	2	1	5
Others	0	3	3	6
Source: v 204, p 73				

9.1.9.2. Subject demographics

Demographic data by treatment group are summarized in Table 70. The groups were similar in respect to their demographics.

Table 70. EBA 109, Demographic summary

	Placebo	10 mg BID	20 mg AM	Total
Number	73	74	77	224
Sex: male/female %	48/52	47/53	68/32	54/46
Age: years (range)	31 (14-77)	33 (12-64)	30 (12-60)	32 (12-77)
Race: Cauc/others %	93/7	97/3	97/3	96/4
Source: v 204, p 73				

9.1.9.3. Protocol deviations

There were no significant deviations from the protocol in the study.

9.1.9.4. Efficacy endpoint outcomes

Results of the reflective perennial index scores during the double-blind treatment period for 24 hours (protocol specified primary efficacy variable), and 1st and 2nd 12 hours are shown in Table 71. Both the 10 mg BID dose and 20 mg QD dose taken in the morning were effective in relieving the symptoms of PAR as compared to placebo. The favorable response for the 10 mg BID dose and 20 mg QD dose persisted at the end of each week of treatment (Table 72). The superiority of both the doses of ebastine was consistent in reducing the individual symptoms of PAR, some of which reached statistical significance (Table 73). The reductions of symptom score tended to be greater in the first 12 hours as compared to the second 12 hours, although for most of the measures both were statistically superior to placebo. For the rating of efficacy by patients, 20 mg QD dose was better than placebo (Table 74). The overall efficacy was consistent when the data were stratified based on gender (male, female), race (Caucasian, non-Caucasian), and age groups (12-16 years, 17-59 years, over 60 years), although the differences did not reach statistical significance at 0.05 (v 204, p 20-46, 75-81). In this study ebastine at a dose of 10 mg BID or 20 mg QD was better than placebo in reducing the symptoms of PAR, and for most of the measures, the 10 mg BID dose tended to be better than the 20 mg QD dose.

Table 71. EBA 109, Reflective perennial index scores[*] for the three week treatment period

Time	Treatment	N	Baseline mean	Change from baseline, mean±SE	p-value vs. placebo[†]
24 hours	10 mg BID	73	5.88	-2.40 ± 0.23	0.015
	20 mg AM	77	5.67	-2.23 ± 0.19	0.018
	Placebo	73	5.85	-1.70 ± 0.19	
1st 12 hours (PM scores)	10 mg BID	73	5.84	-2.36 ± 0.24	0.036
	20 mg AM	77	5.60	-2.17 ± 0.21	0.035
	Placebo	73	5.85	-1.75 ± 0.22	
2nd 12 hours (AM scores)	10 mg BID	73	5.82	-2.32 ± 0.20	0.009
	20 mg AM	77	5.61	-2.17 ± 0.20	0.014
	Placebo	77	5.85	-1.63 ± 0.20	

[*] Symptom score is the sum of nasal discharge, sneezing, and itchy nose
[†] Based on a two-tailed test

Source: volume 204, p 44

Table 72. EBA 109, Reflective perennial index scores[*] by treatment weeks

Treatment	Week 1		Week 2		Week 3	
	Change from baseline, mean ± SE (n)	p-value[†]	Change from baseline, mean ± SE (n)	p-value[†]	Change from baseline, mean ± SE (n)	p-value[†]
24 hours:						
10 mg BID	-2.26 ± 0.22 (73)	0.011	-2.43 ± 0.26 (71)	0.024	-2.57 ± 0.25 (69)	0.039
20 mg AM	-2.10 ± 0.18 (77)	0.017	-2.29 ± 0.20 (75)	0.012	-2.38 ± 0.22 (73)	0.035
Placebo	-1.52 ± 0.20 (73)		-1.68 ± 0.22 (71)		-1.83 ± 0.22 (69)	
1st 12 hours (PM scores):						
10 mg BID	-2.21 ± 0.23 (73)	0.031	-2.40 ± 0.28 (72)	0.036	-2.55 ± 0.27 (69)	0.095
20 mg AM	-2.02 ± 0.20 (77)	0.039	-2.19 ± 0.22 (75)	0.021	-2.37 ± 0.24 (73)	0.061
Placebo	-1.57 ± 0.23 (73)		-1.69 ± 0.25 (71)		-1.95 ± 0.24 (69)	

Treatment	Week 1		Week 2		Week 3	
	Change from baseline, mean ± SE (n)	p-value[†]	Change from baseline, mean ± SE (n)	p-value[†]	Change from baseline, mean ± SE (n)	p-value[†]
2nd 12 hours (AM scores):						
10 mg BID	-2.18 ± 0.22 (73)	0.010	-2.38 ± 0.26 (72)	0.023	-2.48 ± 0.25 (69)	0.028
20 mg AM	-2.02 ± 0.19 (77)	0.017	-2.14 ± 0.21 (76)	0.044	-2.30 ± 0.21 (74)	0.026
Placebo	-1.46 ± 0.20 (73)		-1.68 ± 0.21 (72)		-1.76 ± 0.22 (69)	
* Symptom score is the sum of nasal discharge, sneezing, and itchy nose						
† Vs. placebo, based on a two-tailed test.						
Source: v 204, p 44						

Table 73. EBA 109, Summary of individual reflective rhinitis symptom scores for the three weeks of treatment

Treatment	N	First 12-hour		Second 12-hour		24-hour	
		Change from baseline	p-value vs. Placebo*	Change from baseline	p-value vs. Placebo*	Change from baseline	p-value vs. Placebo*
Nasal discharge:							
10 mg BID	73	-0.80	0.168	-0.75	0.104	-0.79	0.089
20 mg AM	77	-0.74	0.008	-0.73	0.041	-0.76	0.031
Placebo	73	-0.55		-0.54		-0.54	
Sneezing:							
10 mg BID	73	-0.74	0.034	-0.80	0.004	-0.79	0.010
20 mg AM	77	-0.77	0.043	-0.75	0.013	-0.76	0.023
Placebo	73	-0.58		-0.53		-0.56	
Itchy nose:							
10 mg BID	73	-0.82	0.022	-0.78	0.012	-0.82	0.013
20 mg AM	77	-0.67	0.115	-0.69	0.046	-0.71	0.064
Placebo	73	-0.62		-0.56		-0.59	
Nasal stuffiness:							
10 mg BID	73	-0.56	0.527	-0.48	0.519	-0.53	0.457
20 mg AM	77	-0.55	0.343	-0.50	0.367	-0.55	0.277
Placebo	73	-0.44		-0.39		-0.42	
* Based on two-tailed t-test							
Source: volume 204, p 41-45							

Table 74. EBA 109, Summary of patients' evaluation of efficacy

Treatment	N	Improved		No	Worsened		p-value*
		Greatly	Somewhat	Change	Somewhat	Greatly	
Patients' evaluation		N (%)	N (%)	N (%)	N (%)	N (%)	
10 mg BID	73	15 (11)	43 (31)	37 (27)	4 (3)	1 (1)	0.051
20 mg AM	77	9 (7)	55 (42)	32 (25)	3 (2)	1 (1)	0.028
Placebo	73	6 (5)	44 (32)	38 (28)	6 (4)	6 (4)	
* One-sided p-value calculated using Cochran-Mantel Hazel test adjusting for investigator and AM and PM scores compared to placebo							
Source: volume 204, p 81							

9.1.10. Safety outcomes

9.1.10.1. Total drug exposure

All patients enrolled in the study were included in the safety analysis. The mean duration of exposure across the treatment groups was 20 days (v 204, p 81).

9.1.10.2. Adverse events

Adverse events reported by at least 3% of patients in any treatment groups are presented in Table 75. There were no serious adverse events reported in this study. Investigators concluded that most of the adverse events were not related to the study medication. Headache was the most frequently reported adverse event and it was comparable among the treatment groups. Dry mouth and somnolence was more frequent in the ebastine treated groups (v 204, p 81-84).

Table 75. EBA 109, Common adverse experience reported by patients[*]

	Placebo (n=73)	Ebastine 10 mg BID (n=74)	Ebastine 20 mg QD (n=77)
Total with adverse experience	36 (49.3 %)	32 (43.2 %)	31 (40.3 %)
Body as a whole			
Asthenia	0 (0.0 %)	0 (0.0 %)	3 (3.9 %)
Headache	12 (16.4 %)	15 (20.3 %)	11 (14.3 %)
Digestive system			
Dyspepsia	3 (4.1 %)	4 (5.4 %)	1 (1.3 %)
Nervous system			
Dry mouth	0 (0.0 %)	3 (4.1 %)	1 (1.3 %)
Somnolence	0 (0.0 %)	4 (5.4 %)	2 (2.6 %)
Respiratory system			
Epistaxis	2 (2.7 %)	0 (0.0 %)	3 (3.9 %)
Pharyngitis	3 (4.1 %)	3 (4.1 %)	3 (3.9 %)
Rhinitis	5 (6.8 %)	4 (5.4 %)	8 (10.8 %)
Sinusitis	4 (5.5 %)	1 (1.4 %)	0 (0.0 %)
Urogenital system			
Dysmenorrhea	3 (4.1 %)	3 (4.1 %)	1 (1.3 %)
[*] Events reported by ≥3% of patients in any group is listed (number and %) as Costart preferred term.			
Source: v 207, p 241-243			

9.1.10.3. Premature withdrawals due to adverse events

A total of 5 patients were withdrawn due to adverse events (Table 69). The events are summarized in Table 76 (v 183, p 146).

Table 76. EBA 109, Discontinued patients due to adverse events

Group	Patient	Event	Days on study medication	Severity	Relationship to study med.
Placebo	4022	Pharyngitis	6	Moderate	None
	4062	Nausea, vomiting, headache	15	Severe	Probable
20 mg QD	4245	Pneumonia	25	Moderate	None
	4242	Pharyngitis	9	Mild	None
	4529	Nasal dryness, Asthenia	3	Mild	Possible

Group	Patient	Event	Days on study medication	Severity	Relationship to study med.
Source: v 204, p 82					

9.1.10.4. Physical examination and laboratory measures

There were no clinically significant changes in physical examination or vital signs in any of the patients. No patient was discontinued from the study for ECG abnormality. The results of the QTc data analysis is shown in Table 77. There were no significant mean percentage changes from baseline in QTc in the ebastine groups compared to placebo. A total of 3 patients, 1 from each group, had greater that 15% increase in QTc during treatment as compared to the baseline. The increase was by 55 msec for the patient in 10 mg BID group (4241), and 57 msec for the patients in the 20 mg QD group (4274) and the placebo group (4225). A total of 83 patients had 24-hour Holter monitoring done at baseline and at the end of the study. There were no clinically relevant findings in the Holter data. For the laboratory values, there were no clinically relevant changes for any parameters (v 204, p 84-91).

Table 77. EBA 109, Summary of QTc changes

Treatment week	Treatment group	N	Baseline mean in msec	Post-treatment mean in msec	Mean raw % change	p-value s. placebo
Week 1	10 mg BID	74	405	404	-0.030	0.735
	20 mg AM	76	400	405	1.272	0.225
	Placebo	73	401	402	0.255	
Week 2	10 mg BID	71	406	404	-0.383	0.726
	20 mg AM	75	400	402	0.546	0.376
	Placebo	71	401	400	-0.117	
Week 3	10 mg BID	69	407	406	-0.094	0.317
	20 mg AM	74	400	401	0.345	0.637
	Placebo	68	401	404	0.724	
* Based on a two-tailed t-test for comparisons of each ebastine dose to placebo						
Source: v 204, p 85						

9.1.11. Conclusion from EBA 109 study results

This study evaluated the efficacy and safety of ebastine 10 mg BID and 20 mg QD in patients with PAR. The results show that ebastine 10 mg BID or 20 mg QD taken in the morning was effective in relieving symptoms of PAR. The improvement in total symptom score relative to placebo for the two dose schedules persisted at the end of each week of treatment for the 3-week duration of treatment. The reductions of symptom score tended to be greater in the first 12 hours as compared to the second 12 hours. The 10 mg BID dose tended to be better than the 20 mg QD dose. The results of this study support ebastine at a 10 mg BID dose or 20 mg QD dose for relief of symptoms of PAR. Safety parameters show that ebastine was well tolerated in this study population. In the ebastine treated groups dry mouth and somnolence was more frequently seen. The QTc interval was not effected by ebastine treatment in this study.

9.2. EBA 110: Multicenter, double-blind, parallel group, randomized comparison of ebastine and placebo in patients with perennial allergic rhinitis.

9.2.1. Investigators and centers

The study was conducted in 8 sites in the US. The principal investigators, study sites, and number of patients enrolled are listed below (v 204, p 57).

Edwin A. Bronsky, MD, Salt Lake City, Utah	25 patients
Kraig W. Jacobson, MD, Eugene, Oregon	24 patients
John T. Klimas, MD, Charlotte, North Carolina	24 patients
Craig LaForce, Raleigh, North Carolina	27 patients
John Norton, MD, Colorado Springs, Colorado	24 patients
Paul Steinberg, MD, Minneapolis, Minnesota	26 patients
Sheryl Talbot, MD, Philadelphia, Pennsylvania	21 patients
John Winder, MD, Sylvania, Ohio	24 patients

9.2.2. Objective

The objective of this study was to compare the efficacy and safety of ebastine 20 mg administered once a day to placebo in patients with PAR (v 211, p 130).

9.2.3. Study population

Patients 12 years of age and above with a 2 year history of PAR were selected for participation in the study. The inclusion and exclusion criteria were similar to the previous PAR study (EBA 109). The ECG exclusion criteria at screening with or without accompanying Holter monitoring, Holter monitoring criteria at screening and for patient discontinuation, and ECG criteria for patient discontinuation were same as in the SAR study EBA 132 and is given in section VIII.B.4 (v 211, p 131-134, 174-178).

9.2.4. Study design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of ebastine 20 mg in patients with PAR (v 211, p 73).

9.2.5. Study procedures

The study was conducted between January and April, 1993. The study procedures were similar to the previous PAR study (EBA 109) as outlined in Table 78 with some differences as described below. Unlike the previous PAR study where only rhinitis symptoms reflective of the previous 12 hours were recorded, in this study scoring of symptoms of the previous 12 hours (reflective symptom score) and at the time of recording ("snap-shot" symptom score) were done (similar to SAR study EBA 132). For calculating the required minimum score for randomization, only the reflective scores were used. In this study, eligible patients were randomized into 2 study groups - ebastine 20 mg QD, and placebo (v 211, p 73-78, 135-144).

Table 78. EBA 110, Schedules of observations

Procedures	Visit 1 Pre-Screening	Visit 2 Screening/ Lead in Day -11 to -1	Visit 3 Baseline Day 1	Visit 4 Day 8 ± 1	Visit 5 Day 15 ± 1	Visit 6 Day 22 ± 1
Informed consent	x					
Nasal smear & skin test[*]	x					
Medical history		x				
Physical exam		x				x
Fasting, midnight to visit		x				x
Laboratory tests[†]		x				x
Dispense medication			x			
Collect medication						x
Dispense diary		x	x	x	x	
Collect and review diary			x	x	x	x
ECG[‡]		x		x	x	x
24-hour Holter (optional)[§]		x				x
Symptom evaluation			x	x	x	x
Patient global assessment						x
Physician global assess.						x
Adverse events			x	x	x	x

[*] Skin test done within one year was acceptable.
[†] Same as study EBA 124, listed in Table 43 footnote (v 211, p 81).
[‡] Obtained on screening day and on visits 4 and 5 at 3-4 hours after medication, and at anytime at visit 6
[§] For centers performing Holter, patients to report to clinic 24-hours prior to the visit.

Source: v 211, p 173

9.2.6. Efficacy parameters

The primary efficacy variable was the mean change from baseline in the reflective perennial index score (the sum of the scores for nasal discharge, sneezing, and itchy nose) averaged over the double-blind treatment period for 24 hours. The 24-hour score was the average of the evening measurement on that day and the morning measurement of the following day. Secondary variables were the mean changes from baseline in the reflective score for each symptom, nasal index (sum of the scores for nasal discharge, nasal stuffiness, sneezing, and itchy nose), and global perception of efficacy by the patient and the physician for each week separately, and on days 1 through 4 for the 24 hours, first 12 hours, and second 12 hours. Additional secondary variables were mean changes from baseline in the "snap-shot" scores of the variables listed above (v 211, p 84).

9.2.7. Safety analysis

Safety analysis included laboratory values, ECG, Holter monitoring, physical examination, and adverse events (v 211, p 145-150).

9.2.8. Statistical considerations

9.2.8.1. Sample size

A sample size of 86 patients per group was calculated to detect a mean change of one in symptom score from baseline between ebastine and placebo group with a power of 90 at a two-sided α level of 0.05. The projected standard deviation used in the calculation was 2. In the actual analysis, the standard deviation was 2.2 and with the sample size of 97 per group, the detectable difference was about 1.05. (v 211, p 86)

9.2.8.2. Statistical analysis

The primary efficacy variable was analyzed using a two-way ANCOVA with treatment group and investigator as main effects and no interaction term. The baseline score was included in the model as a covariate. For the primary and secondary diary variables, a two-sided test was done for the comparison of ebastine 20 mg versus placebo. For the patients' and physicians' global evaluation, the Cochran-Mantel-Haenszel test was used to compare the treatment group to placebo. (v 211, p 13, 86)

9.2.9. Results

9.2.9.1. Patients enrolled/analyzed

A total of 326 patients were screened, 131 failed the screening, and 195 were randomized. Of the randomized patients, 14 patients discontinued from the study during double blind treatment period. Disposition of the randomized patients and reasons for discontinuation is shown in Table 79. One patient (00207) in the ebastine group had no recorded diary efficacy data, 2 patients on placebo (00187, 00211) and 3 patients on ebastine (00219, 00228, 00238) did not have baseline data for snap shot measures, and one patient in the ebastine (00149) did not have the patient's and investigator's global evaluation of efficacy. These patients were excluded from the respective analysis. (v 211, p 12, 87-99)

Table 79. EBA 110, Disposition of study patients

	Placebo	20 mg QD	Total
Enrolled	101	94	195
Completed	97	84	206
Discontinued	4	10	14
Reasons for discontinuation:			
Drug ineffective	2	0	2
Deviation from protocol	0	2	2
Adverse event	1	4	5
Consent withdrawn	0	1	1
Lost to follow-up	0	1	1
Others	1	2	3
Source: v 211, p 88			

9.2.9.2. Subject demographics

Demographic data by treatment group are summarized in Table 80. The groups were similar in respect to their demographics.

Table 80. EBA 110, Demographic summary

	Placebo	20 mg QD	Total
Number	101	94	195
Sex: male/female %	65/35	50/50	58/42
Age: years (range)	28 (12-53)	29 (12-64)	29 (12-64)
Race: Cauc/others %	98/2	96/4	96/4
Source: v 211, p 90			

9.2.9.3. Protocol deviations

Two patients (00049, 00078) who were discontinued because of protocol deviations (v 211, p 88).

9.2.9.4. Efficacy endpoint outcomes

Results of the reflective perennial index scores during the double-blind treatment period for 24 hours (protocol specified primary efficacy variable), scores for 1st and 2nd 12 hours, and snap-shot scores are shown in Table 81. Ebastine at a daily dose 20 mg given in the morning was effective in controlling the symptoms of PAR as compared to placebo. The reduction was first seen at day 1, however, the effect did not persist through the next 2 days (Table 82). On weekly measures, the favorable response was seen to persist at the end of each week of treatment (Table 83). On analysis of the individual symptom scores, the favorable response was seen to be carried mainly by the sneezing and itchy nose scores (Table 85). The reduction of symptoms for the composite and individual scores were greater at the end of first 12 hours as compared to the end of second 12 hours suggesting a waning of effect towards the end of the dosing interval. The snap-shot scores for the various measures were same as the reflective scores (perennial index scores by treatment weeks are shown in Table 84, other data not shown). The improvement in global symptoms between the ebastine 20 mg group and placebo group was significant for the patients' ratings and better but not significant for the physicians' ratings. The overall efficacy was consistent when the data were stratified based on gender (male, female), race (Caucasian, non-Caucasian), and age groups (12-16 years, 17-59 years, over 60 years), although the differences did not reach statistical significance at 0.05 (v 211, p 20-46, 75-81). In this study, the 20 mg QD dose of ebastine was better than placebo in reducing the symptoms of PAR.

Table 81. EBA 110, Reflective and snap-shot perennial index scores[*] for the three week treatment period

Time	Treatment	N	Baseline mean	Change from baseline, mean±SE	p-value vs. placebo[†]
Reflective scores:					
24 hours	20 mg QD	93	5.89	-2.06 ± 0.19	0.019
	Placebo	101	6.05	-1.51 ± 0.16	
1st 12 hours (PM scores)	20 mg QD	93	5.87	-2.02 ± 0.20	0.019
	Placebo	101	6.05	-1.47 ± 0.17	
2nd 12 hours (AM scores)	20 mg QD	93	5.89	-2.08 ± 0.20	0.025
	Placebo	101	6.05	-1.55 ± 0.17	

Time	Treatment	N	Baseline mean	Change from baseline, mean±SE	p-value vs. placebo[†]
Snap-shot scores:					
24 hours	20 mg QD	90	5.21	-1.72 ± 0.18	0.013
	Placebo	99	5.19	-1.14 ± 0.16	
1st 12 hours	20 mg QD	90	5.00	-1.64 ± 0.19	0.045
(PM scores)	Placebo	100	5.04	-1.13 ± 0.16	
2nd 12 hours	20 mg QD	90	5.41	-1.80 ± 0.18	0.007
(AM scores)	Placebo	100	5.28	-1.10 ± 0.17	
[*] Symptom score is the sum of nasal discharge, sneezing, and itchy nose [†] Based on t-test for a two-way main effects analysis of covariance with treatment and center main effects and no interaction term					
Source: volume 211, p 44, 50					

Table 82. EBA 110, Reflective perennial index scores[*] for days 1 to 3

Treatment	Day 1		Day 2		Day 3	
	Change from baseline[†], mean ± SE (n)	p-value[‡]	Change from baseline[†], mean ± SE (n)	p-value[‡]	Change from baseline[†], mean ± SE (n)	p-value[‡]
24 hours:						
20 mg QD	-1.72 ± 0.18 (92)	0.008	-1.64 ± 0.20 (92)	0.069	-1.74 ± 0.21 (91)	0.086
Placebo	-1.03 ± 0.18 (99)		-1.13 ± 0.19 (100)		-1.24 ± 0.20 (99)	
1st 12 hours (PM scores):						
20 mg QD	-1.59 ± 0.20 (92)	0.020	-1.68 ± 0.22 (92)	0.035	-1.75 ± 0.24 (91)	0.072
Placebo	-0.93 ± 0.19 (99)		-1.02 ± 0.21 (100)		-1.16 ± 0.23 (99)	
2nd 12 hours (AM scores):						
20 mg QD	-0.06 ± 0.12 (96)	0.326	-1.80 ± 0.22 (93)	0.022	-1.62 ± 0.23 (91)	0.172
Placebo	-0.22 ± 0.11 (100)		-1.11 ± 0.21 (101)		-1.19 ± 0.22 (101)	
[*] Symptom score is the sum of nasal discharge, sneezing, and itchy nose [†] Adjusted for imbalance among investigators [‡] vs. placebo, based on a two-tailed test						
Source: v 211, p 103						

Table 83. EBA 110, Reflective perennial index scores[*] by treatment weeks

Treatment	Week 1		Week 2		Week 3	
	Change from baseline, mean ± SE (n)	p-value[†]	Change from baseline, mean ± SE (n)	p-value[†]	Change from baseline, mean ± SE (n)	p-value[†]
24 hours:						
20 mg QD	-1.86 ± 0.19 (93)	0.016	-2.18 ± 0.21 (90)	0.017	-2.25 ± 0.20 (87)	0.022
Placebo	-1.31 ± 0.15 (101)		-1.54 ± 0.17 (100)		-1.65 ± 0.18 (97)	
1st 12 hours (PM scores):						
20 mg QD	-1.81 ± 0.20 (93)	0.017	-2.13 ± 0.22 (90)	0.017	-2.23 ± 0.20 (87)	0.025
Placebo	-1.26 ± 0.17 (101)		-1.49 ± 0.19 (100)		-1.63 ± 0.20 (97)	
2nd 12 hours (AM scores):						
20 mg QD	-1.88 ± 0.19 (93)	0.022	-2.21 ± 0.22 (90)	0.021	-2.25 ± 0.21 (87)	0.026
Placebo	-1.35 ± 0.16 (101)		-1.60 ± 0.19 (100)		-1.67 ± 0.20 (97)	
[*] Symptom score is the sum of nasal discharge, sneezing, and itchy nose [†] Based on t-test for a two-way main effects analysis of covariance with treatment and center main effects and no interaction term						
Source: v 211, p 44						

Table 84. EBA 110, Snap shot perennial index scores* by treatment weeks

Treatment	Week 1		Week 2		Week 3	
	Change from baseline, mean ± SE (n)	p-value[†]	Change from baseline, mean ± SE (n)	p-value[†]	Change from baseline, mean ± SE (n)	p-value[†]
24 hours:						
20 mg QD	-1.61 ± 0.18 (90)	0.010	-1.77 ± 0.20 (85)	0.014	-1.84 ± 0.19 (83)	0.031
Placebo	-1.00 ± 0.16 (99)		-1.12 ± 0.17 (96)		-1.27 ± 0.18 (95)	
1ˢᵗ 12 hours (PM scores):						
20 mg QD	-1.51 ± 0.21 (90)	0.058	-1.72 ± 0.21 (86)	0.030	-1.69 ± 0.20 (84)	0.121
Placebo	-1.02 ± 0.17 (100)		-1.12 ± 0.18 (97)		-1.26 ± 0.19 (96)	
2ⁿᵈ 12 hours (AM scores):						
20 mg QD	-1.69 ± 0.19 (90)	0.004	-1.85 ± 0.21 (85)	0.005	-1.97 ± 0.19 (83)	0.011
Placebo	-0.93 ± 0.18 (100)		-1.06 ± 0.18 (98)		-1.23 ± 0.20 (96)	

* Symptom score is the sum of nasal discharge, sneezing, and itchy nose
† Based on t-test for a two-way main effects analysis of covariance with treatment and center main effects and no interaction term

Source: v 211, p 50

Table 85. EBA 110, Summary of individual reflective rhinitis symptom scores* for the three weeks of treatment

Treatment	N	First 12-hour		Second 12-hour		24-hour	
		Change from baseline	p-value vs. Placebo[†]	Change from baseline	p-value vs. Placebo[†]	Change from baseline	p-value vs. Placebo[†]
Nasal discharge:							
20 mg QD	93	-0.60	0.209	-0.61	0.159	-0.61	0.176
Placebo	101	-0.51		-0.50		-0.51	
Sneezing:							
20 mg QD	93	-0.70	0.001	-0.72	0.007	-0.71	0.002
Placebo	101	-0.45		-0.51		-0.48	
Itchy nose:							
20 mg QD	93	-0.72	0.022	-0.74	0.028	-0.74	0.018
Placebo	101	-0.51		-0.54		-0.52	
Nasal stuffiness:							
20 mg QD	93	-0.41	0.376	-0.35	0.747	-0.39	0.803
Placebo	101	-0.36		-0.41		-0.39	

* Adjusted for imbalance among investigators
† Based on t-test for a two-way main effects analysis of covariance with treatment and center main effects and no interaction term

Source: volume 204, p 41-45

Table 86. EBA 110, Summary of patients' and physicians' evaluation of efficacy

Treatment	N	Improved		No	Worsened		p-value*
		Greatly	Somewhat	Change	Somewhat	Greatly	
Patients' evaluation		N (%)	N (%)	N (%)	N (%)	N (%)	
20 mg QD	92	20 (18)	48 (44)	26 (24)	5 (5)	1 (1)	0.000
Placebo	101	4 (4)	37 (38)	51 (51)	6 (6)	3 (3)	
Physicians' evaluation		N (%)	N (%)	N (%)	N (%)	N (%)	
20 mg QD	92	21 (19)	39 (36)	34 (31)	5 (5)	1 (1)	0.100

| Treatment | N | Improved | | No | Worsened | | p-value* |
		Greatly	Somewhat	Change	Somewhat	Greatly	
Placebo	101	9 (9)	39 (39)	50 (50)	3 (3)	0 (0)	
* One-sided p-value calculated using Cochran-Mantel Hazel test adjusting for investigator and AM and PM scores compared to placebo							
Source: volume 211, p 107, 108							

9.2.10. Safety outcomes

9.2.10.1. Total drug exposure

All patients enrolled in the study were included in the safety analysis. The mean duration of exposure was 20.0 days for the ebastine group, and 20.8 days for the placebo group (v 211, p 109).

9.2.10.2. Adverse events

Adverse events reported by at least 3% of patients in any treatment group are presented in Table 87. Most of the adverse events were mild to moderate and not related tot the study medication. Headache was the most frequently reported adverse event and was more common in the ebastine group. There was one serious adverse event reported in this study. A 35-year old female (87) in the placebo group had left knee injury. There were no death reported in this study. (v 211, p 109)

Table 87. EBA 110, Common adverse experience reported by patients*

	Placebo (n=101)	Ebastine 20 mg QD (n=94)
Total with adverse experience	40 (39.6 %)	41 (43.6 %)
Body as a whole		
Asthenia	3 (3.0 %)	2 (2.1 %)
Fever	3 (3.0 %)	0 (0.0 %)
Flu syndrome	2 (2.0 %)	4 (4.3 %)
Headache	7 (6.9 %)	12 (12.8 %)
Accidental injury	3 (3.0 %)	2 (2.1 %)
Back pain	3 (3.0 %)	4 (4.3 %)
Digestive system		
Nausea	5 (5.0 %)	3 (3.2 %)
Vomiting	3 (3.0 %)	2 (2.1 %)
Musculoskeletal system		
Arthralgia	3 (3.0 %)	2 (2.1 %)
Nervous system		
Dry mouth	1 (1.0 %)	2 (2.1 %)
Nervousness	0 (0.0 %)	3 (3.2 %)
Somnolence	1 (1.0 %)	2 (2.1 %)
Respiratory system		
Epistaxis	1 (1.0 %)	6 (6.4 %)
Pharyngitis	10 (9.9 %)	8 (8.5 %)
Rhinitis	3 (3.0 %)	5 (5.3 %)
* Events reported by ≥3% of patients in any group is listed (number and %) as Costart preferred term. Dry mouth and somnolence is included because of the relevance of this adverse event to this application.		
Source: v 215, p 37-39		

9.2.10.3. Premature withdrawals due to adverse events

A total of 4 patients were withdrawn due to adverse events (Table 79). The events are summarized in Table 88. Patients 0133, 0149, and 0173 did not receive any study medication (v 211, p 100; v 215, p 44).

Table 88. EBA 110, Discontinued patients due to adverse events

Group	Patient	Event	Days on study medication	Severity	Relationship to study med.
Placebo	0181	Bronchitis	15	Moderate	None
Ebastine	0118	Headache, diarrhea, nervousness	9	Moderate	Possible
	0133	Sinusitis	1	Moderate	None
	0149	Pharyngitis	1	Severe	None
	0173	Asthma	-2	Severe	None
Source: v 211, p 88, 110; v 215, p 44					

9.2.10.4. Physical examination and laboratory measures

There were no clinically significant changes in physical examination or vital signs in any of the patients. No patient was discontinued from the study for ECG abnormality. The results of the QTc data analysis is shown in Table 89. There was a small increase in QTc in the ebastine treated group compared to placebo, which reached statistical significance for week 1. A total of 5 patients, 3 from ebastine group, and 2 from placebo group had greater that 15% increase in QTc during treatment as compared to the baseline. The increase ranged form 52 to 66 msecs. A total of 26 patients had 24-hour Holter monitoring done at baseline and at the end of the study. There were no clinically relevant findings in the Holter data. One patient (0050) in the ebastine group had a second degree AV block at screening and at the final visit. The patient's QTc values were 409 msec at baseline, 440 msec at week 1, 431 msec at week 2, and 435 msec at week 3. For the laboratory values, there were no clinically relevant changes for any parameters (v 211, p 112-118).

Table 89. EBA 110, Summary of QTc changes

Treatment week	Treatment group	N	Baseline mean in msec	Post-treatment mean in msec	Mean raw % change	p-value s. placebo
Week 1	20 mg QD	89	408	415	1.770	0.028
	Placebo	100	405	405	-0.021	
Week 2	20 mg QD	86	408	414	1.653	0.303
	Placebo	96	405	408	0.729	
Last value	20 mg QD	93	408	415	1.793	0.676
	Placebo	101	406	411	1.458	
* Based on a two-tailed t-test for comparisons of each ebastine dose to placebo						
Source: v 211, p 113						

9.2.11. Conclusion from EBA 110 study results

This study evaluated the efficacy and safety of ebastine 20 mg QD in patients with PAR. The results show that ebastine 20 mg QD was effective in relieving symptoms of PAR. The improvement in total symptom score relative to placebo persisted at the end of each treatment week for the 3-week duration of treatment. On analysis of the individual symptom

scores, the favorable response was carried mainly by the sneezing and itchy nose scores. The reduction of symptoms scores was greater at the end of first 12 hours as compared to the end of second 12 hours suggesting a waning of effect towards the dosing interval. The results of this study support the efficacy of ebastine 20 mg QD for relief of symptoms of PAR. Safety parameters show that ebastine was well tolerated in this study population. In the ebastine treated groups headache was more frequently seen. Ebastine treatment caused a small increase in QTc interval.

9.3. CR 2714: A multicenter, double-blind, placebo-controlled, randomized, group comparative study to assess the absolute efficacy and safety of ebastine 10 mg and 20 mg once daily for twelve weeks on the symptoms of perennial allergic rhinitis in adolescent and adult patients.

9.3.1. Investigators and centers

This was a multicenter European study that had 25 investigators in France, and 6 investigators each in Spain and Portugal. Each center recruited 5-10 patients.

9.3.2. Objectives

The primary objective of this study was to demonstrate absolute efficacy of ebastine 10 mg/day on the symptoms of PAR over a 12-week treatment period, with the possible additional benefit of ebastine 20 mg/day. The secondary objective of the study was to assess the tolerability and safety of the ebastine treatment (v 231, p 32).

9.3.3. Study population

Patients with PAR meeting the following criteria were selected for participation.

9.3.3.1. Inclusion criteria (v 231, p 137)

1. Male or females 12-65 (inclusive) years of age.
2. Diagnosis of PAR for at least 2 years, and positive skin test or RAST within the last 2 years to *D. pteronyssinus* and/or *D. Farinae*.
3. Minimum total rhinitis symptom score of 135 (out of 336) over the last 2 weeks of screening period/baseline (scoring described below).

9.3.3.2. Exclusion criteria (v 183, p 167)

1. Pregnancy, or lactation, or females of childbearing potential not using contraception.
2. Significant acute or chronic disease, or clinically relevant screening laboratory values outside the normal range.
3. Presence of any of the following: acute upper respiratory tract infection, sinusitis, otitis media, nasal polyps, and acute asthma. Nasal surgery within the past 6 months.
4. History of hypersensitivity to ebastine or to sodium cromoglycate or to any of their excipients.

5. Use of any of the following: H₁-antagonist (except astemizole) within 7 days, astemizole within 12 weeks, depot corticosteroids within 2 months, short acting systemic or topical (intranasal, and ocular) corticosteroids, and topical (intranasal, and ocular) 4% cromoglycate or nedocromil within 1 week, ketotifen within 1 week.

6. Medication which may suppress or exacerbate symptoms of PAR (e.g., centrally acting cardiovascular drugs, neuroleptic drugs, etc.,)

7. Immunotherapy start within 6 months.

8. Investigational treatment within the past 3 months.

9. Night shift (11 PM to 8 AM) workers.

9.3.4. Study design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study (v 231, p 137).

9.3.5. Study procedures

The study was conducted between September 1995 and April 1996, outside the pollen season to avoid interference with seasonal allergy. The study procedures are outlined in Table 90. The study had a day of screening, a 2 week baseline period, followed by 12 weeks of double-blind treatment. Patients satisfying the inclusion/exclusion criteria (described above) were dispensed with diary cards and asked to record severity of 4 rhinitis symptoms (nasal discharge, nasal stuffiness, sneezing, itchy nose) on a 4-point scale (0 = absent, no symptoms; 1 = mild, symptoms present but not annoying to self; 2 = moderate, symptoms present and annoying to self; 3 = severe, symptoms interfere with activities of daily living) twice a day - upon arising in the morning, and in the evening before going to bed. Scoring was to reflect symptom severity over the previous 12 hours. To be eligible for randomization (visit 2), patients were required to have an aggregated sum of rhinitis symptom score over the 2 weeks of baseline of at least 135 points out of a maximum possible of 336. This was the baseline score.

Eligible patients were randomized into 3 study groups (ebastine 10 mg QD, ebastine 20 mg QD, and placebo). Study medications were administered in the morning immediately after breakfast. During the study patients were allowed to use 2% sodium cromoglycate nasal spray and eye drops as rescue medication, and one ≤10 day course of nasal decongestant was allowed. Other medications for alleviating the symptoms of rhinitis, or for another indication that could relieve or produce symptoms of allergic rhinitis were not allowed. Throughout the study, patients continued recording rhinitis symptom scores (reflective scores for the previous 12 hours) twice daily - prior to dosing in the morning, and before going to bed. In addition, at the end of the study (visit 5), patients and physicians separately recorded the global evaluation of efficacy on a 5 point scale (0 = greatly improved, 1 = somewhat improved, 2 = no change, 3 = somewhat worsened, 4 = greatly worsened) relative to the baseline (v 231, p 137, 145-157).

Table 90. CR 2714, Schedules of observations

Procedures	Visit 1 Screening Day 0	Visit 2 Baseline Week 2 ± 1	Visit 3 Week 6 ± 1	Visit 4 Week 10 ± 1	Visit 5 Week 14 ± 1
Informed consent	x				
Check eligibility	x	x			
Dispense rescue medication	x	x	x	x	
Collect rescue medication		x	x	x	x
Dispense test medication		x	x	x	
Collect test medication			x	x	x
Dispense diary	x	x	x	x	
Collect and review diary		x	x	x	x
Symptom evaluation		x	x	x	x
Physician global assessment					x
Patient global assessment					x
Patient's weights	x	x	x	x	x
Adverse events		x	x	x	x
Source: v 231, p 140					

9.3.6. Efficacy parameters

The primary efficacy variable was the mean change from baseline in the perennial index (sum of scores for nasal discharge, sneezing, and itchy nose) score averaged over the 12 week double-blind treatment period for 24 hours. Secondary variables were the mean changes from baseline for each symptom, for nasal index (sum of the scores for nasal discharge, nasal stuffiness, sneezing, and itchy nose), for eye watering and conjunctival irritation, for perennial index for each week of treatment, patient withdrawal due to lack of efficacy, frequency of rescue medication use, global perception of efficacy by the patient and the physician, and mean change from baseline in body weight. (v 231, p 50-52, 162)

9.3.7. Safety analysis

Safety analysis was based on patient reporting of adverse events (v 231, p 43).

9.3.8. Statistical considerations

9.3.8.1. Sample size

A sample size of 95 patients per group was calculated to detect a mean change of one in symptom score from baseline between ebastine and placebo group with a power of 95 at a two-sided α level of 0.05. The projected standard deviation used in the calculation was 1.7 based on study EBA 109 and 110 results. (v 231, p 47)

9.3.8.2. Statistical analysis

The primary efficacy variable was analyzed using a two-way ANOVA with country and treatment group as fixed effect with no interaction term. If significant at p<0.05, pairwise comparisons were then carried out using a pooled estimate of variance from the ANOVA. All contrast tests were two-sided at a 0.05 level. Patient's and investigator's overall opinion of treatment efficacy were analyzed using Kruskall-Wallis test on the overall population,

followed by paired comparisons when significant at p<0.05 using Wilcoxon's test (v 231, p 53,54).

9.3.9. Results

9.3.9.1. Patients enrolled/analyzed

A total of 383 patients were screened, 93 failed the screening, and 290 were randomized. Of the randomized patients, 42 patients discontinued from the study during double blind treatment period. Disposition of the randomized patients and reasons for discontinuation is shown in Table 91. All 290 patients tool at least one dose of the study medication, therefore, the ITT population was 290. (v 231, p 57-60)

Table 91. CR 2714, Disposition of study patients

	Placebo	10 mg QD	20 mg QD	Total
Enrolled	100	88	102	290
Completed	83	77	88	206
Discontinued	17	11	14	42
Reasons for discontinuation:				
Worsening of disease	5	1	2	8
Intercurrent illness	0	2	2	4
Other adverse event	1	1	2	4
No change in disease under study	3	4	4	11
Failure to meet entry criteria	2	1	1	4
Protocol violation	2	0	1	3
Lost to follow-up	2	1	0	3
Non compliance	1	0	0	1
Withdrew consent	1	1	1	3
Unplanned departure abroad	0	0	1	1
Source: v 231, p 60				

9.3.9.2. Subject demographics

Demographic data by treatment group are summarized in Table 92. The groups were similar in respect to their demographics.

Table 92. CR 2714, Demographic summary

	Placebo	10 mg QD	20 mg AM	Total
Number	73	74	77	224
Sex: male/female %	53/47	50/50	45/55	49/51
Age: years (range)	26 (12-55)	26 (12-61)	25 (12-63)	26 (12-63)
Race: Cauc/others %	97/3	99/1	93/7	96/4
Source: v 231, p 65				

9.3.9.3. Protocol deviations

The protocol deviations were minor. The deviations included failure to meet the required minimum entry score, duration of rhinitis less than 2 years, no documented skin test or RAST results, use of forbidden treatment during run-in, and deviations from the follow-up schedules. (v 231, p 60-62)

9.3.9.4. Efficacy endpoint outcomes

Results of the reflective perennial index scores during the double-blind treatment period for 24 hours (protocol specified primary efficacy variable), and scores for the 1st and 2nd 12 hours are shown in Table 93. Ebastine at a daily dose of 20 mg significantly reduced the perennial index score compared to placebo, and ebastine at a daily dose of 10 mg had a favorable trend. The superiority of ebastine 20 mg over placebo was consistent for individual symptoms of rhinitis, and for patients' and physicians' ratings of symptoms (Table 94). The separation of 20 mg dose from the 10 mg dose and from the placebo was persistent for each week of treatment, however, for most of the time points the differences were not statistically significant (Figure 5) (v 231, p 29, 68-98). The results of this study demonstrate that 20 mg ebastine administered as a single daily dose is effective in the treatment of PAR. Ebastine 10 mg also tended to be superior to placebo, but did not reach statistical significance. There were no statistically significant differences in the direct comparisons between the two doses of ebastine.

Table 93. CR 2714, Reflective perennial index scores[*] for the twelve week treatment period

Time	Treatment	N	Baseline mean	Change from baseline[†], mean±SE	p-value vs. placebo[‡]
24 hours	10 mg QD	87	4.47	-1.66 ± 0.19	0.082
	20 mg QD	101	4.92	-1.87 ± 0.18	0.007
	Placebo	97	4.68	-1.24 ± 0.18	
1st 12 hours (PM scores)	10 mg QD	87	4.33	-1.60 ± 0.20	0.051
	20 mg QD	101	4.79	-1.86 ± 0.19	0.006
	Placebo	97	4.69	-1.28 ± 0.19	
2nd 12 hours (AM scores)	10 mg QD	87	4.60	-1.71 ± 0.20	0.051
	20 mg QD	101	5.06	-1.88 ± 0.19	0.006
	Placebo	97	4.67	-1.21 ± 0.19	

[*] Symptom score is the sum of nasal discharge, sneezing, and itchy nose
[†] Adjusted for imbalance among treatment groups and countries using a two-way analysis of variance model with treatment and country as main effects
[‡] Based on a two-tailed t-test without adjustment for multiple comparisons
Source: volume 232, p 242

Table 94. CR 2714, Summary result of the efficacy variables for the twelve week treatment period

	Placebo	Ebastine 10 mg	Ebastine 20 mg	E10 vs P	E20 vs P
Efficacy variable	Mean change from baseline			p-value[‡]	
Perennial index[*]	-1.24	-1.66	-1.87	0.082	0.007
Nasal index[†]	-1.84	-2.39	-2.58	0.078	0.015
Nasal stuffiness	-0.34	-0.48	-0.45	0.15	0.23
Sneezing	-0.51	-0.69	-0.73	0.061	0.014
Nasal discharge	-0.45	-0.66	-0.68	0.032	0.013
Itchy nose	-0.54	-0.57	-0.71	0.75	0.05
Eyes watering	-0.11	-0.28	-0.29	0.023	0.014
Conjunctival irritation	-0.16	-0.28	-0.36	0.16	0.01
Efficacy assessment	Great/somewhat improved			p-value[‡]	
Investigator opinion	58%	76%	84%	0.004	<0.001
Patient opinion	58%	72%	84%	0.017	<0.001

Pivotal Perennial Allergic Rhinitis (PAR) Efficacy Studies, CR 2714

	Placebo	Ebastine 10 mg	Ebastine 20 mg	E10 vs P	E20 vs P
Efficacy variable	Mean change from baseline			p-value[‡]	
[*] Symptom score is the sum of nasal discharge, sneezing, and itchy nose [†] Symptom score is the sum of nasal discharge, nasal stuffiness, sneezing, and itchy nose [‡] vs. Placebo, based on a two-tailed test.					
Source: v 231, p 29					

Figure 5. CR 2714, Weekly change in perennial score from baseline

Statistically significant treatment effect was seen at week 1 (p = 0.01 for ebastine 10 vs placebo, p = 0.001 for ebastine 20 vs placebo), week 2 (p = 0.019 for ebastine 10 vs placebo), and week 6 (p = 0.012 for ebastine 20 vs placebo).
Source: v 231, p 80

9.3.10. Safety outcomes

9.3.10.1. Total drug exposure

All patients enrolled in the study were included in the safety analysis. The mean duration of exposure for the ebastine 20 mg group was 78 days (range: 10-103 days) and for the ebastine 10 mg group was 77 days (range: 25-105 days) (v 231, p 109).

9.3.10.2. Adverse events

Adverse events reported by at least 3% of patients in any treatment groups are presented in Table 95. Headache, pharyngitis, and rhinitis were the most frequently reported adverse events. There were no differences in frequency of these and other adverse events among the treatment groups. All of the adverse events were of mild to moderate in intensity, except for one patient in the placebo group who reported a severe adverse event of dyslalia. There was no death reported in the study (v 231, p 110).

Table 95. CR 2714, Common adverse experience reported by patients*

	Placebo (n=100)	Ebastine 10 mg QD (n=88)	Ebastine 20 mg QD (n=102)
Total with adverse experience	57 (57.0 %)	47 (53.4 %)	51 (50.0 %)
Body as a whole			
Flu syndrome	4 (4.0 %)	11 (12.5 %)	4 (3.9 %)
Headache	13 (13.0 %)	13 (14.8 %)	10 (9.8 %)
Pain abdomen	3 (3.0 %)	5 (5.7 %)	2 (2.0%)
Digestive system			
Nausea	2 (2.0 %)	4 (4.5 %)	2 (2.0 %)
Vomiting	2 (2.0 %)	3 (3.4 %)	0 (0.0 %)
Nervous system			
Dry mouth	1 (1.0)	1 (1.1 %)	0 (0.0 %)
Somnolence	3 (3.0 %)	1 (1.1 %)	1 (1.0 %)
Respiratory system			
Asthma	2 (2.0 %)	6 (6.8 %)	5 (4.9 %)
Bronchitis	3 (3.0 %)	5 (5.7 %)	6 (5.9 %)
Epistaxis	3 (3.0 %)	2 (2.3 %)	2 (2.0 %)
Pharyngitis	16 (16.0 %)	9 (10.2 %)	9 (8.8 %)
Rhinitis	16 (16.0 %)	10 (11.4 %)	8 (7.8 %)
Sinusitis	3 (3.0 %)	3 (3.4 %)	2 (2.0 %)
Urogenital system			
Dysmenorrhea	3 (4.1 %)	3 (4.1 %)	1 (1.3 %)

* Events reported by ≥3% of patients in any group is listed (number and %) as Costart preferred term. Dry mouth is included because of the relevance of this adverse event to this application.

Source: v 234, p 282-285

9.3.10.3. Premature withdrawals due to adverse events

A total of 16 patients were withdrawn due to adverse events (Table 91). The events are summarized in Table 96 (v 231, p 112).

Table 96. CR 2714, Discontinued patients due to adverse events

Group	Patient	Event	Days on study medication	Severity	Relationship to study med.
Placebo	095	Dizziness	2	Moderate	Probable
	104	Rhinitis	49	Moderate	Probable
	135	Urticaria	14	Moderate	Possible
	260	Rhinitis	38	Moderate	Remote
	277	Rhinitis	28	Moderate	Remote
	296	Rhinitis	9	Mild	Remote
Ebastine 10 mg	037	Bronchitis, sinusitis	61	Moderate	Possible
	045	Otitis media	60	Moderate	Remote
	127	Headache	80	Moderate	Possible
	145	Rhinitis	1	Moderate	None
Ebastine 20 mg	096	Nausea	29	Moderate	Probable
	148	Sinusitis	46	Moderate	None
	212	Headache	1	Moderate	Probable
	257	Rhinitis	16	Moderate	Remote
	261	Bronchitis	74	Mild	Remote

Group	Patient	Event	Days on study medication	Severity	Relationship to study med.
	336	Pruritus	20	Moderate	Possible
Source: v 231, p 113					

9.3.10.4. Physical examination and laboratory measures

Patients treated with ebastine had a small but progressive increase in weight over the 12-week treatment period, while patients in the placebo groups showed no change in weight. Patients in the ebastine groups had 0.7 kg increase in weight at the final visit compared to the baseline. Difference between treatment groups for weight gain were statistically significant at the end of study. No other changes in physical examination were seen. Clinical laboratory and ECG were not done in this study (v 231, p 117-118).

9.3.11. Conclusion from CR 2714 study results

This study evaluated the efficacy and safety of ebastine 10 mg QD and 20 mg QD in patients with PAR. The results show that ebastine 20 mg QD was effective in relieving the symptoms of PAR, and the 10 mg QD had a favorable trend. All symptoms except nasal stuffiness improved with ebastine. Adverse events were comparable among the ebastine and placebo groups. The results of this study supports the efficacy of ebastine 20 mg administered as a single dose for relief of symptoms of PAR.

10. ONSET OF ACTION STUDY

The sponsor has submitted one onset of action study in PAR patients. In this study ebastine was given at a single dose of 20 mg. The study is reviewed in the following section.

10.1. EBA 133: A double-blind, placebo controlled, parallel group, field study on the onset of action of ebastine 20 mg in patients with seasonal allergic rhinitis.

10.1.1. Investigator and center

The study was conducted in a single site in US.

Investigator: Robert J. Dockhorn, MD, Lenexa, Kansas.

10.1.2. Objective

The objectives of the study were to determine the onset of action of ebastine 20 mg relative to placebo, and to evaluate the efficacy and safety on ebastine 20 mg over a period of 24-hours in patients with SAR (v 247, p 61, 98)

10.1.3. Study population

Patients 12 years of age and above with at least 2 year history of SAR with a positive skin test to grass allergens that were present in the patient's environment during the field study were recruited. The exclusion criteria were similar to SAR study EBA 124, except that the drug exclusion list was expanded to exclude patients who have taken ketoconazole, itraconazole, or any macrolide antibiotics within 4 weeks of the study. The ECG exclusion criteria were similar to SAR study EBA 132 (v 247, p 98-101, 125).

10.1.4. Study design

This was a one-day, single-center, double-blind, placebo-controlled, parallel group field study (v 247, p 61).

10.1.5. Study procedures

The study was conducted in June 1993. The study consisted of a screening visit and a one-day field trial phase. Patients meeting the screening inclusion/exclusion criteria were taken to a field at 7 AM. At 8:30 AM and 9:30 AM patients recorded the severity of 6 rhinitis symptoms (nasal discharge, nasal stuffiness, sneezing, itchy nose, itchy eyes, and watery eyes) on a 3-point scale (0 = none; 1 = mild, symptoms present by not annoying to self, 2 = moderate, symptoms present and annoying to self; 3 = severe, symptoms cause significant impairment of activity). The scores were "snap shot", which were reflective of the time of recording. Patients with a baseline sum score of at least 21 (maximum possible was 36) were randomized to receive ebastine 20 mg or placebo. Study medication was given at 10:00 AM. Patients recorded rhinitis scores hourly from 11:00 AM to 8:00 PM while they were in the field. They returned to their home at 8:00 PM, and recorded rhinitis scores at 10:00 PM, upon arising the next morning, and at 10:00 AM the next morning (24-hour post-

dose). Pollen counts were done hourly for the duration of the field study. (v 247, 57, 101-110)

10.1.6. Study parameters and statistical considerations

The primary variable was the area under the curve between 0 and 10 hours (AUC_{0-10hr}) of the mean change from baseline in the total symptom score. The mean change from baseline in all the time-point scores was also analyzed. A sample size of 60 patients per group was calculated to detect a mean symptom score change of 1.2 from baseline with a power of 90% at a two-sided α level of 0.05. The estimated standard deviation was 2.0 based on other studies of the sponsor. The primary variable was analyzed using two-way ANCOVA with the baseline score as the covariate. Safety was assessed by recording of adverse event during the study, and by physical examination, laboratory measure, and ECG done at the screening visit and at the end of the study. (v 247, p 16, 72, 106, 110)

10.1.7. Results

A total of 106 patients were enrolled in the study and divided equally between the two groups. The mean age of the patients was 28 years with a range of 12 to 69 years. Most were Caucasian (86%) with a larger percentage of males than females (60% vs 40%). Two patients from the placebo group discontinued from the study (patient 061 for lack of efficacy, and patient 090 for allergic reaction), therefore, 104 patients were included for the AUC_{0-10hr} calculation. For analyses of hourly scores, and for safety assessment, all 106 patients were included. The analysis of primary efficacy variable (AUC_{0-10hr}) showed that ebastine 20 mg was significantly better than placebo. Onset of action (defined as the first time-point when statistically significant difference between ebastine 20 mg and placebo was seen that persisted to the next time-points) for total symptom score was hour 4, and for total symptom score without nasal stuffiness was hour 3 (Table 97). None of the individual symptom score had an onset of action earlier than hour 3 (data not shown). The reduction of symptom by ebastine as compared to placebo did not persist for 24 hours. No clinically relevant changes in physical examination, laboratory values, and ECG were seen. The incidence of adverse event was low (9.4% in ebastine group, and 18.9% in placebo group). Headache was the most frequently reported adverse event that was reported by 11.3% patients in the placebo group and 7.5% patients in the ebastine group. The pollen count during the recording of baseline scores at 8:30 AM and 9:30 AM was 6/cum and 44/cum respectively, and through the study day ranged from 130/cum to 226/cum as shown in Table 97. (v 247, p 74-89)

Onset of Action Study, EBA 133

Table 97. EBA 133, Summary results of snap-shot rhinitis symptom scores[*] after treatment

Time in hr (POLLEN COUNT IN CUM)	Group	N	Baseline mean	Change from baseline, mean±SE	p-value vs. placebo[†]	Baseline mean	Change from baseline, mean±SE	p-value vs. placebo[†]
			Total symptom score (TSS):			TSS without nasal stuffiness:		
AUC_{0-10hr}	20 mg	53	142.1	-50.4±4.8	0.014	118.0	-44.1±4.2	0.014
	Placebo	51	144.5	-33.4± 4.9		120.6	-29.2± 4.2	
Hour 1 (172)	20 mg	53	14.95	-2.28±0.5	0.271	12.42	-1.93±0.5	0.245
	Placebo	53	15.15	-1.45±0.5		12.63	-1.16±0.5	
Hour 2 (194)	20 mg	53	14.95	-4.63±0.6	0.105	12.42	-3.94±0.5	0.126
	Placebo	53	15.15	-3.27±0.6		12.63	-2.83±0.5	
Hour 3 (188)	20 mg	53	14.95	-5.72±0.6	0.057	12.42	-4.98±0.5	0.042
	Placebo	53	15.15	-4.10±0.6		12.63	-3.47±0.5	
Hour 4 (198)	20 mg	53	14.95	-6.79±0.6	0.011	12.42	-5.94±0.5	0.010
	Placebo	53	15.15	-4.62±0.6		12.63	-4.06±0.5	
Hour 5 (200)	20 mg	53	14.95	-6.69±0.6	0.001	12.42	-5.91±0.5	0.001
	Placebo	53	15.15	-3.65±0.6		12.63	-3.19±0.5	
Hour 6 (178)	20 mg	53	14.95	-5.70±0.7	0.007	12.42	-5.01±0.5	0.006
	Placebo	53	15.15	-3.10±0.7		12.63	-2.65±0.5	
Hour 7 (135)	20 mg	53	14.95	-5.39±0.7	0.0084	12.42	-4.77±0.6	0.067
	Placebo	53	15.15	-3.71±0.7		12.63	-3.20±0.6	
Hour 8 (130)	20 mg	53	14.95	-5.39±0.7	0.045	12.42	-4.74±0.6	0.071
	Placebo	53	15.15	-3.48±0.7		12.63	-3.21±0.6	
Hour 9 (226)	20 mg	53	14.95	-5.29±0.6	0.067	12.42	-4.67±0.6	0.090
	Placebo	53	15.15	-3.60±0.6		12.63	-3.27±0.6	
Hour 10 (192)	20 mg	53	14.95	-4.94±0.6	0.197	12.42	-4.30±0.6	0.250
	Placebo	53	15.15	-3.74±0.7		12.63	-3.35±0.6	
Hour 12	20 mg	53	14.95	-4.77±0.6	0.282	12.42	-4.22±0.6	0.364
	Placebo	53	15.15	-3.77±0.7		12.63	-3.47±0.6	
AM day 2	20 mg	53	14.95	-4.52±0.6	0.345	12.42	-4.22±0.5	0.370
	Placebo	53	15.15	-3.70±0.6		12.63	-3.53±0.5	
Hour 24	20 mg	53	14.95	-4.70±0.7	0.324	12.42	-4.25±0.6	0.331
	Placebo	53	15.15	-3.78±0.7		12.63	-3.47±0.6	

[*] Symptom score is the sum of nasal discharge, nasal stuffiness, sneezing, itchy nose, and itchy eyes, itchy throat, watery eyes scored on a 0-3 scale
[†] Based on t-test for a two-way main effects analysis of covariance with treatment as main effects and baseline as the covariate

Source: volume 247, p 38, 48

10.1.8. Conclusion from study results

This study evaluated the onset of action of a single dose of ebastine 20 mg in SAR patients in a setting of nature exposure to pollen in a field. Onset of action (defined as the first time-point when statistically significant difference between ebastine 20 mg and placebo was seen that persisted to the next time-points) for total symptom score was hour 4, and for total symptom score without nasal stuffiness was hour 3. None of the individual symptom score had an onset of action earlier than hour 3. In this study, the efficacy did not persist till the end of the dosing interval.

11. US COMPARATIVE SAR EFFICACY STUDIES

The applicant submitted six comparative SAR efficacy studies. These studies were not submitted to the original NDA, but were submitted as part of the complete response. They were designed to compare ebastine against loratadine to show an efficacy advantage (and therefore a public health benefit) because of the safety burden of QT prolongation. Four were US comparative SAR efficacy studies (CM.030.ALGY, CM.031.ALGY, EBA.GMA.402, and M/EBS/28) and are reviewed in the sections that follow. Two non-US comparative studies were not reviewed because of lack of precision in defining the primary endpoint (CM.14.ALGY) and flexible dosing of ebastine according to symptom severity (CM.14.ALGY).

All four US studies were very similar in design. The first three used identical protocols, which are described within the first study, CM.030.ALGY. The fourth (M/EBS/28) used a variation of the same protocol. All four studies were four weeks in duration, but M/EBS/28 set the primary variable as the first two weeks of the four-week treatment period to conform to the suggestion in the Guidance for Industry entitled *Allergic Rhinitis: Clinical Programs for Drug Products* published by the FDA in April of 2000. All variations from the first protocol are reviewed at the beginning of each study review.

All four studies used the comparison between ebastine 20 mg with loratadine 10 mg as the primary efficacy variable. The first three also included a 10 mg ebastine arm as a secondary comparison against loratadine 10 mg. All were placebo controlled, with the comparison between active drugs and placebo as secondary efficacy variables. Two out of the four showed a statistically significant difference between ebastine 20 mg and loratadine 10 mg, but two did not. None showed significant differences between ebastine 10 mg and loratadine 10 mg. All showed efficacy of both doses of ebastine against placebo. All but the last study showed efficacy of loratadine 10 mg against placebo.

11.1. CM.030.ALGY: Multicenter, double-blind, parallel group, randomized comparison of ebastine 20 mg and 10 mg versus loratadine 10 mg and placebo in patients with seasonal allergic rhinitis.

11.1.1. Investigators and centers

The study was conducted in 16 sites in the US between August and October of 1997. The principal investigators, study sites, and number of patients enrolled are listed below (v 2.98, p 18, 25-6).

Charles Banov, MD, Charleston, North Carolina	48 patients
David Bernstein, MD, Cincinnati, Ohio	38 patients
Robert Dockhorn, MD, Lenexa, Kansas	48 patients
Stanley Fineman, MD, Marietta, Georgia	21 patients
Sandra Gawchik, DO, Chester/Upland, Pennsylvania	48 patients
Michael Katlan, MD, Albany, New York	22 patients
Kirk Kinberg, MD, Lincoln, Nebraska	24 patients
John Klimas, MD, Charlotte, North Carolina	24 patients
Julian Melamed, MD, Chelmsford, Massachusetts	48 patients

Louis Mendelson, MD, West Hartford, Connecticut	23 patients
Anjuli Nayak, MD, Normal, Illinois	24 patients
Eric Schenkel, MD, Easton, Pennsylvania	45 patients
Nathan Segall, MD, Atlanta, Georgia	45 patients
William Storms, MD, Colorado Springs, Colorado	37 patients
John Winder, MD, Sylvania, Ohio	24 patients
John Yarbrough, MD, Gainesville, Georgia	48 patients

11.1.1. Objective

The objective of this study was to compare the efficacy and safety of ebastine 20 mg, ebastine 10 mg, and loratadine 10 mg administered once a day for four weeks to placebo in patients with SAR (v 2.98, p 24). The primary comparison, described below, was between ebastine 20 mg and loratadine 10 mg.

11.1.2. Study population

Patients 12 to 70 years of age with a 2 year history of SAR with fall ragweed sensitivity were selected for participation in the study. Each center attempted to enroll at least 10 patients who were 12 to 17 years of age.

11.1.2.1. Inclusion criteria (v 2.98, p 29, 195-6)

1. Male or females 12 to 70 years of age . Female were to be nonpregnant, or without childbearing potential, or using an accepted method of contraception.
2. Diagnosis of fall seasonal SAR with sensitivity to ragweed for at least 2 years, and positive skin test to ragweed allergen.
3. Minimum total rhinitis symptom score of 42 (out of 105), with at least one symptom at moderate or severe level, over 3 out of the last 4 days of screening period plus the morning of the randomization visit.
4. Meet the screening criteria (described below) for ECG (maximum QTc <0.444 seconds).
5. Have no cardiovascular, neurological hepatic, renal, respiratory, or other medical condition that may significantly interfere with the study.
6. Have no history of hypersensitivity to antihistamines.
7. Screening physical exam without clinically significant abnormalities.

11.1.2.2. Exclusion criteria (v 2.98, p 30-1, 196-8)

1. Pregnant or lactating.
2. Use of any of the following: H_1-antagonist (except astemizole) within 7 days, astemizole within 12 weeks, depot corticosteroids within 2 months, short acting systemic or topical (inhaled, intranasal, and ocular) corticosteroids and intranasal cromolyn within 21 days, nasal or oral decongestants within 2 days at screening. Use of rhinitis medications within 5 days of randomization visit (visit 2)
3. Acute upper respiratory tract infection, otitis media, significant nasal polyp, acute asthma, clinical signs of bacterial sinusitis.
4. Stabilized on immunotherapy for less than one month prior to randomization.

5. Significant concomitant illness which, in the opinion of the investigator, might interfere with evaluation of the study medications.

6. Currently on medication which may suppress or exacerbate symptoms of SAR (e.g., anticholinergics, antihistaminic sleeping aids, anti-inflammatory agents, centrally acting cardiovascular drugs or antidepressants)

7. Have long QTc syndrome or hypokalemia.

8. Clinically relevant screening laboratory values outside the normal range.

9. Investigational treatment within 30 days prior to screening.

10. Must avoid of any drug known to increase QT interval or inhibit CYP3A4 enzymes (such as azole antifungals and macrolide antibiotics) during the study.

11.1.2.3. 12-lead ECG exclusion criteria at screening (v 2.98, p 224)

Note: The protocols for studies CM.030.ALGY, CM.031.ALGY, and EBA.GMA.402 state that the ECG will be evaluated by a "qualified physician," and neither the protocols nor the study reports for these three studies make any statements about how the ECGs were to be read or were actually read. For these studies, there was no independent review of the ECGs by an outside expert. In a separate statement, Almirall states that for these three studies the QT values were automatically calculated by the ECG machines at each of the investigator's sites, and all QTc calculations were carried out using the Bazett method of correction (Submission of October 22, 2002, v 1, p 8). Study M/EBS/28 did a priori declare how ECGs would be evaluated, and how QTc would be corrected (QTcB and QTcF) (see page 161).

1. QTc >0.444 seconds.

2. Fixed second or transient or fixed third degree AV block.

3. Atrial fibrillation.

4. Ventricular dysrhythmia (sustained ventricular tachycardia i.e. >30 sec., *Torsade de Pointes*, ventricular flutter, ventricular fibrillation).

5. High grade ventricular ectopy (R on T phenomenon).

6. Three or more premature ventricular beats (PVB) on 3-minute rhythm strip if one or more present on 30-second strip.

7. Any ECG abnormality considered significant by the investigator.

11.1.3. Study design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group 4-week study (v 2.98, p 27).

11.1.4. Study procedures (v 2.98, p 37, 188-209)

The study was conducted between August and October, depending on time of pollination at the different study sites. All patients were enrolled within a 7 day period, after the applicant verified the presence of sufficient ragweed pollen present in the environment and the screened patients started showing SAR symptoms. The study procedures are outlined in Table 98. The study had screening period of up to 28 days, a 5-day baseline period, and a 4-week double-blind treatment period. Patients satisfying the inclusion/exclusion and ECG criteria (described above) were dispensed with diary cards and asked to record severity of 5

"rhinitis" symptoms (nasal discharge, nasal congestion, sneezing, nasal itch, itchy/watery eyes) on a 4-point scale (0 = absent, no symptoms; 1 = mild, symptoms present but not annoying to self; 2 = moderate, symptoms present and annoying to self; 3 = severe, symptoms interfere with activities of daily living) twice a day - upon arising in the morning, and in the evening before bedtime. Scoring was based on symptom severity over the previous 12 hours (reflective symptom assessment) and at the time of recording ("snap-shot" instantaneous symptom assessment). To be eligible for randomization (visit 2), patients could not have taken any medication for rhinitis symptoms for the five days preceding the visit. Patients were also required to have an aggregated sum of reflective rhinitis symptom score over 3 of the last 4 days of lead-in period plus the morning of the visit (total of 7 out of 9 AM and PM ratings) of at least 42 points out of a maximum possible of 105 with at least one of the symptoms present at a moderate or severe level. This was the baseline score.

Eligible patients were randomized into 4 study groups (10 mg ebastine, 20 mg ebastine, 10 mg loratadine, or placebo). Blinding was maintained by placing all study medications within capsules. Study medications were administered in the morning immediately after breakfast (containing solids) with 8 ounces of water. No study medication was administered in the morning of visit 5. During the study, patients were instructed to refrain from using any over the counter or prescription medication for alleviating the symptoms of rhinitis, cold, or cough, or any medication for another indication that could relieve or produce symptoms of allergic rhinitis. Throughout the study patients continued recording rhinitis symptom scores (reflective scores for the previous 12 hours, and a snap-shot scores at the time of recording) daily in the morning and in the evening before study medication administration. In addition, at the end of the study (visit 5), patients and physicians separately recorded the global evaluation of efficacy on a 5 point scale (0 = greatly improved, 1 = somewhat improved, 2 = no change, 3 = somewhat worsened, 4 = greatly worsened) relative to the baseline. Unlike the pivotal SAR efficacy studies, ECG was obtained only at screening and at the last visit of the study (3-5 hours after the last dose of study medication) and Holter monitoring was not done during the study. The screening ECG was used for eligibility, and there were no discontinuation criteria based on ECG findings.

Table 98. CM.030.ALGY, Schedules of observations

Procedures	Visit 1 Screening/Lead in Day -28 to -5	Visit 2 Randomization Day 0	Visit 3 Day 14 ± 3	Visit 4 Day 28 ± 3
Informed consent	x			
Medical history and skin test*	x			
Physical exam, vital signs, laboratory tests†	x			x
Dispense medication		x	x	
Collect medication			x	x
Dispense diary	x	x	x	
Collect and review diary		x	x	x
ECG‡	x			x
Symptom evaluation	x	x	x	x
Physician global assessment				x
Patient global assessment				x
Adverse events		x	x	x
Pollen counts	Daily (at least 5 days a week)			

* Skin test done within one year was acceptable.
† Pregnancy test (Beta-HCG) on females of childbearing potential, urinalysis (ketones, protein, glucose, and microscopic exam), hematology (hemoglobin, hematocrit, WBC count, RBC count, and platelet count), and serum chemistry (creatinine, BUN, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin, AST, ALT calcium, phosphorus, electrolytes: sodium, potassium, chloride, bicarbonate) (v 2.98, p 212).
‡ Obtained at screening visit, and at final visit 3 to 5 hours post-dose (v 2.983, p 40).

Source: v 2.98, p 28, 189

11.1.5. Efficacy parameters

The primary efficacy variable was the mean change from baseline in the mean daily reflective total rhinitis symptom score averaged over the double-blind treatment period, with the primary comparison between the 20 mg ebastine group and the 10 mg loratadine group. Secondary variables were the change from baseline in the mean total snap shot score, mean reflective and snap shot score for each symptom, mean reflective and snap shot nasal index (sum of the scores for nasal discharge, nasal stuffiness, sneezing, and itchy nose), patient drop-out rate due to insufficient therapeutic effect, and patient and physician global perception evaluations. (v 2.98, p 43-4, 217)

As stated above, the primary comparison was between 20 mg ebastine and 10 mg loratadine. Comparisons were made in a step-down test of linear contrasts between 20 mg ebastine and 10 mg loratadine for all endpoints including the secondary endpoints. Step-down comparisons were between 10 mg ebastine and 10 mg loratadine, but only if significance with a two-sided alpha = 0.05 was reached with the primary comparison. Secondary comparisons were between 20 mg and 10 mg ebastine and placebo. Tertiary comparisons were between 10 mg loratadine and placebo.

11.1.6. Safety analysis

Safety analysis included laboratory values, ECG with Lead II/V 30-second rhythm strip, physical examination, and adverse events (v 2.98, p 44, 219).

11.1.7. Statistical considerations

11.1.7.1. Sample size

A sample size of 133 patients per group was calculated to detect difference between treatments of one unit in the 24-hour symptom score with a power of 80% at a two-sided α level of 0.05. The projected standard deviation used in the calculation was 2.9. (v 2.98, p 217-8)

11.1.7.2. Statistical analysis

The primary efficacy variable was analyzed for the ITT population using an ANCOVA with the primary variable as dependent, treatment group and investigator (at a significance level of 0.10, otherwise it was dropped) as factors, and important baseline variables as covariates. The patient drop-out rate due to insufficient therapeutic effect, patients' and physicians' global assessment of efficacy were analyzed by the Cochran-Mantel-Haenszel test (v 2.98, p 43-5, 297).

11.1.8. Results

11.1.8.1. Patients enrolled/analyzed

A total of 567 patients were randomized, of whom 95 patients (16.8%) discontinued from the study during double blind treatment period. Disposition of the randomized patients and reasons for discontinuation is shown in Table 99. Eight patients were not evaluable and were therefore excluded from the ITT population analysis. Two patients (1 ebastine 10 mg, 1 ebastine 20 mg) did not have baseline symptom data. Six patients (2 ebastine 10 mg, 1 ebastine 20 mg, 1 loratadine 10 mg, 2 placebo) were missing symptom scores during treatment. (v 2.98, p 60-1)

Table 99. CM.030.ALGY, Disposition of study patients

	Ebastine 10 mg	Ebastine 20 mg	Loratadine 10 mg	Placebo	Total
Enrolled	142	143	140	142	567
Completed	119	124	110	119	472
Discontinued	23	19	30	23	95
Reasons for discontinuation:					
Drug ineffective	9	4	9	9	31
Adverse event	7	4	9	9	29
Protocol deviation	3	8	7	3	21
Lost to follow-up	2	3	2	2	9
Consent withdrawn	1	0	1	0	2
Others *	1	0	2	0	3
* Two patients (1 ebastine 10 mg, 1 loratadine 10 mg) were discontinued due to compliance reasons; one (00213, loratadine)as a precautionary measure due to an AE of dizziness and drowsiness on D14 and an elevated baseline QTc of 0.402 sec (0.408 sec on follow-up)					
Source: v 2.98, p 46					

11.1.8.2. Subject demographics

Demographic data by treatment group are summarized in Table 100. The majority of patients were Caucasian. There were no important demographic differences between the treatment groups. There were no important differences between treatment groups regarding medical history, medications, or positive skin test reactivity.

Table 100. CM.030.ALGY, Demographic summary

	Ebastine 10 mg	Ebastine 20 mg	Loratadine 10 mg	Placebo	Total
Number	142	143	140	142	567
Sex: male/female %	53/47	52/48	58/42	56/44	
Age: years (range)	33 (12-70)	35 (12-69)	34 (12-69)	34 (12-66)	34 (12-70)
12-17 years N	16	18	24	20	78
Race:					
Cauc./Black/Hisp/others %	89/7/3/1	89/6/4/1	89/7/1/2	88/7/3/2	
Source: v 2.98, p 47-8					

11.1.8.3. Protocol deviations

There were no significant deviations from the protocol in this study.

11.1.8.4. Efficacy endpoint outcomes

Results of the total reflective rhinitis symptom scores for the double-blind treatment period as well as individual, and 'nasal index' (total nasal symptom score or TNSS)[total rhinitis score minus the total eye symptom score] for the ITT population are shown in Table 101. The applicant also carried out several other analyses, including total rhinitis symptom score without congestion and nasal index without congestion, because antihistamines are less effective for the individual score of congestion than for other scores.

The primary efficacy analysis [shown in **bold** in Table 101] of change from baseline in reflective rhinitis scores over the 4-week treatment period for ebastine 20 mg compared to loratadine 10 mg was not statistically significant (p = 0.1069 for the primary variable).

Since the primary family of comparison were not significant for either the primary or secondary variables, step-down comparisons between ebastine 10 mg and loratadine 10 mg were not carried out [shown as NS in table].

Secondary and tertiary reflective comparisons against placebo are presented in Table 101. All three study drugs showed statistically significant differences from placebo for all composite reflective scores [significant results are shaded in table]. Except for loratadine 10 mg vs placebo for congestion, all three active treatments showed statistically significant differences from placebo for each of the five individual reflective scores. Nevertheless, the ebastine 20 mg group exhibited greater change from baseline than either ebastine 10 mg or loratadine 10 mg in all composite and individual scores except the total eye symptom score, where the ebastine 10 mg was equal to the ebastine 20 mg. There was a trend for ebastine 10 mg to show greater change from baseline in most composite and individual reflective scores than loratadine 10 mg.

There was no evaluation of overall efficacy based on gender, race, or age groups (12-16 years, 17-59 years, over 60 years).

Table 101. CM.030.ALGY, Reflective rhinitis symptom scores[†] for the four-week treatment period, ITT population

Reflective Score	Treatment	N	Baseline mean	Change from baseline, LS mean±SE	Change from baseline LS % mean	p-value vs. loratadine*	p-value vs. placebo*
Total Rhinitis[†]	E 10 mg	139	9.35	-3.66 ± 0.23	-38.9	NS	0.0002
	E 20 mg	**141**	**9.17**	**-3.85 ± 0.23**	**-41.7**	**0.1069**	**<0.0001**
	L 10 mg	**139**	**9.51**	**-3.33 ± 0.23**	**-34.9**		**0.0070**
	Placebo	140	9.31	-2.47 ± 0.23	-26.4		
Total Rhinitis without Congestion	E 10 mg	139	7.24	-3.00 ± 0.18	-41.3	NS	0.0001
	E 20 mg	141	7.14	-3.16 ± 0.18	-44.1	0.0774	<0.0001
	L 10 mg	139	7.42	-2.71 ± 0.18	-36.4		0.0054
	Placebo	140	7.25	-2.00 ± 0.18	-27.4		
Nasal Index (TNSS)	E 10 mg	139	7.59	-2.83 ± 0.19	-37.0	NS	0.0009
	E 20 mg	141	7.32	-3.02 ± 0.19	-40.9	0.1023	0.0001
	L 10 mg	139	7.58	-2.59 ± 0.19	-33.9		0.0163
	Placebo	140	7.55	-1.97 ± 0.19	-25.9		
Nasal Index without Congestion	E 10 mg	139	5.47	-2.17 ± 0.14	-39.3	NS	0.0006
	E 20 mg	141	5.29	-2.34 ± 0.14	-43.7	0.0676	<0.0001
	L 10 mg	139	5.49	-1.98 ± 0.14	-35.7		0.0132
	Placebo	140	5.49	-1.49 ± 0.14	-26.8		
Nasal Discharge	E 10 mg	139	1.99	-0.66 ± 0.05	-33.0	NS	0.0041
	E 20 mg	141	1.95	-0.74 ± 0.05	-37.5	0.0792	0.0001
	L 10 mg	139	1.94	-0.61 ± 0.05	-31.2		0.0304
	Placebo	140	1.95	-0.46 ± 0.05	-23.2		
Congestion	E 10 mg	139	2.12	-0.66 ± 0.05	-31.0	NS	0.0133
	E 20 mg	141	2.03	-0.69 ± 0.05	-33.7	0.3062	0.0044
	L 10 mg	139	2.10	-0.61 ± 0.05	-29.1		0.0684
	Placebo	140	2.06	-0.48 ± 0.05	-23.1		
Sneezing	E 10 mg	139	1.65	-0.72 ± 0.05	-42.9	NS	0.0042
	E 20 mg	141	1.58	-0.81 ± 0.05	-50.4	0.0992	<0.0001
	L 10 mg	139	1.74	-0.70 ± 0.05	-39.4		0.0129
	Placebo	140	1.70	-0.52 ± 0.05	-30.2		
Nasal Itch	E 10 mg	139	1.83	-0.78 ± 0.05	-42.7	NS	0.0001
	E 20 mg	141	1.77	-0.79 ± 0.05	-44.7	0.0631	0.0001
	L 10 mg	139	1.81	-0.66 ± 0.05	-36.5		0.0272
	Placebo	140	1.84	-0.50 ± 0.05	-27.3		
Total Eye Symptoms	E 10 mg	139	1.76	-0.84 ± 0.05	-47.8	NS	<0.0001
	E 20 mg	141	1.85	-0.83 ± 0.05	-45.3	0.1544	<0.0001
	L 10 mg	139	1.93	-0.73 ± 0.05	-38.0		0.0029
	Placebo	140	1.76	-0.51 ± 0.05	-29.1		

* Significant p values against placebo are shaded. NS = Analysis not performed since the difference between ebastine 20mg and loratadine 10 mg was not significant.
[†] Rhinitis symptom score = sum of nasal discharge, nasal stuffiness, sneezing, itchy nose, and itchy/watery eyes

Source: volume 2.98, p 62-3

Secondary analyses also included snap shot rhinitis symptom scores (AM, PM and daily) analyzed for the double-blind treatment period and for each week of treatment. These were analyzed for the total rhinitis symptom score, individual, 'nasal index' (TNSS), total rhinitis

minus congestion, and nasal index minus congestion for the ITT population. Snap shot scores are presented in summary fashion only in Table 102. Of significance is that the AM total rhinitis snap shot scores were significant for both doses of ebastine compared to placebo, suggesting that the drug remains effective over the dosing interval.

Table 102. CM.030.ALGY, Snap shot total rhinitis symptom scores[†] for the four-week treatment period, ITT population

Snap Shot Total Rhinitis Score	Treatment	N	Baseline mean	Change from baseline, LS mean±SE	Change from baseline LS % mean	p-value vs. loratadine*	p-value vs. placebo*
Daily	E 10 mg	139	9.10	-3.77 ± 0.23	-36.9	NS	0.0001
	E 20 mg	141	8.69	-3.57 ± 0.23	-40.9	0.0660	<0.0001
	L 10 mg	139	8.88	-2.98 ± 0.23	-33.5		0.0049
	Placebo	140	8.77	-2.08 ± 0.23	-23.7		
AM	E 10 mg	139	9.07	-3.13 ± 0.23	-34.4	NS	<0.0001
	E 20 mg	141	8.62	-3.27 ± 0.22	-37.9	0.0558	<0.0001
	L 10 mg	139	8.81	-2.67 ± 0.23	-30.3		0.0081
	Placebo	140	8.71	-1.84 ± 0.22	-21.1		
PM	E 10 mg	139	9.02	-3.53 ± 0.24	-38.9	NS	0.0002
	E 20 mg	141	8.65	-3.80 ± 0.24	-43.7	0.0804	<0.0001
	L 10 mg	139	8.88	-3.22 ± 0.24	-36.1		0.0152
	Placebo	140	8.83	-2.29 ± 0.24	-25.8		

* Significant p values are shaded. NS = Analysis not performed since the difference between ebastine 20mg and loratadine 10 mg was not significant.
[†] Rhinitis symptom score = sum of nasal discharge, nasal stuffiness, sneezing, itchy nose, and itchy/watery eyes
Source: volume 2.98, p 67, 70, 72

11.1.9. Safety outcomes

11.1.9.1. Total drug exposure

All patients enrolled in the study were included in the safety analysis. The mean duration of exposure was 26.8 days for the 10 mg ebastine group, 27.6 days for the 20 mg ebastine group, 26.2 days for the loratadine 10mg group, and 25.8 days for the placebo group. Compliance ranged from 90.1% for the placebo group to 95.6% for the 20 mg ebastine group. (v 2.98, p 87)

11.1.9.2. Adverse events

Adverse events reported by at least 3% of patients in any treatment group are presented in Table 103. The majority of the adverse events were mild to moderate and not related to the study medication. There were 11 severe adverse events in this study, nine of which were considered not to be related to the study medication. The two events considered possibly related to study drug included one case of dyspepsia in the ebastine 20 mg group, and one case of headache in the loratadine 10 mg group. One patient has a serious adverse event (see next section). There were no pregnancies or deaths. (v 2.98, p 85)

Table 103. CM.030.ALGY, Common adverse experience reported by patients*

	Ebastine 10 mg (n=142)	Ebastine 20 mg (n=143)	Loratadine 10 mg (n=140)	Placebo (n=142)
Total with adverse experience	44 (31.0 %)	51 (35.7 %)	52 (37.1 %)	55 (38.7 %)
Body as a whole				
Accidental injury	1 (0.7 %)	5 (3.5 %)	2 (1.4 %)	2 (1.4 %)
Headache	6 (4.2 %)	9 (6.3 %)	5 (3.6 %)	9 (6.3 %)
Pain	1 (0.7 %)	2 (1.4 %)	1 (0.7 %)	5 (3.5 %)
Cardiovascular system				
Prolonged QTc interval	6 (4.2 %)	7 (4.9 %)	9 (6.4 %)	5 (3.5 %)
Nervous system				
Dry mouth	1 (0.7 %)	1 (0.7 %)	2 (1.4 %)	2 (1.4 %)
Somnolence	1 (0.7 %)	4 (2.8 %)	2 (1.4 %)	0 (0.0 %)
Respiratory system				
Pharyngitis	2 (1.4 %)	1 (0.7 %)	5 (3.6 %)	2 (1.4 %)
Rhinitis (URI)	1 (0.7 %)	4 (2.8 %)	7 (5.0 %)	6 (4.2 %)
Sinusitis	6 (4.2 %)	0 (0.0 %)	6 (4.2 %)	3 (2.1 %)

*Events reported by ≥3% of patients in any group is listed (number and %) as Costart preferred term. Dry mouth and Somnolence are included because of the relevance of these adverse events to this application.

Source: v 2.98, p 88; v2.99, p 316

11.1.9.3. Premature withdrawals due to adverse events

A total of 30 patients were withdrawn due to adverse events (Table 99). The events are summarized in Table 104. One patient (00393), a 42 year old white male in the 20 mg ebastine group had a serious adverse event of superficial phlebitis on Day 20 of the study and was discontinued. (v 2.98, p 93-4)

Table 104. CM.030.ALGY, Discontinued patients due to adverse events

Group	Patient	Event	Days on study medication	Severity	Relationship to study med.
Placebo	00357	Rhinitis	10	Moderate	None
	00405	Constipation	1	Moderate	Possible
	00573	Contact dermatitis	5	Moderate	None
	00472	Headache	6	Moderate	Possible
	00567	Pruritus	2	Moderate	Possible
	00589	Sinusitis	14	Moderate	None
	00502	Sinusitis	2	Moderate	None
	00145	Infection	23	Moderate	None
	00559	Infection	25	Moderate	None
E 10 mg	00517	Allergic reaction	10	Moderate	None
	00250	Asthma	17	Moderate	None
	00165	Headache	8	Moderate	Possible
	00387	Vesiculo-bullous rash	11	Moderate	None
	00566	Sinusitis	1	Moderate	None
	00597	Sinusitis	11	Moderate	None
	00010	Infection	19	Moderate	None
E 20 mg	00463	Accidental injury	26	Severe	None
	00341	Thinking abnormal	1	Moderate	Probable
		Somnolence	1	Moderate	Probable
	00456	Headache	10	Moderate	Possible
	00393	Phlebitis	20	Severe	None

Group	Patient	Event	Days on study medication	Severity	Relationship to study med.
L 10 mg	00266	Bronchitis	8	Moderate	None
	00147	Diarrhea	2	Moderate	Possible
	00020	Sinusitis	15	Moderate	Possible
	00248	Sinusitis	13	Moderate	None
	00522	Sinusitis	6	Moderate	Remote
	00427	Fly syndrome	10	Moderate	Remote
	00147	Nausea	2	Moderate	Possible
	00077	Rhinitis	7	Moderate	None
	00238	Infection	17	Moderate	None
	00455	UTI	6	Moderate	Probable
Source: v 2.100, p 384-7					

11.1.9.4. Physical examination, ECG, and laboratory measures

There were no clinically significant changes in physical examination or vital signs in any of the patients. Table 105 shows selected laboratory parameters that exhibited shifts over the course of the study. Several of these are predicted, such as the elevation in eosinophil counts. For all three active treatments there was a trend towards a shift from normal to high in SGOT and SGPT. Four patients experienced laboratory parameter adverse events at the last visit (2 ebastine 20 mg, 2 placebo). Of these, one patient on 20 mg ebastine (00106) experienced an elevation in SGPT to 77 U/L at the final visit [*Note: The final visit for this patient was listed as on D17 rather than on D28*]. (v 2.98, p 101-3)

Table 105. CM.030.ALGY, Selected laboratory parameters shift table

Laboratory Parameter	Ebastine 10 mg (n=142)				Ebastine 20 mg (n=143)				Loratadine 10 mg (n=140)				Placebo (n=142)			
	N	L	N	H	N	L	N	H	N	L	N	H	N	L	N	H
Creatinine	0	2			0	3			0	1			0	2		
Glucose	4	8			4	7			0	5			0	6		
SGOT	0	5			2	7			1	7			0	1		
SGPT	0	4			0	8			0	6			1	3		
Uric acid	0	3			1	5			1	2			0	4		
Eosinophils	0	9			0	7			0	5			0	8		
WBC in UA	0	2			0	2			0	2			0	3		
Source: v 2.98, p 102																

The study enrolled patients who had no history of QTc prolongation, and had a QTc < 444 milliseconds at baseline. The results of the QTc data analysis is shown in Table 106 and patients with a $\geq$ 20 msec increase from baseline in QTc interval are shown in Table 107. The mean change from baseline in QTc interval for those patients with a prolonged QTc at the final visit was similar among the treatment groups (10 mg ebastine 20 ± 17 msec, 20 mg ebastine 24 ± 20 msec, 10 mg loratadine 24 ± 8 msec, placebo 47 ± 39 msec). One 33 year old male patient from the 20 mg ebastine group (00519) had a right bundle branch block at the final visit.

Table 106. CM.030.ALGY, Summary of Rate, QT and QTcB changes

Parameter	Treatment	N	Baseline mean	Post-treatment mean	Mean change
Rate (beat/min)	E 10 mg	142	66.528	69.207	3.336
	E 20 mg	143	65.350	70.612	5.065
	L 10 mg	140	65.471	70.723	5.350
	Placebo	142	65.275	67.364	2.171
QT (msec)	E 10 mg	142	389	382	-8
	E 20 mg	143	394	387	-8
	L 10 mg	140	393	384	-10
	Placebo	142	392	388	-4
QTcB (msec)	E 10 mg	142	404	405	1
	E 20 mg	143	408	412	3
	L 10 mg	140	406	410	5
	Placebo	142	405	405	0
Source: v 2.98, p 98 and v 2.99, p 330					

Table 107. CM.030.ALGY, Patients with ≥ 20 msec change from baseline in QTcB

Treatment	Patient	Age Sex	Baseline QTcB (msec)	Final QTcB (msec)	Change from baseline in msec
E 10 mg	00190	45 F	424	475	51
	00193	27 M	427	447	20
E 20 mg	00009	42 F	442	468	26
	00021	34 F	421	451	30
	00259	58 M	386	450	64
L 10 mg	00016	65 F	444	467	23
	00047	15 M	440	467	27
	00172	55 F	424	447	23
	00361	28 M	410	448	38
	00455	64 M	414	450	36
Placebo	00013	29 F	437	493	56
	00363	26 M	390	498	108
	00487	40 M	405	449	44
Source: v 2.98, p 97					

11.1.10. Conclusion from CM.030.ALGY study results

This study evaluated the efficacy and safety of ebastine 20 mg/day and 10 mg/day compared to loratadine 10 mg/day in patients with SAR. The primary efficacy comparison between ebastine 20 mg/day and loratadine10 mg/day failed to show any statistically significant difference. However, the secondary efficacy comparisons between ebastine 20 mg/day, 10 mg/day and loratadine 10 mg/day showed that all active treatments were effective in relieving symptoms of ragweed SAR. In addition, AM snap shot scores suggest efficacy over the dosing interval. The results of this study support the efficacy of ebastine 20 mg QD and 10 mg QD for relief of ragweed SAR symptoms, but do not support the claim that ebastine 20 mg was statistically superior to loratadine 10 mg. Safety parameters collected during the study show that ebastine was well tolerated in this study group, however, in the 20 mg ebastine group there was a slightly higher incidence of accidental injuries and somnolence and one episode of elevated SGPT.

11.2. CM.031.ALGY: Multicenter, double-blind, parallel group, randomized comparison of ebastine 20 mg and 10 mg versus loratadine 10 mg and placebo in patients with seasonal allergic rhinitis.

11.2.1. Investigators and centers

The study was conducted in 14 sites in the US between September and November of 1997. The principal investigators, study sites, and number of patients enrolled are listed below (v 2.112, p 21, 28-9).

Jeffrey Adelglass, MD, Dallas Texas	48 patients
Peter Boggs, MD, Shreveport, Louisiana	21 patients
Joseph Diaz, MD, San Antonio, Texas	43 patients
Gary Gross, MD, Dallas, Texas	48 patients
Frank Hampel, Jr, MD, New Braunfels, Texas	48 patients
William Howland III, MD, Austin, Texas	48 patients
Robert Jacobs, MD, San Antonio, Texas	48 patients
William Lumry, MD, Dallas Texas	41 patients
Zev Munk, MD, Houston, Texas	48 patients
John Murray, MD, Nashville, Tennessee	24 patients
Paul Ratner, MD, San Antonio, Texas	48 patients
Kevin Schaffer, MD, Lawrenceville, Georgia	41 patients
Tommy Slim, MD, Friendswood, Texas	33 patients
Julius Van Bavel, MD, Austin, Texas	26 patients

11.2.2. Study protocol and design

The study protocol (including the objectives, population, inclusion, exclusion and ECG criteria, design, procedures, powering, safety and efficacy analyses) was identical to that of study CM.030.ALGY, and therefore will not be repeated here. [*Note: For a full discussion of the protocol, please refer to the description of protocol CM.030.ALGY beginning on page 133*] Briefly, this was a multicenter, randomized, double-blind, placebo-controlled, parallel-group 4-week study in SAR patients 12 to 70 years of age. Study drugs and lot numbers were the same as for study CM.030.ALGY. Just as for study CM.030.ALGY, the primary efficacy variable was the mean change from baseline in the mean daily reflective rhinitis symptom score averaged over the double-blind treatment period, with the primary comparison between the 20 mg ebastine group and the 10 mg loratadine group. [*Note: For a full discussion of the secondary variables and the primary, step-down, secondary and tertiary comparisons, please refer to the statistics section for study CM.030.ALGY on page 137*]. (v 2.112 p 30-49)

11.2.3. Results

11.2.3.1. Patients enrolled/analyzed

A total of 565 patients were randomized, of whom 92 patients (16.3%) discontinued from the study during double blind treatment period. Disposition of the randomized patients and reasons for discontinuation is shown in Table 108. Five patients were not evaluable and

were therefore excluded from the ITT population (n = 560) analysis. One patient (ebastine 10 mg) did not have baseline symptom data. Four patients (2 ebastine 10 mg, 1 loratadine, 2 placebo) were missing symptom scores during treatment. (v 2.112, p 70)

Table 108. CM.031.ALGY, Disposition of study patients

	Ebastine 10 mg	Ebastine 20 mg	Loratadine 10 mg	Placebo	Total
Enrolled	140	143	141	141	565
Completed	119	118	120	116	473
Discontinued	21	25	21	25	92
Reasons for discontinuation:					
Drug ineffective	8	6	8	15	37
Adverse event	5	6	2	2	15
Protocol deviation	5	9	8	4	26
Lost to follow-up	3	1	2	3	9
Consent withdrawn	0	2	1	1	4
Others *	0	1	0	0	1
* One patients (10531) on ebastine 20 mg was discontinued due to "going out of state for four weeks."					
Source: v 2.112, p 50					

11.2.3.2. Subject demographics

Demographic data by treatment group are summarized in Table 109. The majority of patients were Caucasian. Unlike study CM.030.ALGY, this study enrolled a significant number of Hispanic patients to all groups. There were no important demographic differences between the treatment groups. There were no important differences between treatment groups regarding medical history, medications, or positive skin test reactivity. Significantly fewer patients 12-17 years of age were enrolled than planned. (The plan was for 10 patients per center, or about 140 patients.)

Table 109. CM.031.ALGY, Demographic summary

	Ebastine 10 mg	Ebastine 20 mg	Loratadine 10 mg	Placebo	Total
Number	140	143	141	141	565
Sex: male/female %	51/49	47/53	43/57	55/45	
Age: years (range)	39 (12-68)	38 (12-69)	38 (12-70)	39 (12-70)	38 (12-70)
12-17 years N	8	10	7	11	36
Race:					
Cauc./Black/Hisp/others %	76/6/16/1	78/6/15/1	72/11/15/2	77/6/17/1	
Source: v 2.112, p 52					

11.2.3.3. Protocol deviations

There were no significant deviations from the protocol in this study.

11.2.3.4. Efficacy endpoint outcomes

Results of the total reflective rhinitis symptom scores for the double-blind treatment period as well as individual, and 'nasal index' (total nasal symptom score or TNSS)[total rhinitis score minus the total eye symptom score] for the ITT population are shown in Table 110. The applicant also carried out several other analyses, including total rhinitis symptom score

without congestion and nasal index without congestion, because antihistamines are less effective for the individual score of congestion than for other scores.

The primary efficacy analysis [shown in **bold** in Table 110] of change from baseline in reflective total rhinitis scores over the 4-week treatment period for ebastine 20 mg compared to loratadine 10 mg was statistically significant (p = 0.0454 for the primary variable).

Since the primary comparison was significant, step-down comparison between ebastine 10 mg and loratadine 10 mg was carried out for the primary variable but was not significant [shown as NS in table]. Within the primary family of comparisons for secondary variables, there were several that were significant, including total rhinitis without congestion, nasal index, nasal index without congestion, and the individual symptom scores of nasal discharge and sneezing. When any of the primary family of comparisons were significant, the step-down comparison between ebastine 10 mg and loratadine 10 mg was carried out, but this comparison was not significant for any of the secondary variables.

Secondary and tertiary reflective comparisons against placebo are presented in Table 110. All three study drugs showed statistically significant differences from placebo for all composite and each of the five individual reflective scores [significant results are shaded in table]. While ebastine 20 mg showed greater change from baseline in mean reflective total rhinitis score than loratadine 10 mg, ebastine 10 mg was roughly equal to loratadine 10 mg in composite and individual scores.

There was no evaluation of overall efficacy based on gender, race, or age groups (12-16 years, 17-59 years, over 60 years).

Table 110. CM.031.ALGY, Reflective rhinitis symptom scores[†] for the four-week treatment period, ITT population

Reflective Score	Treatment	N	Baseline mean	Change from baseline, LS mean±SE	Change from baseline LS % mean	p-value vs. loratadine*	p-value vs. placebo*
Total Rhinitis[†]	E 10 mg	137	9.90	-3.63 ± 0.23	-36.6	0.7979	0.0006
	E 20 mg	**143**	**9.85**	**-4.18 ± 0.23**	**-42.5**	**0.0454**	**<0.0001**
	L 10 mg	**140**	**9.76**	**-3.54 ± 0.23**	**-36.3**		**0.0015**
	Placebo	139	9.71	-2.52 ± 0.23	-25.9		
Total Rhinitis without Congestion	E 10 mg	137	7.68	-2.98 ± 0.19	-38.9	0.7597	0.0002
	E 20 mg	143	7.74	-3.43 ± 0.18	-44.3	0.0407	<0.0001
	L 10 mg	140	7.56	-2.90 ± 0.18	-38.4		0.0007
	Placebo	139	7.50	-2.02 ± 0.18	-27.0		
Nasal Index (TNSS)	E 10 mg	137	7.95	-2.88 ± 0.19	-36.2	0.7978	0.0006
	E 20 mg	143	7.97	-3.36 ± 0.18	-42.2	0.0330	<0.0001
	L 10 mg	140	7.89	-2.82 ± 0.18	-35.7		0.0013
	Placebo	139	7.92	-1.98 ± 0.18	-25.1		
Nasal Index without Congestion	E 10 mg	137	5.73	-2.24 ± 0.14	-39.1	0.7469	0.0002
	E 20 mg	143	5.86	-2.61 ± 0.14	-44.5	0.0261	<0.0001
	L 10 mg	140	5.69	-2.18 ± 0.14	-38.2		0.0005
	Placebo	139	5.71	-1.49 ± 0.14	-26.1		
Nasal Discharge	E 10 mg	137	2.06	-0.68 ± 0.05	-33.2	0.7181	0.0149
	E 20 mg	143	2.13	-0.82 ± 0.05	-38.6	0.0225	<0.0001
	L 10 mg	140	2.11	-0.66 ± 0.05	-31.0		0.0368
	Placebo	139	2.09	-0.50 ± 0.05	-24.1		

US Comparative SAR Efficacy Studies, CM.031.ALGY

Reflective Score	Treatment	N	Baseline mean	Change from baseline, LS mean±SE	Change from baseline LS % mean	p-value vs. loratadine*	p-value vs. placebo*
Congestion	E 10 mg	137	2.22	-0.64 ± 0.05	-29.0	NS	0.0373
	E 20 mg	143	2.11	-0.76 ± 0.05	-35.9	0.1056	0.0003
	L 10 mg	140	2.20	-0.64 ± 0.05	-29.1		0.0435
	Placebo	139	2.21	-0.49 ± 0.05	-22.3		
Sneezing	E 10 mg	137	1.79	-0.80 ± 0.05	-44.9	0.5062	<0.0001
	E 20 mg	143	1.82	-0.92 ± 0.05	-50.3	0.0214	<0.0001
	L 10 mg	140	1.70	-0.76 ± 0.05	-44.6		0.0001
	Placebo	139	1.75	-0.49 ± 0.05	-27.9		
Nasal Itch	E 10 mg	137	1.89	-0.75 ± 0.05	-39.9	NS	0.0003
	E 20 mg	143	1.91	-0.86 ± 0.05	-45.0	0.1436	<0.0001
	L 10 mg	140	1.88	-0.76 ± 0.05	-40.4		0.0002
	Placebo	139	1.86	-0.50 ± 0.05	-26.6		
Total Eye Symptoms	E 10 mg	137	1.94	-0.75 ± 0.05	-38.7	NS	0.0020
	E 20 mg	143	1.88	-0.82 ± 0.05	-43.8	0.2216	0.0001
	L 10 mg	140	1.87	-0.73 ± 0.05	-39.1		0.0051
	Placebo	139	1.79	-0.52 ± 0.05	-29.1		

* Significant p values are shaded. NS = Analysis not performed since the difference between ebastine 20mg and loratadine 10 mg was not significant.
[†] Rhinitis symptom score = sum of nasal discharge, nasal stuffiness, sneezing, itchy nose, and itchy/watery eyes

Source: volume 2.112, p 72-3

Secondary analyses also included snap shot rhinitis symptom scores (AM, PM and daily) analyzed for the double-blind treatment period and for each week of treatment. These were analyzed for the total rhinitis symptom score, individual, 'nasal index' (TNSS), total rhinitis minus congestion, and nasal index minus congestion for the ITT population. Snap shot scores are presented in summary fashion only in Table 111. Of significance is that the AM total rhinitis snap shot scores were significant for both doses of ebastine compared to placebo, suggesting that the drug remains effective over the dosing interval.

Table 111. CM.031.ALGY, Snap shot total rhinitis symptom scores[†] for the four-week treatment period, ITT population

Snap Shot Total Rhinitis Score	Treatment	N	Baseline mean	Change from baseline, LS mean±SE	Change from baseline LS % mean	p-value vs. loratadine*	p-value vs. placebo*
Daily	E 10 mg	137	9.50	-3.41 ± 0.23	-35.9	0.6501	0.0056
	E 20 mg	143	9.32	-3.97 ± 0.23	-42.6	0.0290	<0.0001
	L 10 mg	140	9.29	-3.26 ± 0.23	-35.1		0.0195
	Placebo	140	9.22	-2.51 ± 0.23	-27.2		
AM	E 10 mg	137	9.51	-3.20 ± 0.23	-33.7	0.3585	0.0046
	E 20 mg	143	9.35	-3.77 ± 0.23	-40.3	0.0075	<0.0001
	L 10 mg	140	9.27	-2.90 ± 0.23	-31.3		0.0525
	Placebo	139	9.18	-2.27 ± 0.23	-24.7		
PM	E 10 mg	137	9.50	-3.64 ± 0.23	-38.3	NS	0.0053
	E 20 mg	143	9.23	-4.16 ± 0.23	-45.1	0.0979	<0.0001
	L 10 mg	140	9.30	-3.63 ± 0.23	-39.0		0.0057
	Placebo	139	9.26	-2.72 ± 0.23	-29.4		

* Significant p values are shaded.
[†] Rhinitis symptom score = sum of nasal discharge, nasal stuffiness, sneezing, itchy nose, and itchy/watery eyes

Source: volume 2.112, p 79, 81, 83

11.2.4. Safety outcomes

11.2.4.1. Total drug exposure

All patients enrolled in the study were included in the safety analysis. The mean duration of exposure was 27.4 days for the 10 mg ebastine group, 27.3 days for the 20 mg ebastine group, 27.5 days for the loratadine 10mg group, and 26.2 days for the placebo group. Compliance ranged from 90.8% for the placebo group to 94.4% for the 20 mg ebastine group and 95.2 for the 10 mg loratadine group. (v 2.112, p 100)

11.2.4.2. Adverse events

Adverse events reported by at least 3% of patients in any treatment group are presented in Table 112. The majority of the adverse events were mild to moderate and not related to the study medication. There were 40 severe adverse events reported by 27 patients in this study, most of which were considered not to be related to the study medication. Severe adverse events considered possibly related to study drug included two cases each of abdominal pain (both in Patient 10209) and somnolence, and one case of headache in the 10 mg ebastine group, once case each of somnolence and insomnia, and three cases of headache in the 20 mg ebastine group, once case each of somnolence, migraine, and dizziness in the 10 mg loratadine group, and two cases of headache in the placebo group. Only one of these resulted in premature discontinuation (somnolence in Patient 10276 in the 10 mg ebastine group(v 2.112, p 98). One patient experienced two serious adverse events (see next section). There were no pregnancies or deaths.

Table 112. CM.031.ALGY, Common adverse experience reported by patients*

	Ebastine 10 mg (n=140)	Ebastine 20 mg (n=143)	Loratadine 10 mg (n=141)	Placebo (n=141)
Total with adverse experience	48 (34.3 %)	46 (32.2 %)	44 (31.2 %)	40 (28.4 %)
Body as a whole				
Accidental injury	0 (0.0 %)	0 (0.0 %)	2 (1.4 %)	5 (3.5 %)
Headache	6 (4.3 %)	9 (6.3 %)	12 (8.5 %)	6 (4.3 %)
Cardiovascular system				
Prolonged QTc interval	6 (4.3 %)	5 (3.5 %)	5 (3.5 %)	1 (0.7 %)
Nervous system				
Dry mouth	2 (1.4 %)	2 (1.4 %)	2 (1.4 %)	0 (0.0 %)
Somnolence	5 (3.6 %)	2 (1.4 %)	5 (3.5 %)	2 (1.4 %)
Respiratory system				
Rhinitis (URI)	4 (2.9 %)	7 (4.9 %)	7 (5.0 %)	4 (2.8 %)
* Events reported by ≥3% of patients in any group is listed (number and %) as Costart preferred term. Dry mouth is included because of the relevance of this adverse event to this application.				
Source: v 2.112, p 102, 118				

11.2.4.3. Premature withdrawals due to adverse events

A total of 15 patients were withdrawn due to adverse events (Table 108). The events are summarized in Table 113. One patient had two serious adverse events, 37 year old Caucasian female(10363) in the 20 mg ebastine group had cholecystitis (non-serious), cholelithiasis (serious), and an incarcerated umbilical hernia (serious) on Day 30 of the study, one day following the end of treatment. (v 2.112, p 108-9)

Table 113. CM.031.ALGY, Discontinued patients due to adverse events

Group	Patient	Event	Days on study medication	Severity	Relationship to study med.
Placebo	10253	Sinusitis	3	Moderate	None
	10574	Respiratory disease	14	Moderate	None
		Sinusitis	14	Moderate	None
E 10 mg	10179	Migraine	16	Severe	None
	10197	Sinusitis	3	Severe	None
	10276	Somnolence	1	Severe	Probable
	10341	Bronchitis	15	Moderate	None
	10072	Bronchitis	25	Mild	None
E 20 mg	10113	Infection	21	Severe	None
	10254	Sinusitis	15	Moderate	None
	10325	Abdominal pain	22	Severe	None
	10363	Cholecystitis	30	Severe	None
		Cholelithiasis	30	Severe	None
		Hernia	30	Severe	None
	10648	Laryngitis	10	Mild	None
	10653	Myalgia	1	Mild	Possible
L 10 mg	10280	Headache	4	Mild	Possible
	10643	Sinusitis	4	Moderate	None
Source: v 2.114, p 289-292					

11.2.4.4. Physical examination, ECG, and laboratory measures

There were no clinically significant changes in physical examination or vital signs in any of the patients. Table 114 shows selected laboratory parameters that exhibited shifts over the course of the study. Several of these are predicted, such as the elevation in eosinophil counts. For all treatments there was a trend towards a shift from normal to high in SGOT and SGPT, but less for loratadine. Two patients experienced laboratory parameter adverse events at the last visit (1 ebastine 10 mg, 1 placebo). Of these, one 26 year old male patient in the placebo group (10277) experienced an elevation in SGPT to 71 U/L at the final visit on D29, with a repeat value of 87 on D35. (v 2.112, p 126-8)

Table 114. CM.031.ALGY, Selected laboratory parameters shift table

Laboratory Parameter	Ebastine 10 mg (n=140)				Ebastine 20 mg (n=143)				Loratadine 10 mg (n=141)				Placebo (n=141)			
	N	L	N	H	N	L	N	H	N	L	N	H	N	L	N	H
Creatinine	0	2			0	1			0	1			0	2		
Glucose	4	10			2	3			5	10			2	10		
SGOT	1	4			0	6			0	2			0	3		
SGPT	0	5			0	9			1	3			0	5		
Uric acid	0	8			0	2			0	2			1	4		
Eosinophils	0	7			0	10			0	6			0	8		
RBC in UA	0	1			0	4			0	1			0	2		
WBC in UA	0	3			0	4			0	1			0	3		
Source: v 2.112, p 127																

The study enrolled patients who had no history of QTc prolongation, and had a QTc < 444 milliseconds at baseline. The results of the QTc data analysis is shown in Table 115 and patients with a ≥ 20 msec increase from baseline in QTc interval are shown in Table 116.

The mean change from baseline in QTc interval for those patients with a prolonged QTc at the final visit was 50 ± 39 msec for 10 mg ebastine, 31 ± 22 msec for 20 mg ebastine, 55 ± 62 msec for 10 mg loratadine, while the placebo group had one patient with an abnormal QTc of 446 and a prolongation of 12 msec. One 45 year old female patient from the 10 mg loratadine group (10239) had non-specific intraventricular block and T-wave abnormality at the final visit.

Table 115. CM.031.ALGY, Summary of Rate, QT and QTcB changes

Parameter	Treatment	N	Baseline mean	Post-treatment mean	Mean change
Rate (beat/min)	E 10 mg	140	66.093	69.794	4.000
	E 20 mg	143	64.916	70.693	5.964
	L 10 mg	141	65.071	68.799	3.770
	Placebo	141	63.532	66.628	2.934
QT (msec)	E 10 mg	140	391	386	-5
	E 20 mg	143	395	384	-11
	L 10 mg	141	398	388	-10
	Placebo	141	400	394	-6
QTcB (msec)	E 10 mg	140	403	408	5
	E 20 mg	143	405	407	3
	L 10 mg	141	407	406	-1
	Placebo	141	406	406	0
Source: v 2.112, p 116					

Table 116. CM.031.ALGY, Patients with $\geq$ 20 msec change from baseline in QTcB

Treatment	Patient	Age Sex	Baseline QTcB (msec)	Final QTcB (msec)	Change from baseline in msec
E 10 mg	10001	50 F	393	482	89
	10037	33 M	372	473	101
	10097	49 M	426	479	53
	10276	47 F	420	452	32
E 20 mg	10040	62 F	416	473	57
	10044	51 F	394	451	57
	10387	26 F	436	457	21
L 10 mg	10067	61 M	418	445	27
	10239	45 F	435	599	164 *
	10287	19 M	374	396	22
	10391	51 F	414	455	41
	10476	46 F	423	447	24
Placebo	None				
* Non-specific intraventricular block and T-wave abnormality					
Source: v 2.112, p 115					

11.2.5. Conclusion from CM.031.ALGY study results

This study evaluated the efficacy and safety of ebastine 20 mg/day and 10 mg/day compared to loratadine 10 mg/day in patients with SAR. Unlike study CM.030.ALGY, the primary efficacy comparison between ebastine 20 mg/day and loratadine 10 mg/day showed a statistically significant difference between ebastine 20 mg and loratadine 10 mg for the composite endpoint of total rhinitis scores and for 2 of the 5 individual scores (nasal

discharge and sneeze). However, the step-down efficacy comparison between ebastine 10 mg/day and loratadine 10 mg/day failed to show statistically significant differences. Secondary efficacy comparisons between ebastine 20 mg/day, ebastine 10 mg/day, and loratadine 10 mg/day with placebo showed that all active treatments were effective in relieving symptoms of SAR. Ebastine 10 mg was roughly equal in efficacy to loratadine 10 mg. In addition, AM snap shot scores suggest efficacy over the dosing interval. The results of this study support the efficacy of ebastine 20 mg QD and 10 mg QD, and the claim that ebastine 20 mg was statistically superior to loratadine 10 mg for relief of ragweed SAR symptoms. Safety parameters collected during the study show that ebastine was well tolerated in this study group.

11.3. EBA.GMA.402: Multicenter, double-blind, parallel group, randomized comparison of ebastine 20 mg and 10 mg versus loratadine 10 mg and placebo in patients with seasonal allergic rhinitis.

11.3.1. Investigators and centers

The study was conducted in 18 sites in the US between September and December of 1999. The principal investigators, study sites, and number of patients enrolled are listed below (v 2.126, p 22, 31-2).

Jeffrey Adelglass, MD, Dallas Texas	29 patients
Charles Banov, MD, Charleston, South Carolina	56 patients
Peter Boggs, MD, Shreveport, Louisiana	48 patients
Robert Cohen, MD, Conyers, Georgia	9 patients
Gary Gross, MD, Dallas, Texas	24 patients
Frank Hampel, Jr, MD, New Braunfels, Texas	56 patients
William Howland III, MD, Austin, Texas	56 patients
Robert Jacobs, MD, San Antonio, Texas	64 patients
William Lumry, MD, Dallas Texas	45 patients
Bruce Martin, DO, San Antonio, Texas	64 patients
Zev Munk, MD, Houston, Texas	25 patients
John Murray, MD, Nashville, Tennessee	24 patients
Paul Ratner, MD, San Antonio, Texas	14 patients
Nathan Segall, MD, Stockbridge, Georgia	28 patients
Tommy Slim, MD, Friendswood, Texas	48 patients
Julius Van Bavel, MD, Austin, Texas	64 patients
Suzanne Weakly, MD, Houston, Texas	33 patients
John Yarbrough, MD, Gainesville, Georgia	20 patients

11.3.2. Study protocol and design

Except for minor differences described below, the study protocol (including the objectives, population, inclusion, exclusion and ECG criteria, design, procedures, safety and efficacy analyses) was identical to that of study CM.030.ALGY and CM.031.ALGY , and therefore will not be repeated here. [*Note: For a full discussion of the protocol, please refer to the description of protocol CM.030.ALGY beginning on page 133*] Differences between this

study protocol and studies CM.030/031.ALGY included the following. Since many of the investigators participating in this study had participated in the two previous comparative efficacy studies, the protocol carried an exclusion criterion that patients who had been enrolled in studies 030 / 031 could not be enrolled in this study. In addition, the powering calculations changed from the calculations done for the previous two studies, and the powering for this study was more robust. A sample size of 178 patients per group was calculated to detect difference between treatments of one unit in the 24-hour symptom score with a power of 90% at a two-sided α level of 0.05 and a standard deviation of 2.9. [*Note: The previous studies used 80% power to detect the same one unit of difference with the same standard deviation.*]

Briefly, this was a multicenter, randomized, double-blind, placebo-controlled, parallel-group 4-week study in SAR patients 12 to 70 years of age. Study drugs used in this study were the same as for CM.030.ALGY and CM.031.ALGY, but the lot numbers were not the same. Just as for the previous two comparative studies, the primary efficacy variable was the mean change from baseline in the mean daily reflective rhinitis symptom score averaged over the double-blind treatment period, with the primary comparison between the 20 mg ebastine group and the 10 mg loratadine group. [*Note: For a full discussion of the secondary variables and the primary, step-down, secondary and tertiary comparisons, please refer to the statistics section for study CM.030.ALGY on page 137*]. (v 2.126 p 30-53)

11.3.3. Results

11.3.3.1. Patients enrolled/analyzed

A total of 749 patients were randomized, of whom 100 patients (13.4%) discontinued from the study during double blind treatment period. Disposition of the randomized patients and reasons for discontinuation is shown in Table 117. All patients had baseline and symptom score data, and were therefore included in the ITT population (n = 749) analysis. (v 2.126, p 75)

Table 117. EBA.GMA.402, Disposition of study patients

	Ebastine 10 mg	Ebastine 20 mg	Loratadine 10 mg	Placebo	Total
Enrolled	188	186	189	186	749
Completed	158	167	163	161	649
Discontinued	30	19	26	25	100
Reasons for discontinuation:					
Drug ineffective	6	5	7	9	27
Adverse event	6	1	12	1	20
Protocol deviation	9	6	2	8	25
Lost to follow-up	4	5	3	4	16
Consent withdrawn	5	1	2	2	10
Others *	0	1	0	1	2
* Two patients were discontinued due to going out of state for an extended period of time.					
Source: v 2.126, p 54					

11.3.3.2. Subject demographics

Demographic data by treatment group are summarized in Table 118. The majority of patients were Caucasian. Like study CM.031.ALGY, this study enrolled a significant number of Hispanic patients to all groups. There were no important demographic differences between the treatment groups. There were no important differences between treatment groups regarding medical history, medications, or positive skin test reactivity.

Table 118. EBA.GMA.402, Demographic summary

	Ebastine 10 mg	Ebastine 20 mg	Loratadine 10 mg	Placebo	Total
Number	188	186	189	186	749
Sex: male/female %	53/47	46/54	46/54	50/40	
Age: years (range)	39 (12-69)	37 (12-70)	36 (12-70)	38 (12-66)	37 (12-70)
12-17 years N	14	15	18	18	65
Race:					
Cauc./Black/Hisp/others %	76/6/15/2	76/7/16/1	75/7/18/1	74/10/13/2	
Source: v 2.126, p 56-7					

11.3.3.3. Protocol deviations

There were no significant deviations from the protocol in this study.

11.3.3.4. Efficacy endpoint outcomes

Results of the total reflective rhinitis symptom scores for the double-blind treatment period as well as individual, and 'nasal index' (total nasal symptom score or TNSS)[total rhinitis score minus the total eye symptom score] for the ITT population are shown in Table 119. The applicant also carried out several other analyses, including total rhinitis symptom score without congestion and nasal index without congestion, because antihistamines are less effective for the individual score of congestion than for other scores.

The primary efficacy analysis [shown in **bold** in Table 119] of change from baseline in reflective total rhinitis scores over the 4-week treatment period for ebastine 20 mg compared to loratadine 10 mg <u>was</u> <u>not</u> statistically significant (p = 0.0614 for the primary variable).

Since the primary comparison was not significant, step-down comparison between ebastine 10 mg and loratadine 10 mg was not carried out for the primary variable [shown as NS in table]. Within the primary family of comparisons for secondary variables, there were several that were significant. When any of the primary family of comparisons were significant, the step-down comparison between ebastine 10 mg and loratadine 10 mg was carried out, but this comparison was not significant for any of the secondary variables.

Secondary and tertiary reflective comparisons are presented in Table 119. Unlike studies CM.030.ALGY and CM.031.ALGY, all three study drugs did not show statistically significant improvement in total rhinitis scores when compared to placebo [significant results are shaded in table]. Ebastine 20 mg showed statistically significant differences from placebo for all composite and each of the five individual reflective scores. Ebastine 10 mg showed statistically significant differences from placebo for all composite scores, but failed to show significance for the individual reflective scores of nasal discharge and congestion.

The comparison between loratadine 10mg and placebo was not significant for total rhinitis score and the individual scores of nasal discharge and congestion, while the nasal index (TNSS) and other individual scores were significant. There was a trend for ebastine 10 mg to show greater change from baseline in most composite and individual reflective scores than loratadine 10 mg.

There was no evaluation of overall efficacy based on gender, race, or age groups (12-16 years, 17-59 years, over 60 years).

Table 119. EBA.GMA.402, Reflective rhinitis symptom scores[†] for the four-week treatment period, ITT population

Reflective Score	Treatment	N	Baseline mean	Change from baseline, LS mean±SE	Change from baseline LS % mean	p-value vs. loratadine*	p-value vs. placebo*
Total Rhinitis[†]	E 10 mg	185	10.21	-3.64 ± 0.20	-35.9	NS	0.0083
	E 20 mg	**183**	**9.83**	**-3.92 ± 0.20**	**-39.3**	**0.0614**	0.0003
	L 10 mg	**183**	**10.25**	**-3.40 ± 0.20**	**-33.3**		0.0785
	Placebo	182	9.72	-2.91 ± 0.20	-28.2		
Total Rhinitis without Congestion	E 10 mg	185	7.89	-2.95 ± 0.16	-37.4	NS	0.0060
	E 20 mg	183	7.55	-3.19 ± 0.16	-41.7	0.0737	0.0001
	L 10 mg	183	7.97	-2.80 ± 0.16	-35.3		0.0407
	Placebo	182	7.50	-2.34 ± 0.16	-28.7		
Nasal Index (TNSS)	E 10 mg	185	8.25	-2.88 ± 0.16	-34.3	0.3303	0.0115
	E 20 mg	183	7.91	-3.11 ± 0.16	-38.0	0.0426	0.0003
	L 10 mg	183	8.33	-2.66 ± 0.16	-32.2		0.1208
	Placebo	182	7.94	-2.32 ± 0.16	-27.7		
Nasal Index without Congestion	E 10 mg	185	5.93	-2.19 ± 0.12	-34.8	0.4367	0.0075
	E 20 mg	183	5.63	-2.39 ± 0.12	-41.1	0.0478	0.0001
	L 10 mg	183	6.06	-2.06 ± 0.12	-34.4		0.0585
	Placebo	182	5.72	-1.74 ± 0.12	-28.6		
Nasal Discharge	E 10 mg	185	2.16	-0.68 ± 0.05	-30.1	0.1453	0.0707
	E 20 mg	183	2.08	-0.76 ± 0.05	-34.0	0.0048	0.0015
	L 10 mg	183	2.21	-0.59 ± 0.05	-26.5		0.7245
	Placebo	182	2.07	-0.56 ± 0.05	-23.8		
Congestion	E 10 mg	185	2.32	-0.69 ± 0.05	-29.3	NS	0.0800
	E 20 mg	183	2.28	-0.73 ± 0.05	-27.4	0.0515	0.0215
	L 10 mg	183	2.28	-0.60 ± 0.05	-23.9		0.7241
	Placebo	182	2.22	-0.58 ± 0.05	-24.4		
Sneezing	E 10 mg	185	1.80	-0.74 ± 0.04	-37.5	0.6738	0.0048
	E 20 mg	183	1.72	-0.84 ± 0.04	-45.2	0.0362	<0.0001
	L 10 mg	183	1.86	-0.71 ± 0.04	-37.3		0.0169
	Placebo	182	1.75	-0.56 ± 0.04	-26.6		
Nasal Itch	E 10 mg	185	1.97	-0.77 ± 0.05	-40.3	NS	0.0120
	E 20 mg	183	1.83	-0.80 ± 0.05	-41.2	0.5167	0.0042
	L 10 mg	183	1.99	-0.76 ± 0.05	-37.2		0.0270
	Placebo	182	1.90	-0.61 ± 0.05	-30.0		
Total Eye Symptoms	E 10 mg	185	1.96	-0.76 ± 0.05	-41.1	NS	0.0151
	E 20 mg	183	1.92	-0.81 ± 0.05	-44.0	0.2938	0.0021
	L 10 mg	183	1.91	-0.74 ± 0.05	-37.6		0.0425
	Placebo	182	1.78	-0.60 ± 0.05	-27.8		

Reflective Score	Treatment	N	Baseline mean	Change from baseline, LS mean±SE	Change from baseline LS % mean	p-value vs. loratadine*	p-value vs. placebo*
* Significant p values are shaded. NS = Analysis not performed since the difference between ebastine 20mg and loratadine 10 mg was not significant. † Rhinitis symptom score = sum of nasal discharge, nasal stuffiness, sneezing, itchy nose, and itchy/watery eyes							
Source: volume 2.126, p 77-9							

Secondary analyses also included snap shot rhinitis symptom scores (AM, PM and daily) analyzed for the double-blind treatment period and for each week of treatment. These were analyzed for the total rhinitis symptom score, individual, 'nasal index' (TNSS), total rhinitis minus congestion, and nasal index minus congestion for the ITT population. Snap shot scores are presented in summary fashion only in Table 120. Of significance is that the AM total rhinitis snap shot scores were significant for both doses of ebastine compared to placebo, suggesting that the drug remains effective over the dosing interval.

Table 120. EBA.GMA.402, Snap shot total rhinitis symptom scores† for the four-week treatment period, ITT population

Snap Shot Total Rhinitis Score	Treatment	N	Baseline mean	Change from baseline, LS mean±SE	Change from baseline LS % mean	p-value vs. loratadine*	p-value vs. placebo*
Daily	E 10 mg	188	9.73	-3.28 ± 0.20	-33.5	0.1513	0.0015
	E 20 mg	186	9.32	-3.46 ± 0.20	-35.8	0.0344	0.0001
	L 10 mg	189	9.69	-2.89 ± 0.20	-29.8		0.0778
	Placebo	186	9.19	-2.42 ± 0.20	-24.4		
AM	E 10 mg	188	9.76	-2.95 ± 0.20	-29.7	0.1313	0.0074
	E 20 mg	186	9.30	-3.19 ± 0.20	-32.3	0.0171	0.0004
	L 10 mg	189	9.56	-2.55 ± 0.20	-24.8		0.2372
	Placebo	186	9.37	-2.23 ± 0.20	-22.2		
PM	E 10 mg	185	9.70	-3.61 ± 0.21	-36.4	NS	0.0025
	E 20 mg	186	9.33	-3.80 ± 0.21	-39.0	0.1097	0.0003
	L 10 mg	183	9.82	-3.33 ± 0.21	-34.6		0.0407
	Placebo	182	9.02	-2.74 ± 0.21	-26.5		
* Significant p values are shaded † Rhinitis symptom score = sum of nasal discharge, nasal stuffiness, sneezing, itchy nose, and itchy/watery eyes							
Source: volume 2.126, p 85, 87, 89							

11.3.4. Safety outcomes

11.3.4.1. Total drug exposure

All patients enrolled in the study were included in the safety analysis. The mean duration of exposure was 26.8 days for the 10 mg ebastine group, 27.7 days for the 20 mg ebastine group, 26.8 days for the loratadine group, and 27.4 days for the placebo group. Compliance ranged from 90.6% for the loratadine group to 94.8% for the 20 mg ebastine group (10 mg ebastine 92.4%, placebo 93.5%). (v 2.126, p 104)

11.3.4.2. Adverse events

Adverse events reported by at least 3% of patients in any treatment group are presented in Table 121. The majority of the adverse events were mild to moderate and not (or remotely) related to the study medication. There were 40 severe adverse events reported by 30 patients in this study, most of which were considered not to be related to the study medication. The severe adverse events considered possibly related to study drug included seven cases of headache (six in Patient 00666), and one case each of sinusitis and abdominal pain in the 10 mg ebastine group, one case each of somnolence, conjunctivitis, and kidney calculus in the 20 mg ebastine group, two cases of headache and one case of rhinitis in the 10 mg loratadine group, and two cases of headache in the placebo group. Two of these resulted in premature discontinuation (severe headache (00342), and severe abdominal pain (00657)), both in the 10 mg ebastine group. (v 2.126, p 102)

One patient, a 25 year old Caucasian female (00622) on 10 mg loratadine had a positive serum β–HCG on the final visit. Medication was stopped. She delivered a 6 lb 9 oz male by spontaneous vaginal delivery (Apgars 9/9) 8 months later. Initial examination of the newborn was unremarkable. Two patients experienced serious adverse events, one of whom was not discontinued. A 33 year old Caucasian female (00402) on 20 mg ebastine had a right kidney stone which was removed by cystoscopy. The adverse event was considered remotely related, and the patient continued in the study. There were no deaths. (v2.126, p 112-3)

Table 121. EBA.GMA.402, Common adverse experience reported by patients[*]

	Ebastine 10 mg (n=188)	Ebastine 20 mg (n=186)	Loratadine 10 mg (n=189)	Placebo (n=186)
Total with adverse experience	54 (28.7 %)	58 (31.2 %)	63 (33.3 %)	48 (25.8 %)
Body as a whole				
Headache	8 (4.3 %)	6 (3.2 %)	11 (5.8 %)	8 (4.3 %)
Pain	4 (2.1 %)	5 (2.7 %)	4 (2.1 %)	8 (4.3 %)
Cardiovascular system				
Prolonged QTc interval	6 (3.2 %)	4 (2.2 %)	3 (1.6 %)	1 (0.5 %)
Digestive system				
Dyspepsia	2 (1.1 %)	6 (3.2 %)	2 (1.1 %)	0 (0.0 %)
Nervous system				
Dry mouth	3 (1.6 %)	4 (2.2 %)	1 (0.5 %)	2 (1.1 %)
Somnolence	3 (1.6 %)	4 (2.2 %)	1 (0.5 %)	1 (0.5 %)
Respiratory system				
Pharyngitis	6 (3.2 %)	3 (1.6 %)	5 (2.6 %)	8 (4.3 %)
Rhinitis (URI)	5 (2.7 %)	3 (1.6 %)	4 (2.1 %)	7 (3.8 %)
Sinusitis	4 (2.1 %)	3 (1.6 %)	6 (3.2 %)	3 (1.6 %)
[*] Events reported by ≥3% of patients in any group is listed (number and %) as Costart preferred term. Dry mouth is included because of the relevance of this adverse event to this application.				
Source: v 2.126, p 106, 122				

11.3.4.3. Premature withdrawals due to adverse events

A total of 20 patients were withdrawn due to adverse events (Table 117). The events are summarized in Table 122. Two patients had serious adverse events, but only one was discontinued, a 41 year old Caucasian male (00401) in the 10 mg loratadine group had acute appendicitis on Day 8 of the study. (v 2.126, p 112)

Table 122. EBA.GMA.402, Discontinued patients due to adverse events

Group	Patient	Event	Severity	Relationship to study med.
Placebo	00370	Euphoria	Moderate	None
		Insomnia	Moderate	None
		Anxiety	Moderate	Possible
E 10 mg	00004	Sinusitis	Mild	None
	00342	Headache	Severe	Possible
	00434	URI	Moderate	None
		Viral pharyngitis	Moderate	None
	00657	Abdominal pain	Severe	Possible
	00689	URI	Severe	None
	00764	Sinusitis	Moderate	None
E 20 mg	00432	Sinusitis	Mild	Remote
L 10 mg	00027	Mononucleosis	Moderate	None
	00091	Intestinal flu	Moderate	None
	00267	Bronchitis	Moderate	None
	00271	Sore throat	Moderate	None
		Sinusitis	Moderate	None
	00394	URI	Mild	None
		Conjunctivitis	Mild	Remote
	00401	Appendectomy	Severe	None
	00465	URI	Moderate	None
	00521	URI	Moderate	None
	00551	Sinusitis	Moderate	None
	00564	Sinusitis	Moderate	None
	00662	Sinusitis	Moderate	None
		Bilat cervical adenopathy	Mild	None
	00764	Flu	Moderate	None
Source: v 2.130, p 79-81				

11.3.4.4. Physical examination, ECG, and laboratory measures

There were no clinically significant changes in physical examination or vital signs in any of the patients. Table 123 shows selected laboratory parameters that exhibited shifts over the course of the study. Several of these are predicted, such as the elevation in eosinophil counts. For all treatments there was a trend towards a shift from normal to high in SGOT and SGPT. Thirteen patients experienced laboratory parameter adverse events at the last visit (2 ebastine 10 mg, 7 ebastine 20 mg, 3 loratadine, 1 placebo). Of these, one patient in the 10 mg ebastine group, two patients in the 20 mg ebastine group, and one patient in the loratadine group had elevations in both SGOT and SGPT at the final visit, as shown in Table 124. (v 2.126, p 129-30)

Table 123. EBA.GMA.402, Selected laboratory parameters shift table

Laboratory Parameter	Ebastine 10 mg (n=188)				Ebastine 20 mg (n=186)				Loratadine 10 mg (n=189)				Placebo (n=186)			
	N	L	N	H	N	L	N	H	N	L	N	H	N	L	N	H
Creatinine	0		3		0		0		0		1		0		2	
Glucose	1		4		1		4		3		3		1		2	
SGOT	0		5		0		3		0		7		0		4	
SGPT	0		6		0		6		0		6		0		7	
Uric acid	0		8		0		1		1		6		0		8	
Eosinophils	0		7		0		3		0		2		0		3	
RBC in UA	0		5		0		5		0		7		0		4	
WBC in UA	0		4		0		4		0		5		0		1	
Source: v 2.126, p 129																

Table 124. EBA.GMA.402, Patients who experienced elevations in SGOT or SGPT

Group	Patient	Age / Sex	Laboratory Event	Baseline Value	Final Value
E 10 mg	00103	27 F	SGOT	24	43
			SGPT	15	68
E 20 mg	00670	33 M	SGOT	33	51
			SGPT	66	115
	00852	26 M	SGOT	27	48
			SGPT	31	55
L 10 mg	00681	40 M	SGOT	32	59
			SGPT	65	79
Upper limits of normal for SGOT = 36 U/L, SGPT = 43 U/L					
Source: v 2.126, p 129					

The study enrolled patients who had no history of QTc prolongation, and had a QTc < 444 milliseconds at baseline. The results of the QTc data analysis is shown in Table 125 and patients with a ≥ 20 msec increase from baseline in QTc interval are shown in Table 126. The mean change from baseline in QTc interval for those patients with a prolonged QTc at the final visit was 22 ± 9 msec for 10 mg ebastine, 26 ± 12 msec for 20 mg ebastine, 21 ± 4 msec for 10 mg loratadine, while no patients in the placebo group had a prolongation of QTc. One 37 year old female patient from the 10 mg ebastine group (00009) had deep T-wave inversion suggesting ischemia at both the screening and the final visit (not noted at the screening visit). One 64 year old male patient (00845) in the 10 mg loratadine group had Q waves in the inferior leads, suggesting old cardiac infarction (QTc interval increased 8 msec during the study).

Table 125. EBA.GMA.402, Summary of Rate, QT and QTcB changes

Parameter	Treatment	N	Baseline mean	Post-treatment mean	Mean change
Rate (beat/min)	E 10 mg	186	66.610	71.474	4.614
	E 20 mg	188	64.697	72.178	7.708
	L 10 mg	189	66.283	71.011	4.927
	Placebo	186	65.670	69.769	4.325
QT (msec)	E 10 mg	186	392	383	-9
	E 20 mg	188	398	382	-16
	L 10 mg	189	395	384	-12
	Placebo	186	393	385	-9
QTcB (msec)	E 10 mg	186	405	407	2
	E 20 mg	188	406	408	1
	L 10 mg	189	408	407	-1
	Placebo	186	404	406	1
Source: v 2.126, p 119					

Table 126. EBA.GMA.402, Patients with ≥ 20 msec change from baseline in QTcB

Treatment	Patient	Age Sex	Baseline QTcB (msec)	Final QTcB (msec)	Change from baseline in msec
E 10 mg	00235	44 F	424	454	30
	00238	65 F	437	469	32
	00768	40 F	418	446	28
E 20 mg	00221	51 M	420	448	28
	00328	43 F	418	450	32
	00603	44 F	412	447	35
L 10 mg	00218	17 M	442	463	21
	00226	64 F	434	459	25
Placebo	None				
* Non-specific intraventricular block and T-wave abnormality					
Source: v 2.126, p 118					

11.3.5. Conclusion from EBA.GMA.402 study results

Like studies CM.030.ALGY and CM.031.ALGY, this study evaluates the efficacy and safety of ebastine 20 mg/day and 10 mg/day compared to loratadine 10 mg/day in patients with SAR. Like study CM.030.ALGY, the primary efficacy comparison between ebastine 20 mg/day and loratadine 10 mg/day failed to show a statistically significant difference between ebastine 20 mg and loratadine 10 mg for the composite endpoint of total rhinitis scores. However, individual scores for nasal discharge and sneezing showed statistically significant differences between ebastine 20 mg and loratadine 10 mg. The step-down efficacy comparisons between ebastine 10 mg/day and loratadine 10 mg/day for individual scores were not statistically significant. Secondary efficacy comparisons between ebastine 20 mg/day, ebastine 10 mg/day, and loratadine 10 mg/day with placebo showed that all active treatments were effective in relieving symptoms of SAR. Ebastine 10 mg was roughly equal in efficacy to loratadine 10 mg. In addition, AM snap shot scores suggest efficacy over the dosing interval. The results of this study support the efficacy of ebastine 20 mg QD and 10 mg QD for relief of ragweed SAR symptoms, but do not support the claim

that ebastine 20 mg was statistically superior to loratadine 10 mg. Safety parameters collected during the study show that ebastine was well tolerated in this study group.

11.4. M/EBS/28: Multicenter, double-blind, parallel group, randomized comparison of ebastine 20 mg versus loratadine 10 mg and placebo in patients with seasonal allergic rhinitis.

11.4.1. Investigators and centers

The study was conducted in 21 sites in the US between September and November of 2001 (v 2.146, p 26). The principal investigators, study sites, and number of patients enrolled are listed below (v 2.146, p 38-40).

Bob Berkowitz, MD, Woodstock, Georgia	40 patients
Albert Finn, MD, Charleston, South Carolina	30 patients
Linda Ford, MD, Papillion, Nebraska	20 patients
Gary Gross, MD, Dallas, Texas	40 patients
Frank Hampel, Jr, MD, New Braunfels, Texas	50 patients
William Howland III, MD, Austin, Texas	34 patients
Robert Jacobs, MD, San Antonio, Texas	50 patients
Kirk Kinberg, MD, Lincoln, Nebraska	30 patients
John Klimas, MD, Charlotte, North Carolina	25 patients
William Lumry, MD, Dallas Texas	30 patients
Bruce Martin, DO, San Antonio, Texas	50 patients
Dale Mohar, MD, Kerrville, Texas	60 patients
Anjuli Nayak, MD, Bloomington, Illinois	20 patients
Nicholas Nayak, MD, Peoria, Illinois	20 patients
Paul Ratner, MD, San Antonio, Texas	60 patients
Constantine Saadeh, MD, Amarillo, Texas	36 patients
Eric Schenkel, MD, Easton, Pennsylvania	18 patients
Tommy Slim, MD, Friendswood, Texas	23 patients
Julius Van Bavel, MD, Austin, Texas	25 patients
Suzanne Weakly, MD, Houston, Texas	35 patients
John Yarbrough, MD, Gainesville, Georgia	7 patients

11.4.2. Study protocol and design

Except for minor differences described below, the study protocol was identical to that of studies CM.030.ALGY, CM.031.ALGY, and EBA.GMA.402, and therefore will not be repeated here. [*Note: For a full discussion of the basic protocol, please refer to the description of protocol CM.030.ALGY beginning on page 133*]

This study compared ebastine 20 mg, loratadine 10 mg, and placebo, but did not study ebastine 10 mg. Lot numbers were not the same as for the other comparative studies. The previous three comparative studies restricted enrollment to patients who were sensitive to ragweed, but this study enrolled patients who were also sensitive to other fall allergens. Due to shipping delays, the enrollment duration was also increased from 7 to 14 days

(Amendment 2, v 2.147, p 76). Patients who had been enrolled in studies 030, 031, or 402 could not be enrolled in this study. The primary endpoint was changed from the four-week double-blind treatment period to the first two weeks of treatment, but the primary variable remained the comparison between ebastine 20 mg and loratadine 10 mg for the total rhinitis score. Powering calculations changed; a sample size of 115 patients per group was calculated to detect difference between treatments of 0.9 unit in the 24-hour symptom score with a power of 80% at a two-sided α level of 0.05 and a standard deviation of 2.8. In addition, the randomization schema was different, randomizing patients in a 2:2:1 fashion for ebastine:loratadine:placebo to obtain 230:230:115 patients per group. Blinding was changed from one capsule enclosing the study drugs to a double-dummy technique using ebastine or placebo tablets plus loratadine or placebo capsules. Unlike the previous comparative studies, the protocol specified exclusionary criterion of QTc by Bazett's correction, as read at the study site. The ECG inclusion/exclusion criteria were otherwise the same as for the previous comparative studies. All ECGs were also sent to eResearch Technology's (Peterborough, UK) for reading using a high-resolution ECG measurement system, with calculation of QTc by Bazett and Fridericia correction (v 2.146, p 68-9, v 2.147, p83-6). Finally, in selected patients the study evaluated bioavailability of both ebastine and loratadine and their respective metabolites at baseline and at the final visit, 3-5 hours after the last dose (at about the same time as the final ECG) (v 2.147, p 16).

11.4.3. Results

11.4.3.1. Patients enrolled/analyzed

A total of 703 patients were randomized, of whom 85 patients (12.1%) discontinued from the study during double blind treatment period. Disposition of the randomized patients and reasons for discontinuation is shown in Table 127. All patients had baseline and symptom score data, and were therefore included in the ITT population (n = 703) analysis. (v 2.146, p 100)

Table 127. M/EBS/28, Disposition of study patients

	Ebastine 20 mg	Loratadine 10 mg	Placebo	Total
Enrolled	282	279	142	703
Completed 4 weeks of Tx	249	250	119	618
Discontinued	33	29	23	85
Reasons for discontinuation:				
Drug ineffective	3	6	6	15
Adverse event	9	6	3	18
Protocol deviation	16	14	11	41
Lost to follow-up	1	0	1	2
Consent withdrawn	1	1	1	3
Others *	3	2	1	6
* Six patients were discontinued due to: did not bring back diary cards (1), leaving town or moving out of state (2), took extra medication throughout the study (1), and prior participation in an ebastine study (1).				
Source: v 2.146, p 71				

11.4.3.2. Subject demographics

Demographic data by treatment group are summarized in Table 128. The majority of patients were Caucasian. Like studies CM.031.ALGY and EBA.GMA.402, this study enrolled a significant number of Hispanic patients to all groups. There were no important demographic differences between the treatment groups. There were no important differences between treatment groups regarding medical history, medications, or positive skin test reactivity.

Table 128. M/EBS/28, Demographic summary

	Ebastine 20 mg	Loratadine 10 mg	Placebo	Total
Number	282	279	142	703
Sex: male/female %	39/61	39/61	37/63	
Age: years (range)	38 (12-75)	39 (12-70)	38 (12-70)	38 (12-70)
12-17 years N	24	18	14	56
Race:				
Cauc./Black/Hisp/others %	74/9/16/1	74/6/19/2	68/10/18/4	
Source: v 2.146, p 76				

11.4.3.3. Protocol deviations

There were no significant deviations from the protocol in this study.

11.4.3.4. Efficacy endpoint outcomes

Results of the total reflective rhinitis symptom scores for the first two weeks of the treatment period as well as individual, and 'nasal index' (total nasal symptom score or TNSS)[total rhinitis score minus the total eye symptom score] for the ITT population are shown in Table 129, whereas the results for total reflective rhinitis symptom scores by treatment week and for the 4-week treatment period are shown in Table 130.

The primary efficacy analysis [shown in **bold** in Table 129] of change from baseline in reflective total rhinitis scores over the first two weeks of the 4-week treatment period for ebastine 20 mg compared to loratadine 10 mg was statistically significant (p = 0.0018 for the primary variable).

Ebastine 20 mg also showed statistically significant differences from loratadine 10mg in secondary comparisons for composite scores and individual scores. These scores were significant starting in Week 1, and continuing through the entire four weeks of the study. Because of the unequal randomization, this study was not specifically powered for the comparisons between either of the active drugs and placebo. However, unlike previous comparative studies, only ebastine 20 mg showed statistically significant differences from placebo for all composite and each of the five individual reflective scores, whereas the comparison between loratadine 10mg and placebo was not significant.

There was no evaluation of overall efficacy based on gender, race, or age groups (12-16 years, 17-59 years, over 60 years).

Table 129. M/EBS/28, Reflective rhinitis symptom scores[†] for the first two weeks of the treatment period, ITT population

Reflective Score	Treatment	N	Baseline mean	Change from baseline, LS mean±SE	Change from baseline LS % mean	p-value vs. loratadine*	p-value vs. placebo*
Total Rhinitis[†]	E 20 mg	282	10.76	-3.46 ± 0.16	-32.3	0.0018	0.0024
	L 10 mg	278	10.59	-2.77 ± 0.17	-24.6		0.6292
	Placebo	141	10.84	-2.64 ± 0.23	-23.4		
Nasal Index (TNSS)	E 20 mg	282	8.58	-2.74 ± 0.13	-31.9	0.0016	0.0032
	L 10 mg	278	8.49	-2.18 ± 0.13	-24.2		0.7194
	Placebo	141	8.63	-2.10 ± 0.18	-23.5		
Nasal Discharge	E 20 mg	282	2.21	-0.67 ± 0.04	-25.7	0.0045	0.0044
	L 10 mg	278	2.28	-0.53 ± 0.04	-21.5		0.6013
	Placebo	141	2.32	-0.50 ± 0.05	-19.9		
Congestion	E 20 mg	282	2.39	-0.62 ± 0.04	-25.1	0.0033	0.0315
	L 10 mg	278	2.37	-0.48 ± 0.04	-18.6		0.7959
	Placebo	141	2.37	-0.50 ± 0.05	-18.4		
Sneezing	E 20 mg	282	1.85	-0.72 ± 0.04	-38.9	0.0075	0.0013
	L 10 mg	278	1.81	-0.58 ± 0.04	-25.0		0.2994
	Placebo	141	1.86	-0.52 ± 0.05	-19.9		
Nasal Itch	E 20 mg	282	2.13	-0.73 ± 0.04	-35.1	0.0065	0.0191
	L 10 mg	278	2.03	-0.58 ± 0.04	-22.3		0.9147
	Placebo	141	2.08	-0.58 ± 0.05	-25.8		
Total Eye Symptoms	E 20 mg	282	2.18	-0.72 ± 0.04	-33.5	0.0207	0.0066
	L 10 mg	278	2.10	-0.59 ± 0.04	-25.4		0.4137
	Placebo	141	2.21	-0.54 ± 0.06	-27.3		

* Significant p values are shaded
[†] Rhinitis symptom score = sum of nasal discharge, nasal stuffiness, sneezing, itchy nose, and itchy/watery eyes over the first 2 weeks of the 4-week study

Source: volume 2.146, p 101-4

Table 130. M/EBS/28, Reflective total rhinitis symptom scores by treatment week and over 4-week treatment period, ITT population

Reflective Score	Treatment	N	Baseline mean	Change from baseline, LS mean±SE	Change from baseline LS % mean	p-value vs. loratadine*	p-value vs. placebo*
Week 1	E 20 mg	282	10.76	-3.27 ± 0.16	-30.5	0.0049	0.0014
	L 10 mg	278	10.59	-2.66 ± 0.16	-24.0		0.3743
	Placebo	141	10.84	-2.42 ± 0.22	-21.4		
Week 2	E 20 mg	282	10.76	-3.66 ± 0.19	-34.1	0.0022	0.0195
	L 10 mg	278	10.59	-2.88 ± 0.19	-25.4		0.8647
	Placebo	141	10.84	-2.94 ± 0.26	-26.9		
Week 3	E 20 mg	282	10.76	-4.07 ± 0.19	-38.2	0.0084	0.0197
	L 10 mg	278	10.59	-3.38 ± 0.20	-30.2		0.8505
	Placebo	141	10.84	-3.31 ± 0.27	-30.5		
Week 4	E 20 mg	282	10.76	-4.27 ± 0.20	-39.9	0.0066	0.0472
	L 10 mg	278	10.59	-3.52 ± 0.20	-31.8		0.8377
	Placebo	141	10.84	-3.59 ± 0.29	-32.5		
Over 4 weeks	E 20 mg	282	10.76	-3.78 ± 0.17	-35.3	0.0024	0.0039
	L 10 mg	278	10.59	-3.09 ± 0.17	-27.6		0.6901
	Placebo	141	10.84	-2.98 ± 0.23	-26.8		

Reflective Score	Treatment	N	Baseline mean	Change from baseline, LS mean±SE	Change from baseline LS % mean	p-value vs. loratadine*	p-value vs. placebo*
* Significant p values are shaded † Rhinitis symptom score = sum of nasal discharge, nasal stuffiness, sneezing, itchy nose, and itchy/watery eyes							
Source: v 2.151, p 53-4; v 2.153, p 1-4							

Secondary analyses also included snap shot rhinitis symptom scores (AM, PM and daily) analyzed for the double-blind treatment period and for each week of treatment. These were analyzed for the total rhinitis symptom score, individual, and 'nasal index' (TNSS) for the ITT population. Snap shot scores are presented in summary fashion only in Table 131.

Table 131. M/EBS/28, Snap shot total rhinitis symptom scores[†] for the first two weeks of the treatment period, ITT population

Snap Shot Total Rhinitis Score	Treatment	N	Baseline mean	Change from baseline, LS mean±SE	Change from baseline LS % mean	p-value vs. loratadine*	p-value vs. placebo*
Daily	E 20 mg	282	10.34	-3.17 ± 0.17	-28.3	0.0080	0.0068
	L 10 mg	278	10.29	-2.57 ± 0.17	-21.9		0.5945
	Placebo	141	10.32	-2.43 ± 0.23	-20.0		
AM	E 20 mg	282	10.40	-3.01 ± 0.17	-24.0	0.0061	0.0067
	L 10 mg	278	10.35	-2.39 ± 0.17	-18.9		0.6443
	Placebo	141	10.32	-2.26 ± 0.23	-15.8		
PM	E 20 mg	282	10.28	-3.33 ± 0.18	-31.2	0.0152	0.0099
	L 10 mg	278	10.22	-2.75 ± 0.18	-23.2		0.5533
	Placebo	141	10.30	-2.58 ± 0.23	-22.5		
* Significant p values are shaded † Rhinitis symptom score = sum of nasal discharge, nasal stuffiness, sneezing, itchy nose, and itchy/watery eyes							
Source: volume 2.146, p 118, 121, 124							

11.4.4. Safety outcomes

11.4.4.1. Total drug exposure

All patients enrolled in the study were included in the safety analysis. The mean duration of exposure was 27.9 days for the 20 mg ebastine group, 28.1 days for the loratadine group, and 27.1 days for the placebo group. Compliance was 95.7% for the 20 mg ebastine group, 95.5% for the loratadine group, and 93.4% for the placebo group. (v 2.146, p 136)

11.4.4.2. Adverse events

Adverse events reported by at least 3% of patients in any treatment group are presented in Table 132. The majority of the adverse events were mild to moderate and not (or remotely) related to the study medication. There were 34 severe adverse events reported in this study, most of which were considered not to be related to the study medication. The only severe adverse events reported by two or more patients within a treatment group were two cases of headache in the 10 mg loratadine group.

There were two pregnancies and one serious adverse event during the study. A 37 year old black female (00035) on 10 mg loratadine had a negative screening β–HCG, but positive β–HCG on the final visit. She had been on Ortho Novum 1/35 during the study, but had

missed at least one day. She miscarried one month later. A 21 year old Caucasian female (00718) on placebo had a negative screening β–HCG, but positive β–HCG on the final visit. She had been on Orthotricyclen during the study, but had missed several days. The study report states that the patient is being followed during the pregnancy. A 62 year old Caucasian female (00535) on 10 mg loratadine had diverticulitis the day after completing the study. The adverse event was considered not related to study drug. There were no deaths. (v 2.146, p 144-5)

Table 132. M/EBS/28, Common adverse experience reported by patients[*]

	Ebastine 20 mg (n=282)	Loratadine 10 mg (n=279)	Placebo (n=142)
Total with adverse experience	83 (29.4 %)	93 (33.3 %)	36 (25.4 %)
Body as a whole			
Headache	2 (0.7 %)	10 (3.6 %)	3 (2.1 %)
Infection	12 (4.3 %)	6 (2.2 %)	0 (0.0 %)
Pain	6 (2.1 %)	9 (3.2 %)	1 (0.7 %)
Cardiovascular system			
Prolonged QTc interval	11 (3.9 %)	10 (3.6 %)	8 (5.6 %)
Nervous system			
Dry mouth	8 (2.8 %)	0 (0.0 %)	2 (1.4 %)
Somnolence	2 (0.7 %)	1 (0.4 %)	1 (0.7 %)
Respiratory system			
Pharyngitis	6 (2.1 %)	10 (3.6 %)	2 (1.4 %)
[*] Events reported by ≥3% of patients in any group is listed (number and %) as Costart preferred term. Dry mouth is included because of the relevance of this adverse event to this application.			
Source: v 2.146, p 138, 160			

11.4.4.3. Premature withdrawals due to adverse events

A total of 19 patients were withdrawn due to adverse events (Table 127). The events are summarized in Table 133.

Table 133. M/EBS/28, Discontinued patients due to adverse events

Group	Patient	Event	Severity	Relationship to study med.
Placebo	00463	Sinusitis	Severe	None
	00522	Sinusitis	Moderate	None
	00718	Pregnancy	Severe	None
E 20 mg	00128	Sinusitis	Moderate	Unlikely
	00143	URI	Moderate	None
	00218	Accidental injury, abrasions Pain from fractured ribs	Severe	None
	00252	URI	Mild	None
	00456	Abdominal pain, diarrhea	Moderate	Possible
	00525	Sinusitis	Moderate	None
	00617	URI	Mild	None
	00701	Rash	Mild	Possible
	00713	URI	Moderate	None
L 10 mg	00043	Poison sumac	Moderate	None
	00069	URI	Mild	Unlikely

Group	Patient	Event	Severity	Relationship to study med.
	00134	Dizziness	Severe	Possible
		Stomach cramps	Moderate	Possible
	00248	URI	Mild	None
	00377	URI	Severe	None
	00461	Headache	Mild	None
	00587	Back pain	Moderate	None
Source: v 2.155, p 51-2				

11.4.4.4. Physical examination, ECG, and laboratory measures

There were no clinically significant changes in physical examination or vital signs in any of the patients. Table 134 shows selected laboratory parameters that exhibited shifts over the course of the study. Several of these are predicted, such as the elevation in eosinophil counts. For both active treatments there was a trend towards a shift from normal to high in ALT and AST. One patient (00611) on placebo experienced laboratory parameter adverse event at the last visit of mild bilirubinemia. (v 2.146, p 169)

Table 134. M/EBS/28, Selected laboratory parameters shift table

Laboratory Parameter	Ebastine 20 mg (n=282)		Loratadine 10 mg (n=278)		Placebo (n=142)	
	N L	N H	N L	N H	N L	N H
ALT	0	8	0	10	0	5
AST	0	8	0	7	0	1
BUN	0	7	1	8	1	2
Cholesterol	0	23	0	17	0	11
Creatinine	0	2	0	1	0	2
Glucose	5	39	7	40	2	23
Uric acid	3	6	3	17	0	7
Eosinophils	0	18	0	28	0	14
Lymphocytes	1	21	1	15	2	4
Ketones in UA	0	21	0	12	0	8
Protein in UA	0	8	0	1	0	2
RBC in UA	0	40	0	36	0	17
Epithelial cells in UA	0	49	0	47	0	23
WBC in UA	0	55	0	66	0	17
Source: v 2.146, p 168						

The study enrolled patients who had no history of QTc prolongation, and had a QTcB < 444 milliseconds at baseline. The results of the QTc data analysis is shown in Table 135 and patients with a ≥ 20 msec increase from baseline in QTc interval are shown in Table 136. Retrospective analyses of QTc by Bazett and Fridericia corrections, along with outliers (patients with QTc corrected by either method who had a QTc of >440 msec and an individual increase of >10 msec over baseline) are shown in Table 137 and Table 138.

Table 135. M/EBS/28, Summary of Rate, QT and QTcB changes

Parameter	Treatment	N	Baseline mean	Post-treatment mean	Mean change
Rate (beat/min)	E 20 mg	281	65.738	71.332	5.610
	L 10 mg	278	64.342	71.687	5.322
	Placebo	141	65.670	68.847	3.397
QT (msec)	E 20 mg	281	395	384	-11
	L 10 mg	278	394	382	-13
	Placebo	141	399	390	-9
QTcB (msec)	E 20 mg	281	407	409	2
	L 10 mg	278	408	408	0
	Placebo	141	410	410	-1
Source: v 2.146, p 150; v 2.152, p 184-5, 218,					

Table 136. M/EBS/28, Patients with ≥ 20 msec change from baseline in QTcB (msec)

Treatment	Patient	Age Sex	Baseline QTcB (msec)	Final QTcB (msec)	Change from baseline in msec
E 20 mg	00096	62 F	428	448	20
	00158	45 F	423	447	25
	00337	71 F	423	446	23
	00375	57 F	397	457	60
	00444	31 F	441	463	22
	00685	12 M	424	447	23
	00716	45 M	386	441	55 *
L 10 mg	00033	53 M	433	466	33
	00050	64 F	424	447	23
	00468	67 M	415	450	35
	00680	35 F	430	457	27
	00687	56 M	427	448	21
	00730	62 F	428	475	37
Placebo	00279	55 F	435	398	-37 [†]
	00439	56 F	426	450	24
	00480	49 F	426	456	30
	00536	50 M	422	453	31
	00576	26 M	414	458	44
	00686	52 F	439	471	32
* Increased heart rate of 99, repeat had heart rate of 73 [†] T-wave changes					
Source: v 2.146, p 149					

Table 137. M/EBS/28, Retrospective summary of QTcB and QTcF changes, ITT population

Parameter	Treatment	N	Baseline mean	Post-treatment mean	Mean change
QTcB (msec)	E 20 mg	280	396.56	401.31	4.632
	L 10 mg	277	397.81	400.49	2.841
	Placebo	139	399.86	400.75	1.00
QTcF (msec)	E 20 mg	280	391.04	390.29	-0.882
	L 10 mg	277	391.48	388.95	-2.379
	Placebo	139	394.32	391.87	-2.460
Source: v 2.152, p 218					

Table 138. M/EBS/28, Retrospective summary of outlier[†] QTc changes

Parameter	Treatment	N	Baseline mean	Post-treatment mean	Mean change	Difference from placebo
QTcB (msec)	E 20 mg	3	420.67	446.00	25.33	3.58
	L 10 mg	9	422.67	444.67	22.00	0.25
	Placebo	4	421.75	443.75	21.75	
QTcF (msec)	E 20 mg	0				
	L 10 mg	2	419.00	444.50	25.5	
	Placebo	0				
[†] QTc (B, F) >440 msec and individual increase >10 msec over baseline						
Source: v 2.152, p 218-						

11.4.5. Conclusion from M/EBS/28 study results

Like studies CM.030.ALGY, CM.031.ALGY, and EBA.GMA.402, this study evaluated the efficacy and safety of ebastine 20 mg/day compared to loratadine 10 mg/day in patients with SAR. Like study CM.031.ALGY, the primary efficacy comparison between ebastine 20 mg/day and loratadine10 mg/day was statistically significant for the composite endpoint of total rhinitis scores. Unlike two of the previous three studies where the only individual scores that were significant were nasal discharge and sneezing (CM.031.ALGY and EBA.GMA.402), all individual scores in this study were statistically significant for the comparison between ebastine 20 mg and loratadine 10 mg. In secondary efficacy comparisons between ebastine 20 mg/day and loratadine 10 mg/day with placebo, only ebastine was effective in relieving symptoms of SAR. Reflective total and individual scores by week support these findings. AM snap shot scores suggest efficacy over the dosing interval. The results of this study support the efficacy of ebastine 20 mg QD and 10 mg QD, and are the strongest of the four studies in supporting the claim that ebastine 20 mg was statistically superior to loratadine 10 mg for relief of ragweed SAR symptoms. Safety parameters collected during the study show that ebastine was well tolerated in this study group.

12. HIGH DOSE CARDIAC SAFETY STUDIES

In the original NDA submission, the applicant submitted two high-dose, multiple-dose studies (EBA 136, and EBA 126) to evaluate the high dose cardiac safety and pharmacokinetics of ebastine. In the complete response, the applicant submitted one further study (M/EBS/21), a single-dose, high-dose cardiac safety study. All the studies were done in young (18 to 40 years) healthy male volunteers. The highest dose of ebastine was 100 mg in study EBA 136, 80 mg in study EBA 126, and 500 mg in study M/EBS/21, which are 5-fold, 4-fold, and 25-fold respectively, higher than the proposed maximum dose of ebastine (20 mg). Whereas, EBA 136, and EBA 126 were multiple dose studies allowing evaluation at steady-state ebastine levels, M/EBS/21 was a single-dose study in which steady-state levels were not evaluated. No clinically significant arrhythmias were seen in any of the studies.

The applicant's initial submission of cardiac safety data was based on correction of QT values for differences in heart rate by a formula called the Bazett's formula. The applicant later questioned the validity of that correction method because ebastine was noted to cause some increase in heart rate. Subsequently the applicant submitted reanalysis of cardiac safety data using alternate methods of QT correction, such as Fridericia's method (QTcF), QTc by linear regression, and an individual patient correction method called Malik's correction (QTcM). The applicant's justification for re-analysis of the data by other methodology is that in the setting where heart rate is increased, Bazett's correction method tends to overcorrect the QT interval and is therefore not the most appropriate method. The applicant's argument is reasonable. However, one also has to keep in mind that some of the other methods of QT correction for heart rate may also undercorrect the QT.

The applicant's data from study EBA 136 were analyzed and verified by FDA medical and statistical reviewers during the original NDA cycle. The applicant presented the QTc change results as mean QTc, maximum QTc, and AUC QTc. Mean QTc change represents change of the mean QTc from serial ECG at the study day compared to the baseline. Maximum QTc change represents change of the maximum QTc from serial ECG at the study day compared to the maximum QTc at the baseline. In review of study EBA 136 (page 171), the applicant's analysis of data are used unless otherwise specified. Maximum QTc was also calculated from the applicant's data using alternate methods, such as the difference between the minimum QTc at baseline and the maximum QTc at study day. Results on this alternate calculation are very similar to that of the applicant's calculation.

12.1. EBA 136: A randomized, blinded, four-way crossover, electrocardiographic study of ebastine 60 mg/day and ebastine 100 mg/day compared to terfenadine 360 mg/day, and ebastine placebo in healthy adult male volunteers.

12.1.1. Investigators and center

The study was conducted at a single site in the US between August and November of 1995 (v 151, p 18).

Investigator: Dr. Joel Morganroth (PI) and Dr. Scott Waldman (co-investigator)
                   Research Data Worldwide
                   124 South 15th Street
                   Philadelphia, PA 19102-3010

ECG re-analysis: Marek Malik, MD, PhD, DSc (Med), FAAC, FESC
                   Dept. of Cardiological Services
                   St. Georges Hospital Medical School
                   London SW17 ORE
                   UK

12.1.2. Objectives

The objectives of this study were to compare the electrocardiographic effects of high doses of ebastine (60 mg QD, and 100 mg QD) to a high dose of terfenadine (360 mg QD) and to placebo and in normal volunteers, and to investigate the relationship between QTc prolongation and plasma ebastine/carebastine concentrations (v 151, p 18).

12.1.3. Study population

Study subjects were healthy male volunteers 18 to 40 years of age, with normal ECG (ECG exclusion criteria were similar to study EBA 132, page 95), and no relevant clinical, hematological, or biochemical abnormalities. Subjects were required not to have taken astemizole within 3 months, azole antifungals and macrolide antibiotics within 1 month, and any prescription or OTC medications within 2 weeks of the study (v 151, p 99).

12.1.4. Study design

This was a single-center, randomized, investigator-blinded, double-dummy, four-way crossover study (v 151, p 13).

12.1.5. Study procedures

The study procedures are outlined in Table 139. Thirty-two subjects were recruited and assigned in random sequence to 4 treatment periods (ebastine 60 mg QDAM, ebastine 100 mg QDAM, terfenadine 180 mg BID, and placebo) with 7 days of dosing in each period separated by a washout of at least 13 days. In each treatment period, subjects were admitted to a monitored facility 2 days prior to dosing for at least 9 consecutive nights. Each subject was administered study medication for 7 days to attain steady-state conditions. Baseline

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High Dose Cardiac Safety Studies, EBA 136

serial ECGs were done on day -1 and compared to steady-state serial ECGs done on days 5, 6, and 7. In addition, blood samplings were done following each ECG on day 7 in order to correlate ECG effects with plasma concentrations of ebastine and carebastine. Subjects were to be discontinued according to predetermined ECG criteria (QTc >500 msec for two or more ECGs in a single day, or a single increase in QTc over 30% from baseline mean QTc at day -1, or sustained ventricular tachycardia, or *Torsades de Pointes*, ventricular flutter, or ventricular fibrillation, or significant morphological changes, or at the discretion of the physician) and monitored until they revert to baseline (v151, p 18-32, 100-116).

All ECGs were read using Jandel Scientific Sigmascan technology by the investigator in a blinded fashion. The ECG to be measured was mounted on the Digitizing pad and the analysts used crosshair devices and a jeweler's magnifying lamp to measure the intervals. Interval measurements were performed across 4 consecutive cardiac cycles from the optimum technical portion of the lead II rhythm strip. If lead II rhythm strip was not adequate for analysis, lead 5 or the next best available lead was analyzed. QTc was automatically calculated by Bazett's formula on the mean of the RR/QT measurements ($QTc=QT/\sqrt{RR}$), where QTc is the corrected QT interval. An analysis of QTc dispersion was performed by measuring all QTc intervals from the 12-lead ECG for each time point and calculating the difference between the highest and lowest values. All ECG were also evaluated for morphological changes in wave form and for U waves (v 151, p 29-30).

Table 139. EBA 136, Plan of the study and schedule of observations

	Screen	Admit (day -2)	Baseline (day -1)	Dosing days							Release (day 8)	Washout (≥13 days)	End of study
				1	2	3	4	5	6	7			
Consent	x												
Medical history	x	x		x									
Physical exam	x												x
Laboratory	x*	x[†]	x[†]								x[†]		
Dosing[‡]				x----------------------x									
ECG**	x		x	x	x	x	x	x	x	x	x		
Telemetry					x	x	x	x	x	x			
PK sample			x						x		*		
Give diary	x												
Collect diary													x
Adverse event				x	x	x	x	x	x	x	x		x

* Urinalysis (glucose, blood, ketones, and protein), hematology (hemoglobin, hematocrit, WBC count, RBC count, and platelet count), and serum chemistry (creatinine, BUN, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, GGTP, calcium, phosphorus, Electrolytes: sodium, potassium, chloride, bicarbonate, magnesium) (v 151, p 112).
† Serum chemistry were repeated once predose and on day 8 for each treatment period (v 151, p 112).
‡ Blinded to the investigator. Subjects on QD regimen were dosed in the evening with placebo in order to match the BID regimen.
** On days -1, 5, 6, and 7 serial ECG done at 0 (predose), 2, 3, 4, 5, 6, 8, 12, and 23.5 hours

Source: v 151, p 20, 94, 95

12.1.6. Statistical considerations and analysis of QT interval

The sample size of 32 was chosen for this study in order to complete 24 evaluable subjects. A total of 24 subjects would provide 90% power to detect a mean difference of 15 msec

High Dose Cardiac Safety Studies, EBA 136

change from baseline QTc between ebastine treatment and terfenadine treatment at a two-sided test, and between ebastine treatments and placebo at a one-sided test. These assumptions were based on alpha level of 0.05 and a standard deviation of 20 msec that was derived from a previous ebastine study by the applicant. (v 151, p 34-39, 117)

The statistical calculation and the initial analysis were based on QT corrected for heart rate by Bazett's method (QTcB). The primary analysis was the difference in mean change from baseline QTcB measurements (day -1) to steady-state QTc measurements (day 7) in mean QTcB, maximum QTcB, and AUC_{0-12hr} between both ebastine groups versus placebo (one-sided test), terfenadine versus placebo (one-sided test), and both ebastine groups versus terfenadine (two-sided test). The principal analysis was an ANOVA for a crossover trial with the model containing main effects for treatment, period, sequence, and subject nested with sequence. To establish that QTcB changes reached plateau at day 7, one-sided t-test at 5% level of significance was done between values at day 7 and day 5 and then between day 7 and day 6. A linear regression analysis was used to investigate the pharmacokinetic and pharmacodynamic relationship.

Subsequent analyses (post-hoc) corrected QT by various other methods, including Fridericia's method (QTcF), QTc by linear regression, Framingham correction, and an individual patient correction method called Malik's correction (QTcM). In the results section below, initially the results based on QTcB are presented, followed by results based on other correction methodology.

12.1.7. Results

A total of 32 subjects were enrolled in the study. The age range was from 19 years to 40 years, and there were 12 Caucasians, 16 blacks, 3 Hispanics, and 1 oriental in the group. Nine subjects discontinued for reasons shown in Table 140. The discontinuation rate between the groups was not different. No subject was discontinued due to the ECG discontinuation criteria. Of the laboratory parameters, elevation in liver enzyme was seen for all treatment groups as shown in Table 141. The reason for elevation of transaminases is not clear, the possibility of drug causing the elevation cannot be established or excluded from this study (v 151, p 16, 40-77).

Results of the primary analysis of the primary population (subjects who completed at least placebo and ebastine 100 mg/day treatment) is shown in Table 142, and subjects defined as ECG outliers (444 msec prolongation of QTcB and at least 10 msec prolongation of QTcB over baseline) are shown in Table 143. Mean QTcB change over baseline for the different treatment group is shown in Figure 6. QTcB changes at days 5, 6, and 7 showed that day 7 responses reached a plateau. The ebastine 100 mg/day and the terfenadine 360 mg/day groups exhibited statistically significant QTcB prolongation compared to the placebo group. The QTcB prolongation for the ebastine 60 mg/day group was not significantly different from the placebo group. Results of QTcB dispersion are shown in Table 144. There were no differences in QTcB dispersion between the treatment groups. On PK/PD linear regression analysis there was a statistically significant relationship between increasing ebastine and carebastine plasma concentration and QTcB interval changes from the baseline.

Subsequent analyses of QT by other methods, including QTcF, and QTc regression are shown in Table 145. While QTcB showed a dose-ordered relationship between dosage and QTc, this relationship was less clear with other analyses.

Table 140. EBA 136, Reasons for discontinuation

Subject	Treatment before discontinuation	Reason for discontinuation
00005	Ebastine 60 mg/day	Consent withdrawn
00008	Placebo	Consent withdrawn
00009	Ebastine 100 mg/day	Laboratory adverse event[*]
00013	Ebastine 100 mg/day	Consent withdrawn
00015	Ebastine 60 mg/day	Consent withdrawn
00016	Terfenadine 360 mg/day	Lost to follow-up
00020	Placebo	Adverse clinical experience[†]
00025	Terfenadine 360 mg/day	Consent withdrawn
00031	Ebastine 60 mg/day	Deviation from protocol

[*] Three-fold elevated GGTP after first treatment period of ebastine 100 mg/day for 7 days
[†] Patient had dizziness and a near syncopal episode while micturating. On telemetry the rhythms were narrow complex supraventricular tachycardia progressing to asystole for 5 seconds, then to atrial fibrillation, and finally to normal sinus rhythm.

Source: v 151, p 41, 44

Table 141. EBA 136, Subjects with >50% elevation of transaminases

	SGOT	SGPT	GGTP
Ebastine 60 mg	3 (10.3%)	9 (31.0%)	1 (3.5%)
Ebastine 100 mg	4 (14.3%)	11 (39.3%)	3 (10.7%)
Terfenadine 360 mg	4 (13.8%)	5 (17.2%)	3 (10.3%)
Placebo	2 (6.7%)	3 (10.0%)	0 (0.0%)

Results expressed as number of subjects (% of total)

Source: v 151, p 55, 56

Table 142. EBA 136, Summary of primary analysis of QTcB results for the primary population

Variable	Treatment	N	Baseline mean	Adjusted[*] mean change from baseline (SE)	One-sided p-value vs. placebo	Two-sided p-value vs. terfenadine
Mean QTcB (msec)	Placebo	25	383.8	1.4 (2.5)		
	Ebastine 60 mg	24	384.8	3.7 (2.5)	0.2427	0.0000
	Ebastine 100 mg	25	380.9	10.3 (2.5)	0.0034	0.0195
	Terfenadine 360 mg	24	382.7	18.0 (2.5)	0.0000	
Maximum QTcB (msec)	Placebo	25	402.0	0.7 (3.4)		
	Ebastine 60 mg	24	404.3	2.2 (3.5)	0.3636	0.0121
	Ebastine 100 mg	25	399.3	8.2 (3.4)	0.0412	0.2321
	Terfenadine 360 mg	24	402.7	13.3 (3.5)	0.0022	
AUC QTcB (msec*hr)	Placebo	25	4609.0	13.2 (30.6)		
	Ebastine 60 mg	24	4613.0	49.9 (31.4)	0.1894	0.0002
	Ebastine 100 mg	25	4570.9	124.2 (30.6)	0.0041	0.0336
	Terfenadine 360 mg	24	4590.4	213.8 (31.4)	0.0000	

[*] Adjusted for imbalance of primary population (subjects with at least placebo and ebastine 100 mg) in each treatment

Source: v 151, p 59, v 155, p 11

Table 143. EBA 136, Subjects with QTcB prolongation of 440 msec and an increase of 10 msec above baseline

Subject	Treatment	Schedule*		QTc (msec)		
		Day	Time	Baseline	Observed*	Change
00024	Placebo	5	2 hr	429	451	22
00029	Ebastine 60 mg	1	- 30 min	396	457	61
00029	Ebastine 60 mg	6	8 hr	367	445	78
00017	Ebastine 100 mg	7	3 hr	394	442	48
00026	Ebastine 100 mg	6	6 hr	388	451	63
00029	Ebastine 100 mg	4	12 hr	388	446	58
00029	Ebastine 100 mg	7	2 hr	410	442	32
00004	Terfenadine 360 mg	3	12 hr	385	440	55
00004	Terfenadine 360 mg	5	12 hr	385	445	60
00004	Terfenadine 360 mg	7	12 hr	385	440	55
00008	Terfenadine 360 mg	7	3 hr	364	450	86
00010	Terfenadine 360 mg	5	12 hr	402	442	40
00014	Terfenadine 360 mg	6	6 hr	389	440	51
00018	Terfenadine 360 mg	7	5 hr	385	445	60
00029	Terfenadine 360 mg	6	5 hr	410	443	33
* Time at which the prolongation of QTc was observed						
Source: v 151, p 49						

Table 144. EBA 136, Summary of QTcB dispersion results for the primary population

Variable	Treatment	N	Baseline mean	Adjusted* mean change from baseline (SE)	One-sided p-value vs. placebo	Two-sided p-value vs. terfenadine
Mean QTcB (msec)	Placebo	25	53.5	-1.3 (1.6)		
	Ebastine 60 mg	24	49.0	-0.5 (1.7)	Not signif.	Not signif.
	Ebastine 100 mg	25	51.9	-3.1 (1.6)	Not signif.	Not signif.
	Terfenadine 360 mg	24	53.3	-2.6 (1.7)	Not signif.	
Maximum QTcB (msec)	Placebo	25	78.3	-2.3 (3.8)		
	Ebastine 60 mg	24	73.3	-4.0 (3.9)	Not signif.	Not signif.
	Ebastine 100 mg	25	76.3	-5.9 (3.8)	Not signif.	Not signif.
	Terfenadine 360 mg	24	76.0	-4.6 (3.9)	Not signif.	
AUC QTcB (msec*hr)	Placebo	25	636.6	-13.1 (22.3)		
	Ebastine 60 mg	24	577.3	0.07 (23)	Not signif.	Not signif.
	Ebastine 100 mg	25	617.1	-26.7 (22.3)	Not signif.	Not signif.
	Terfenadine 360 mg	24	652.0	-46.0 (22.9)	Not signif.	
* Adjusted for imbalance of primary population (subjects with at least placebo and ebastine 100 mg) in each treatment						
Source: v 151, p 62						

Change in Mean QTc
From baseline
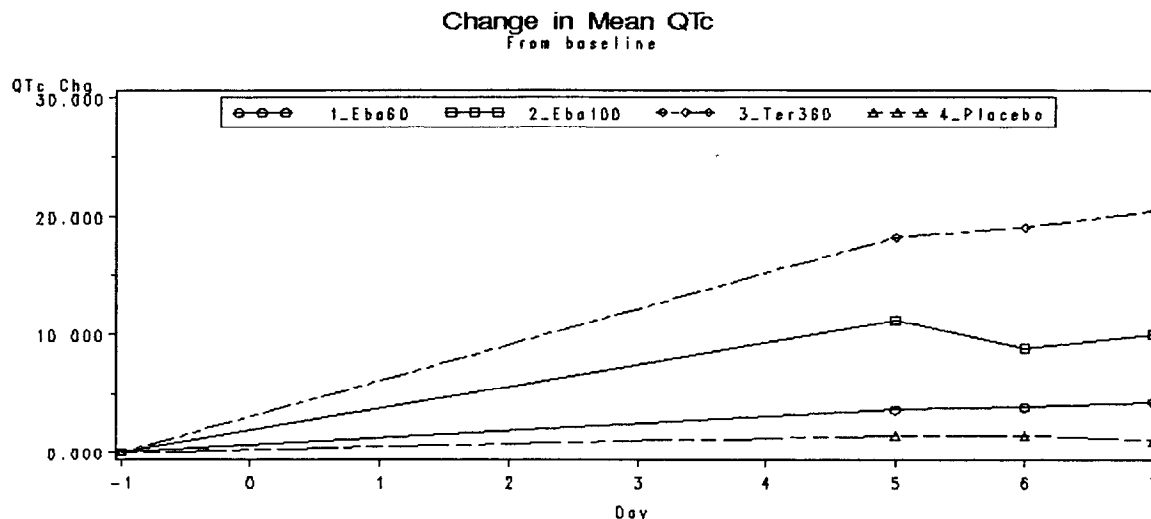
Figure 6. EBA 136, Mean QTcB change of the different treatment groups as compared to baseline
Figure created from applicant's submitted data

Table 145. EBA 136, Corrected and uncorrected mean QT results (multiple QTc analyses)

	Treatment	N	Baseline mean	Adjusted* mean change from baseline (SE)	One-sided p-value vs. placebo	Two-sided p-value vs. terfenadine
Mean Heart Rate (bpm)	Placebo	25	62.5	3.5 (1.0)		
	Ebastine 60 mg	24	62.0	7.6 (1.0)	0.0020	0.0128
	Ebastine 100 mg	25	61.5	9.3 (1.0)	0.0000	0.0003
	Terfenadine 360 mg	24	61.9	4.1 (1.0)	0.3367	
Mean QT[†] (msec)	Placebo	25	378.8	-8.9 (2.4)		
	Ebastine 60 mg	24	380.5	-17.0 (2.5)	0.9877	0.0000
	Ebastine 100 mg	25	378.3	-15.2 (2.4)	0.9630	0.0000
	Terfenadine 360 mg	24	379.0	6.0 (2.5)	0.0000	
Mean QTcB[†] (msec)	Placebo	25	383.8	1.4 (2.5)		
	Ebastine 60 mg	24	384.8	3.7 (2.5)	0.2427	0.0000
	Ebastine 100 mg	25	380.9	10.3 (2.5)	0.0034	0.0195
	Terfenadine 360 mg	24	382.7	18.0 (2.5)	0.0000	
Mean QTcF[†] (msec)	Placebo	25	381.7	-2.1 (2.1)		
	Ebastine 60 mg	24	383.2	-3.2 (2.1)	0.6604	0.0001
	Ebastine 100 mg	25	379.8	1.5 (2.1)	0.0987	0.0001
	Terfenadine 360 mg	24	381.3	14.1 (2.1)	0.0000	
QTc regression (msec)	Placebo	25		-2.2		
	Ebastine 60 mg	24		-4.4		
	Ebastine 100 mg	25		-0.0		
	Terfenadine 360 mg	24		15.3		

* Adjusted for imbalance of primary population in each treatment
[†] QT is uncorrected QT interval, QTcB is Bazett's correction, and QTcF is Fridericia's correction

Source: v 1, p 2, 11/5/99 submission; QTc regression analysis from p 11, 1/5/00 submission

12.1.8. Conclusion

In this study ebastine and terfenadine both caused QTcB prolongation; the effect of terfenadine was more pronounced than ebastine at a dose 3 times the recommended dose for both drugs. The QTc effect was less prominent for the ebastine group when methods other than Bazett's correction were used for correction of the QT interval, presumably due to the effect of ebastine on heart rate. The effect of ebastine was dose-dependent, with more prolongation seen at the higher doses. The PK/PD analysis further supports the dose-dependency. In this study no other ECG abnormalities or clinical cardiac adverse events were seen.

12.2. EBA 126: A placebo-controlled, double-blind, parallel group cardiac safety and pharmacokinetic study of multiple doses of ebastine in healthy male volunteers.

12.2.1. Investigator and center

The study was conducted at a single site in the US between October 7 to 30, 1992 (v 157, p 14).

Investigator: Stuart I. Harris, MD
                South Florida Bioavailability Clinic, Inc.
                11190 Biscayne Blvd
                Miami, FL 33181

12.2.2. Objectives

The objectives of this study was to compare the electrocardiographic effects of ebastine 10, 20, 40, and 80 mg QD to placebo in normal volunteers, and to examine the relationship between QTc prolongation and plasma ebastine/carebastine concentrations (v 157, p 26).

12.2.3. Study population

Study subjects were healthy male volunteers 18 years of age and above, with normal ECG and Holter (ECG and Holter exclusion criteria were similar to study EBA 124), and no relevant clinical, hematological, or biochemical abnormalities. Subjects were required not to have taken astemizole within 3 months, azole antifungals and macrolide antibiotics within 1 month, and any prescription or over-the-counter medications within 1 week of the study (v 157, p 75).

12.2.4. Study design

This was a single-center, randomized, double-blinded, placebo-controlled, parallel group study (v 157, p 67).

12.2.5. Study procedures

The study procedures are outlined in Table 146. A total of 77 subjects were recruited and randomized to the 5 treatment arms. The study was conducted in 2 periods. In the first

period, 14 subjects each were assigned to ebastine 10, 20, 40 mg and placebo. After
establishing cardiac safety in the first period, in the second period 14 subjects were assigned
to ebastine 80 mg and 7 to placebo. Subjects were admitted in the clinical unit the day prior
to dosing and remained as inpatient till day 9 of the study. Each subject was given the study
medication daily in the morning immediately after breakfast in day 1 and then on day 3
through 8. Serial ECGs were done on day -1 (baseline) and on days 1, 5, 6, 7, and 8 (dosing
days). QTcB was determined by hand calculation on leads II, aVF and a single precordial
lead with the longest QT. The examining physician at the study site initially read the ECGs
for safety. All ECG tracings were finally interpreted in the central facility in Philadelphia
(section VIII). Telemetry, Holter and other measures were done at time points shown in
Table 146 (v 157, 14-16, 67-69, 75-85.

Table 146. EBA 126, Plan of the study and schedule of observations

	Screen	Admit	\multicolumn{8}{c}{Dosing days}	Release	Post-dose	End
	day -21	day -1	1	2	3	4	5	6	7	8	day 9	day 10	day 11
Consent	x												
Medical history	x												
Physical exam	x												x
Vital signs	x	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory*	x										x		
Dosing‡			x		x---------------------x								
ECG	x	x	x			x	x	x	x	x	x	x	x
Holter monitoring	x		x						x	x			
Telemetry			x		x	x	x	x	x	x			
PK sample			x			x	x	x	x	x	x	x	x
Adverse event	x	x	x	x	x	x	x	x	x	x	x	x	x

* Same as study EBA 136, listed in Table 139 footnote (v 157, p 89).
‡ x On days -1, 5, 6, 7, and 8 serial ECG done at 0 (predose), 1, 2, 3, 4, 6, 8, 12, and 24 hours

Source: v 157, p 104

12.2.6. Statistical considerations and analysis of QT interval

The primary analysis was the change from baseline QTcB measurements (day -1) to QTcB
measurements in dosing days 5, 6, 7, and 8. The two-sample t-test was used to compare the
mean difference from baseline for each ebastine treated group to the placebo treated group.
All t-tests were two-sided at the 0.05 level of significance (v 157, p 25).

The statistical calculation and the initial analysis were based on QT corrected for heart rate
by Bazett's method (QTcB). Like most of the other cardiac safety studies, the applicant
attempted to have Dr. Malik perform post-hoc analyses for this study. However, Dr. Malik
reported that there was "such an enormous imprecision in the assessment of individual QT
interval corrections that the study is not analyzable in any meaningful sense" (v 2.207, p 32).
Therefore, in the results section below only the results based on QTcB correction
methodology are presented.

12.2.7. Results

A total of 77 patients were enrolled and all completed the study. The age range was from 18 to 57 years, and there were 43 Hispanics, 23 Caucasians, and 11 of other ethnic background. Ebastine had no clinically significant effect on the study patients and on ECG, Holter, and telemetry, and no clinically significant arrhythmia was seen. No clinically relevant changes in any other clinical or laboratory parameters were seen, and no serious adverse event was reported. On Holter recording, 2 subjects (0012 on 10 mg/day, and 0058 on 80 mg/day) had second degree AV block on day 7, one subject (0043 on 40 mg/day) had a single triplet on day 7, and one subject (0013 on 20 mg/day) had a 5 beat single episode of nonsustained VT. (v 157, p 38-77)

The two randomization periods caused essentially two studies; the first where ebastine doses 10 mg, 20 mg, and 40 mg were explored, and the second where ebastine at a dose of 80 mg was explored. Therefore, although it may not be appropriate to compare all doses of ebastine used in this study, it is appropriate to compare the ebastine 10 mg, 20 mg, and 40 mg doses, all of which were used in one randomization period. These three doses of ebastine caused a dose-dependent prolongation of QTc corrected either by Bazett's or other methods of correction. The QTcB measurements comparing baseline to the mean change in each treatment group by study days for lead II is shown in Table 147. Results for other leads were similar. Within the 10 to 40 mg range, successively higher doses of ebastine caused successively higher QTcB prolongation. The number of subjects with QTcB >0.444 seconds at any time point were comparable among the groups - 1 in ebastine 10 mg, 2 each in ebastine 20 mg, 40 mg, 80 mg, and placebo groups. A similar dose-dependent rise in QTc is noted (Table 147) when other methods of correction for the ebastine effects on heart rate are used.

Table 147. EBA 126, Summary of QTcB data for lead II

Treatment day	Treatment group	N	Baseline mean in msec	Mean change from baseline (SE) in msec	p-value vs. placebo
Day 1	10 mg	14	388	03 (1)	0.625
	20 mg	14	373	02 (1)	0.283
	40 mg	14	383	02 (2)	0.471
	80 mg	14	378	03 (1)	0.776
	Placebo	21	380	04 (2)	
Day 5	10 mg	14	388	09 (3)	0.331
	20 mg	14	373	11 (2)	0.109
	40 mg	14	383	11 (3)	0.157
	80 mg	14	378	17 (3)	0.004
	Placebo	21	380	05 (3)	
Day 6	10 mg	14	388	08 (3)	0.167
	20 mg	14	373	11 (2)	0.036
	40 mg	14	383	13 (3)	0.008
	80 mg	14	378	12 (3)	0.025
	Placebo	21	380	03 (3)	
Day 7	10 mg	14	388	11 (3)	0.057
	20 mg	14	373	13 (3)	0.031
	40 mg	14	383	17 (4)	0.002
	80 mg	14	378	13 (3)	0.019
	Placebo	21	380	03 (3)	

Treatment day	Treatment group	N	Baseline mean in msec	Mean change from baseline (SE) in msec	p-value vs. placebo
Day 8	10 mg	14	388	12 (3)	0.310
	20 mg	14	373	14 (3)	0.171
	40 mg	14	383	20 (5)	0.010
	80 mg	14	378	12 (3)	0.376
	Placebo	21	380	07 (3)	
Source: v 157, p 46					

Table 148. EBA 126, Mean QTcB results

Treatment Day	Group	N	Baseline QTcB	Mean change from baseline in msec QTcB	p vs pbo	QTcF	p vs pbo
Day 1	10 mg	14	388	03	0.625	01	0.897
	20 mg	14	373	02	0.283	00	0.520
	40 mg	14	383	02	0.471	00	0.267
	80 mg	14	378	03	0.776	01	0.866
	Pbo	21	380	04		02	
Day 6	10 mg	14	388	08	0.167	06	0.144
	20 mg	14	373	11	0.036	07	0.087
	40 mg	14	383	13	0.008	09	0.041
	80 mg	14	378	12	0.025	08	0.072
	Pbo	21	380	03		01	
Day 7	10 mg	14	388	11	0.057	09	0.056
	20 mg	14	373	13	0.031	09	0.050
	40 mg	14	383	17	0.002	12	0.009
	80 mg	14	378	13	0.019	07	0.146
	Pbo	21	380	03		02	
Day 8	10 mg	14	388	12	0.310	07	0.455
	20 mg	14	373	14	0.171	09	0.168
	40 mg	14	383	20	0.010	12	0.049
	80 mg	14	378	12	0.376	05	0.736
	Pbo	21	380	07		04	
Source: Addendum to July 27, 1999 submission, pages 13, 14							

12.2.8. Conclusion

In this study ebastine at dose ranges from 10 mg to 80 mg QD were well tolerated with no clinically relevant cardiac adverse effects. QTcB prolongation with higher doses of ebastine was seen, however, the differences were numerically small. The QTcB prolongation was dose-dependent between the doses of 10 mg, 20 mg, and 40 mg of ebastine, which were all used in one randomization period. Individual QT variation was so large that post-hoc analyses of QTc by other methodology could not be carried out.

12.3. M/EBS/21: A phase 1, open-label, cardiac safety and pharmacokinetic study of single ascending doses of ebastine in healthy male volunteers.

12.3.1. Investigator and center

The study was conducted at a single site in Germany between July and August of 1999 (v 2.66, p 2, 39).

Investigator: Prof. Dr. Hermann Fuder, MD
                   PAREXEL GmbH, Institute of Clinical Pharmacology
                   Klinikum Westend, Haus 18
                   Spandauer Damm 130
                   D-14050 Berlin, Germany

ECG re-analysis: Marek Malik, MD, PhD, DSc (Med), FAAC, FESC
                   Dept. of Cardiological Services
                   St. Georges Hospital Medical School
                   London SW17 ORE
                   UK

12.3.2. Objectives

The objectives of this study were to compare the safety and tolerability of ascending single doses of 80, 150, 300, and 500 mg of ebastine with placebo in normal volunteers, and to examine the relationship between QTc prolongation and plasma ebastine/carebastine concentrations (v 2.66, p 10, 16). Specifically, the rationale for dose selection was to evaluate the "plateau" effect of single doses up to 25-50 times the proposed ebastine doses of 10-20 mg daily (v 2.66, p 15).

12.3.3. Study population

Study subjects were healthy male volunteers 18 to 40 years of age, with normal ECG and QTcB <430 msec, and no relevant clinical, hematological, or biochemical abnormalities (including nonsmokers with negative HIV-1/2Ab, HbsAg and HC-Ab, blood alcohol and urine drug screens). Subjects were required not to have taken any inducers of hepatic microsomal enzymes (including rifampin, carbamazepine, azole antifungals, and macrolide antibiotics) within 1 month, and any prescription or over-the-counter medications (except ASA up to 650 mg) within 2 weeks of the study (v 2.66, p 49-50).

12.3.4. Study design

This was a single-center, open-label, placebo-controlled, single ascending dose study (v 2.66, p 48).

12.3.5. Study procedures

The study procedures are outlined in Table 146. A total of 6 subjects were recruited. Capsules of ebastine specifically formulated for this study were administered rather than the to-be-marketed ebastine tablets. The study had a pre-study screening period of 2-7 days, a

22-day in-house experimental period, and a post-study follow-up visit. Subjects were admitted in the clinical unit the day prior to dosing and remained as inpatient till day 22 of the study. Four single-doses of 80, 150, 300, and 500 mg of ebastine were successively given on days 1, 6, 11, and 16, followed by placebo on day 21. Each subject was given the study medication in the morning with 240 ml of water immediately after a standardized breakfast. Dietary restrictions included restriction of xanthines and poppy-containing foods. Pharmacokinetic sampling for ebastine and carebastine was done pre-dose out to 120 hours after each dose of ebastine. Overnight Holter ECGs were performed for 12 hours prior to each dosing to establish measures of rate and rhythm. Telemetry was done for 24 hours post-dosing. Serial ECGs were done pre- and post-dosing as outlined in Table 146. Corina Marquette CardioSys v3.01 system software was used to assess HR, RR, PQ, QT, and QTcB (QTcB was calculated automatically by the machine on lead II), with the equipment set to 50 mm/sec and 2 cm/mV. Before each dosing period, QTcB had to comply with the inclusion criterion of <430 msec, as calculated automatically by the machine. Any QTcB >500 msec was immediately measured and calculated by hand by the physician at the study site, and repeated one hour later. In addition, if a subject had an increase of >60 msec of QTcB over the baseline value, the subject was withdrawn from further dosing and followed until the QTcB was below 430 msec. QTc was calculated manually (following the EAEMP CPMP *Points to Consider* guidelines published March, 19 1997) by both Bazett and Fridericia formulas as the mean of 3 to 5 beats.

Table 149. M/EBS/21, Plan of the study and schedule of observations

Day	Pre-study -7 to -1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Post-study +7
Consent	x																								
Medical history	x																								
Physical exam	x																								x
Ambulatory visit	x																								x
Hepatitis B, C, HIV	x																								
Urine drug screen / Breath alcohol	x	x																							
In-house stay		x																						x	
Dosing			80					150						300					500					PLA		
Laboratory*	x		x	x					x		x			x		x			x	x				x		x
Vital signs	x		6	2	1	1		6	2	1	1			6	2	1	1		6	2	1	1		6	1	x
Holter§	x					x					x				x					x						
ECG (12-lead)‡	x		6	2					6	2				6	2				6	2				6	1	x
Telemetry			24h	24h					24h	24h				24h	24h				24h	24h						
PK sampling†			10	2	1	1	1	10	2	1	1	1		10	2	1	1	1	10	2	1	1	1	1		x
Adverse event		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

*Urinalysis (protein, glucose, bilirubin, pH, nitrite, ketones, urobilinogen, blood, leukocytes, and microscopic exam), hematology (hemoglobin, hematocrit, WBC count, RBC count, differential, and platelet count), and serum chemistry (creatinine, BUN, fasting glucose, uric acid, total cholesterol, triglycerides, total protein, total bilirubin, alkaline phosphatase, AST, ALT, GGT, GLDH [glutamate dehydrogenase], LDH, CPK, sodium, potassium, chloride) (v 2.66, p20).

§ 12-hour overnight Holter

‡ 12-lead ECG pre-dose and 1, 2, 4, 8, 12, 24, 36 hours post-dose (36 hours post-dose only after ebastine). Amendment 1. ECG on days 10, 15, and 20: ECG at 23, 22, 20, 16, and 12 hours before dosing on day 11, 16 and 21 respectively.

† Pharmacokinetic sampling pre-dose and after 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, and 120 hours. Total blood drawn for each subject during the study was 440 ml.

Source: v 2.66, p 12, 44

12.3.6. Statistical considerations and analysis of QT interval

The statistical calculation and the initial analysis were based on QT corrected for heart rate by both Bazett's and Fridericia's methods. The primary safety analysis was the QTc evaluation, with mean and maximum QTc and baseline corrected QTc the primary variables of interest. Data from both Bazett's and Fridericia's QTc (calculated manually/visually) assessments were summarized by descriptive statistics for each ebastine and placebo treatment as QTc and QTc corrected for baseline of the same treatment period. Data were analyzed by ANOVA with factors for subject and treatment, with 90% confidence intervals for differences between treatments. There was one amendment, which added additional 'baseline' pre-dose ECG assessments to compensate for the known intra-individual variability of QTc interval. Pharmacokinetic analysis included both individual and mean concentration-time curves plotted for each dose level for both ebastine and carebastine, using actual sampling times, but only concentrations above LOQ were used. (v 2.66, p 21-2)

Subsequent analyses (post-hoc) corrected QT by various other methods, including QTc by linear regression, Framingham correction, and an individual patient correction method called Malik's correction (QTcM). In the results section below, initially the results based on QTcB and QTcF are presented, followed by results based on other correction methodology.

12.3.7. Results

A total of 6 subjects were enrolled and 5 completed the study. The age range was from 18 to 34 years. All were Caucasian males. One subject (003) withdrew his consent in day 14, 4 days after the 300 mg dose and 1 day prior to the 500 mg dose. There were no protocol violations, no serious adverse events, and no deaths. C_{max} for ebastine after 80, 150, 300, and 500 mg of ebastine were 32.3 ± 22.0, 98.9 ± 68.7, 183.5 ± 94.1, and 397.6 ± 23.2 ng/ml respectively. T_{max} ranged from 2.2 to 3.8 hours. AUCs for ebastine were 180.8 ± 67.7, 482.9 ± 268.3, 881.7 ± 447.1, and 3117.1 ± 2051.3 ng.h/ml. C_{max} for carebastine were 0.589 ± 0.144, 1.003 ± 0.323, 2.686 ± 0.330, and 2.279 ± 1.128 µg/ml respectively. T_{max} ranged from 7.2 to 16 hours. AUCs for carebastine were 19.297 ± 3.592, 32.847 ± 6.742, 82.541 ± 13.021, and 105.18 ± 22.63 µg.h/ml.

Mean results for heart rate, QT, QTcB, and QTcF are shown in Table 150. Since the baseline for each dose was different, the baselines are not shown. With incrementally higher single doses of ebastine, heart rate, QTcB, and QTcF are noted to increase incrementally. No single QTcB or QTcF interval greater than 500 msec, and no intra-individual post-dose increase in mean QTcB or QTc F interval greater than 10% was found in this study.

Table 150. M/EBS/21, Mean QTc results

	Ebastine 80	Ebastine 150	Ebastine 300	Ebastine 500	Placebo
Mean Heart Rate	56.0 (7.6)	62.5 (1.9)	63.4 (11.6)	66.7 (13.5)	65.9 (15.5)
Mean QT (msec)	405.1 (17.0)	392.2 (34.8)	393.4 (29.8)	390.9 (31.4)	383.7 (35.5)
Mean QTcB (msec)	384.1 (8.3)	386.6 (7.3)	397.8 (13.3)	405.3 (17.5)	398.1 (22.6)
Mean QTcF (msec)	390.7 (4.4)	388.0 (10.5)	395.8 (5.8)	399.8 (8.7)	392.5 (12.8)
Expressed as Mean (SD)					
Source: v 2.67, p 68-83					

12.3.8. Conclusion

In this pilot study, ebastine in single doses from 150 mg to 500 mg were well tolerated with no clinically relevant cardiac adverse effects. While some trends are noted, the size of the study (n = 5) was too small to make any statements regarding the effect of high-dose single doses of ebastine on the QT interval.

13. DRUG INTERACTION CARDIAC SAFETY STUDIES

In the original NDA submission, the applicant submitted 5 studies (EBA 137, EBA 127, EBA 145, EBA 138, and EBA 130) on drug interaction cardiac safety and pharmacokinetics of ebastine. In the complete response, 3 more drug interaction cardiac safety and pharmacokinetic studies (EBA 148, M/EBS/24,and M/EBS/25) were submitted. In 5 studies, interactions of ebastine and ketoconazole (EBA 137, EBA 127, EBA 148, M/EBS/24,and M/EBS/25) were examined. In two studies (EBA 138, and EBA 130) ebastine and erythromycin were examined.

All the studies were done in young (18 to 40 years of age) healthy non-smoking male volunteers except M/EBS/25, which evaluated young healthy female subjects. All the studies except M/EBS/25 selected subjects with baseline QTc of less than 440 msec as an entry criterion. In 6 studies (EBA 137, EBA 138, EBA 145, EBA148, M/EBS/24,and M/EBS/25) multiple doses of the drugs were used to study the interaction at a steady state, and in 2 studies (EBA 127 and EBA 130) a single dose of ebastine was used. From a design standpoint, the multiple dose studies are more informative. All studies were reviewed from a cardiac safety perspective, and the reviews are presented in the following sections. These studies clearly demonstrated that both ketoconazole and erythromycin significantly increased the plasma concentration of ebastine and prolonged the QTc.

The comparator drug loratadine was evaluated in two studies (EBA 145 and EBA 148). EBS 148 compared ebastine with loratadine (no placebo), and EBS 145 compared loratadine with placebo (no ebastine). In those studies, the addition of ketoconazole altered the loratadine pharmacokinetics, although to a lesser magnitude than that of ebastine. There was an effect on QTc by the addition of ketoconazole to loratadine, but effect was not as large as that for ebastine.

The applicant's initial submission of cardiac safety data was based on correction of QT values for differences in heart rate by a formula called the Bazett's formula. The applicant later questioned the validation of that correction method because ebastine was noted to cause some increase in heart rate. Subsequently the applicant submitted reanalysis of cardiac safety data using alternate methods of QT correction, such as Fridericia's method (QTcF), QTc by linear regression, and an individual patient correction method called Malik's correction (QTcM). The applicant's justification for re-analysis of the data by other methodology is that in the setting where heart rate is increased, Bazett's correction method tends to overcorrect the QT interval and is therefore not the most appropriate method. The applicant's argument is reasonable. However, one also has to keep in mind that some of the other methods of QT correction for heart rate may also undercorrect the QT.

The applicant's data from studies EBA 137, EBA 138, were analyzed and verified by FDA medical and statistical reviewers during the first NDA cycle. The applicant presented the QTc change results as mean QTc, maximum QTc, and AUC QTc. Mean QTc change represents change of the mean QTc from serial ECG at the study day compared to the baseline. Maximum QTc change represents change of the maximum QTc from serial ECG at the study day compared to the maximum QTc at the baseline. In review of studies EBA 137, EBA 138, EBA148, and M/EBS/25 (subsequent sections), the applicant's analysis of

data are used unless otherwise specified. Maximum QTc was also calculated from the applicant's data using alternate methods, such as the difference between the minimum QTc at baseline and the maximum QTc at study day. Results on this alternate calculation are very similar to that of the applicant's calculation.

The applicant's pharmacokinetic but not the pharmacodynamic data from study EBA148 were analyzed and verified by FDA medical and statistical reviewers during the analysis of the complete response. The applicant's pharmacokinetic and pharmacodynamic data from study M/EBS/25 were analyzed and verified by FDA medical, statistical, and clinical pharmacology reviewers during the analysis of the complete response.

Note that of all the studies, M/EBS/25 was the most carefully performed cardiac safety study, and was designed with FDA input. This study was designed to take into account the applicant's concerns regarding possible flaws in previous studies. To take into account the individual variability of QT interval and the effect of heart rate changes on corrected QT, the applicant used the QTcM method of QTc calculation. To obtain individual correction factors, a very large number of ECGs were done both at baseline and throughout the study. Unlike most of the other studies, this was a randomized, double-blind, 2-way crossover design comparing ebastine versus placebo in female subjects. Pharmacokinetic and pharmacokinetic/pharmacodynamic (QTcM) analyses were carried out by both the sponsor and the FDA. The analyses yielded information with more breath and precision than the other studies. Therefore, it is suggested that the reader pay particular attention to the results of study M/EBS/25 (page 213).

13.1. EBA 137: A randomized, blinded, parallel group, multiple-dose, placebo-controlled, ebastine-ketoconazole interaction cardiac safety study in healthy adult male volunteers.

13.1.1. Investigator and center

The study was conducted at a single site in the US between February and May of 1996 (v 165, p 6).

Investigator: Stephen R. Scheiman, MD
                   South Florida Bioavailability Clinic, Inc.
                   11190 Biscayne Blvd
                   Miami, FL 33181

ECG re-analysis: Marek Malik, MD, PhD, DSc (Med), FAAC, FESC
                   Dept. of Cardiological Services
                   St. Georges Hospital Medical School
                   London SW17 ORE
                   UK

13.1.2. Objectives

The objectives of this study were to compare the electrocardiographic effects of ebastine (20 mg QD) or placebo administered concomitantly with ketoconazole (400 mg QD), and to

compare the disposition kinetics of ebastine to ebastine administered with ketoconazole (v 165, p 18).

13.1.3. Study population

Study subjects were healthy male volunteers 18 to 40 years of age, with normal ECG (ECG exclusion criteria were similar to study EBA 132, page 95), and no relevant clinical, hematological, or biochemical abnormalities. Subjects were required not to have taken astemizole within 3 months, ketoconazole, itraconazole, or macrolide antibiotics within 2 months, and prescription or OTC medications within 2 weeks of the study. (v 165, p 104)

13.1.4. Study design

This was a single-center, randomized, investigator-blinded, placebo-controlled, parallel group study (v 165, p 97).

13.1.5. Study procedures

The study procedures are outlined in Table 151. A total of 55 subjects were recruited and randomized into the 2 treatment arms (27 to ebastine and ketoconazole, and 28 to placebo and ketoconazole). The subjects were given ebastine 20 mg QDAM or placebo for 13 consecutive days (day 1-13), and for the last 8 days (day 6-13), ketoconazole 400 mg QDAM was added to the regimen. The subjects were sequestered in the clinical unit from day -2 through day 1, and again from day 4 through day 14. The other study days were done as outpatient. On day -1, serial ECG and PK sampling were done to establish the baseline. On day 5 and day 13 serial ECG and PK sampling were done post dosing (ebastine/placebo with ketoconazole) to reflect the ebastine steady-state and ebastine-ketoconazole steady state, respectively, and compared to the baseline. Telemetry and other measures were done at time points shown in Table 151. Subjects were to be discontinued according to predetermined ECG criteria (same as study EBA 136) and monitored until they revert to baseline. The examining physician at the study site read the ECGs for implementing the discontinuation criteria. All ECG tracings were finally interpreted in the central facility in Philadelphia (section VIII). using the same criteria as described in section XII.A.5 for study EBA 136 (v 165, p 18-29, 98-100, 106-124).

Table 151. EBA 137, Plan of the study and schedule of observations

	Screen day -28	day -1	days 1-4	day 5	days 6-12	day 13	day 14	days 15-20	End day 22
Consent	x								
History	x								
Sequestration		x		x	x	x			
Physical exam	x								x
Vitals	x	x		x	x†				x
Laboratory*	x			x†	x†		x†		
Ebastine/placebo			x----------------------------------x						
Ketoconazole					x----------x				
ECGs	x	x†		x†	x§	x†	x	x	x
Telemetry					x	x	x		
PK sample		x**		x††	x**	x††	x	x	x

	Screen day -28	day -1	days 1-4	day 5	days 6-12	day 13	day 14	days 15-20	End day 22
Distribute diary	x						x		
Collect diary			x						x

* Same as study EBA 136, listed in Table 139 footnote (v 165, p 123).
† Serum chemistry only repeated on day 5, 8, 11, and 14
‡ Serial measurement at -0.5, 1, 2, 4, 6, 8, 12, and 23.5 hours relative to the dose (v 165, p 100)
§ Predose, and 2, 6, and 12 hours postdose
** Pretreatment sample on day -1, and predose sample on days 6, 7, 8, 9, 10, 11, and 12
†† Serial sampling following ECG

Source: v 165, p 99

13.1.6. Statistical considerations and analysis of QT interval

A sample size of 30 per treatment was chosen to provide 90% power to detect a mean difference of 17 msec change from baseline QTc between ebastine + ketoconazole and placebo + ketoconazole groups at a one-sided test. These assumptions were based on alpha level of 0.05 and a standard deviation of 20 msec derived from the EBA 126 ebastine study (v 151, p 33-30).

The statistical calculation and the initial analysis were based on QT corrected for heart rate by Bazett's method (QTcB). The primary analysis were the mean changes from ebastine or placebo steady-state QTcB measurements (day 5) to ebastine + ketoconazole or placebo + ketoconazole steady-state (day 13) QTcB measurements in the mean QTcB, maximum QTcB, and AUC_{0-12hr}. Secondarily, changes from baseline (day -1) to day 5 were compared between the 2 treatment groups. The principal analysis was an ANOVA for a parallel design trial with the model containing main effects for treatment. One-sided t-test at 5% level of significance was done for all comparisons.

Subsequent analyses (post-hoc) corrected QT by various other methods, including Fridericia's method (QTcF), QTc by linear regression, and an individual patient correction method called Malik's correction (QTcM). In the results section below, initially the results based on QTcB are presented, followed by results based on other correction methodology.

13.1.7. Results

A total of 55 subjects were enrolled in the study. The age range was from 21 years to 40 years, and there were 21 Caucasians, 9 blacks, 24 Hispanics, and one of mixed race in the group. Three subjects discontinued from the study. Subject 00002 (ebastine + ketoconazole group) discontinued for adverse experience (tooth disorder), subject 00004 (placebo + ketoconazole group) was non-compliant, and subject 00040 (placebo + ketoconazole group) was lost to follow-up. No serious adverse event was reported. No subject was discontinued due to the ECG discontinuation criteria. One subject (00029) had abnormal cardiac repolarization pattern (abnormal U wave) with 13 msec increase in QTc from baseline (372 msec) to day 13 (385 msec) while on ebastine and ketoconazole concomitantly for 8 days. This subject was reassigned to placebo + ketoconazole and had recurrence of the same abnormal T-U wave on days 8 and 12 with no QTc prolongation (381 msec on day -1, 364 msec on day 5, and 374 on day 13). Abnormal ventricular repolarization was concluded to be unrelated to ebastine by 4 cardiologists consulted by the applicant.

Of the laboratory parameters, a higher incidence of mild transient elevations in liver enzymes were seen in the ebastine + ketoconazole group. A total of 3 subjects (2 in ebastine + ketoconazole group, and 1 in placebo + ketoconazole group) had SGOT values that increased over 50% of baseline, and a total of 6 subjects (5 in ebastine + ketoconazole group, and 1 in placebo + ketoconazole group) had SGPT values that increased over 50% of baseline. (v 165, p 38-77)

On PK measurement, co-administration of ketoconazole was shown to significantly alter the PK parameters of ebastine at steady state (Table 152). Cmax increased about 15 fold, Cmin increased about 70 fold, and AUC_{0-24} of ebastine increased about 40 fold. The PK parameters of carebastine were less affected. The PK/PD linear regression analysis demonstrated that there was significant relationship between increasing ebastine and carebastine plasma concentrations and QTc changes from baseline. (v 165, p 38-77)

QTc analysis results based on Bazett's correction (the primary analysis) are shown in Table 153. Subjects defined as ECG outliers (QTcB prolongation $\geq$ 444 msec and at least 10 msec prolongation of QTcB over baseline) are shown in Table 154. The addition of 400 mg QD of ketoconazole to a 20 mg QD regimen of ebastine caused a significant mean QTcB prolongation when compared to placebo. Prolongation of QTcB by the addition of ketoconazole was seen on each day of treatment and the separation between the groups appeared to widen over time (Figure 7). A total of 16 subjects met the ECG outlier criteria of which 10 were from the ebastine plus ketoconazole group and 6 were from the placebo plus ketoconazole group (Table 154). Results of QTcB dispersion are shown in Table 155. There was no evidence of increase in QTc dispersion for the ebastine group compared to placebo.

Subsequent analyses of QT by other methods, including QTcF, QTc by linear regression, and QTcM are shown in Table 156. The conclusion that ebastine given along with ketoconazole causes a prolongation of QTc as compared to ebastine alone was borne out by all methods of QTc correction. Although the magnitude of the effect was lower when correction methods other than Bazett's was used, all showed a prolongation of QTc compared to placebo when ketoconazole was added to ebastine at steady-state.

Table 152. EBA 137, Mean (%CV) steady-state pharmacokinetic parameters of ebastine and carebastine

Parameter	Ebastine			Carebastine		
	Day 5 Ebastine	Day 13 Eba + Keto	p-value	Day 5 Ebastine	Day 13 Eba + Keto	p-value
AUC_{0-24} (ng*hr/mL)	17.92 (82.0)	761.59 (36.8)	0.0001	5688.4 (29)	8192.2 (22)	0.0001
Cmax (ng/mL)	3.75 (73.2)	58.95 (37.2)	0.0001	344.62 (33)	384.19 (22)	0.0256
Cmin (ng/mL)	0.19 (98.5)	14.85 (35.3)	NA	145.3 (31.5)	333.8 (21.7)	NA
Tmax (hrs)	2.42 (46.9)	4.30 (36.4)	0.0001	4.8 (37.7)	16.4 (102.8)	0.0019
$t_{1/2}$ (hrs)	6.4	87.7	NA	24.6	80.6	NA
Source: v 165, p 70, 71						

Table 153. EBA 137, Summary of primary analysis of QTcB results

Variable	Treatment	Day -1 Baseline mean*	Day 5 Ebastine	Day 13 Ebastine + Ketoconazole	Day 13 - 5 Change with ketoconazole	p-value[†]
Mean QTcB (msec)	Ebastine	383.8±2.9 (27)	383.0±2.4 (27)	401.2±3.1 (26)	18.1±2.5 (26)	0.0023
	Placebo	384.0±3.4 (28)	383.5±3.9 (26)	391.4±3.4 (26)	8.0±2.3 (26)	
Max QTcB (msec)	Ebastine	402.6±3.5 (27)	397.9±2.5 (27)	418.3±4.1 (26)	19.9±3.4 (26)	0.0056
	Placebo	399.5±3.3 (28)	389.9±3.9 (26)	407.2±3.6 (26)	8.3±2.8 (26)	
AUC QTcB (msec*hr)	Ebastine	4605±33 (27)	4561±42 (27)	4822±38 (26)	231±32 (26)	0.0016
	Placebo	4609±41 (28)	4600±47 (26)	4701±41 (26)	101±27 (26)	

* Results expressed as mean±sem (n)
[†] p-value for one-sided test between ebastine and placebo treatment in day 13 minus day 5 change

Source: v 165, p 60

Table 154. EBA 137, Subjects with QTcB prolongation of 440 msec and an increase of 10 msec above baseline

Subject	Treatment	Schedule*		QTc (msec)		
		Day	Time	Baseline	Observed*	Change
00005	Ebastine/Ketocon	13	12 hr	413	451	38
00011	Placebo/Ketocon	13	6 hr	398	440	42
00011	Placebo/Ketocon	15	-30 min	394	448	54
00013	Ebastine/Ketocon	13	12 hr	387	450	63
00014	Placebo/Ketocon	8	2 hr	427	441	14
00014	Placebo/Ketocon	15	-30 min	420	467	47
00014	Placebo/Ketocon	16	-30 min	420	449	29
00014	Placebo/Ketocon	17	-30 min	420	462	42
00014	Placebo/Ketocon	18	-30 min	420	449	29
00014	Placebo/Ketocon	22	-30 min	420	458	38
00015	Ebastine/Ketocon	15	-30 min	397	448	51
00016	Ebastine/Ketocon	14	23.5 hr	407	446	39
00022	Ebastine/Ketocon	15	-30 min	353	441	88
00031	Placebo/Ketocon	7	12 hr	376	448	72
00035	Ebastine/Ketocon	12	2 hr	406	440	34
00035	Ebastine/Ketocon	15	-30 min	417	445	28
00038	Ebastine/Ketocon	10	6 hr	396	440	44
00038	Ebastine/Ketocon	12	6 hr	396	472	76
00041	Placebo/Ketocon	13	2 hr	411	443	32
00043	Placebo/Ketocon	9	12 hr	394	442	48
00044	Ebastine/Ketocon	10	2 hr	398	449	51
00044	Ebastine/Ketocon	12	6 hr	406	447	41
00044	Ebastine/Ketocon	12	12 hr	383	444	61
00044	Ebastine/Ketocon	13	-30 min	394	481	87
00044	Ebastine/Ketocon	13	2 hr	398	449	51
00044	Ebastine/Ketocon	13	6 hr	406	487	81
00044	Ebastine/Ketocon	13	8 hr	388	475	87
00044	Ebastine/Ketocon	14	8 hr	388	446	58
00045	Ebastine/Ketocon	11	12 hr	388	440	52
00045	Ebastine/Ketocon	12	6 hr	395	441	46
00048	Ebastine/Ketocon	22	-30 min	365	451	86
00050	Ebastine/Ketocon	15	-30 min	424	447	23
00044	Ebastine/Ketocon	16	-30 min	424	444	20

* Time at which the prolongation of QTc was observed

Subject	Treatment	Schedule*		QTc (msec)		
		Day	**Time**	**Baseline**	**Observed***	**Change**
Source: v 165, p 49						

Table 155. EBA 137, Summary of QTcB dispersion results

Variable	Treatment	Day –1 Baseline mean*	Day 5 Ebastine	Day 13 Ebastine + Ketoconazole	Day 13 - 5 Change with ketoconazole	p-value[†]
Mean QTcB (msec)	Ebastine	49.6±2.1 (27)	48.9±1.9 (27)	50.5±2.5 (26)	1.5±1.9 (26)	Not sig.
	Placebo	45.3±2.1 (28)	44.8±2.0 (26)	46.9±2.4 (26)	2.1±1.4 (26)	
Max QTcB (msec)	Ebastine	69.4±3.1 (27)	68.5±3.1 (27)	73.5±4.2 (26)	4.5±4.8 (26)	Not sig.
	Placebo	63.5±3.1 (28)	64.9±2.9 (26)	67.8±3.6 (26)	2.9±3.0 (26)	
AUC QTcB (msec*hr)	Ebastine	595.9±25 (27)	578.6±25 (27)	598.9±27 (26)	13.0±21.3 (26)	Not sig.
	Placebo	545.8±27 (28)	541.6±26 (26)	566.2±31 (26)	24.6±18.7 (26)	
* Results expressed as mean±sem (n) † p-value for one-sided Dunnett test between ebastine and placebo treatment in day 13 minus day 5 change						
Source: v 165, p 65						
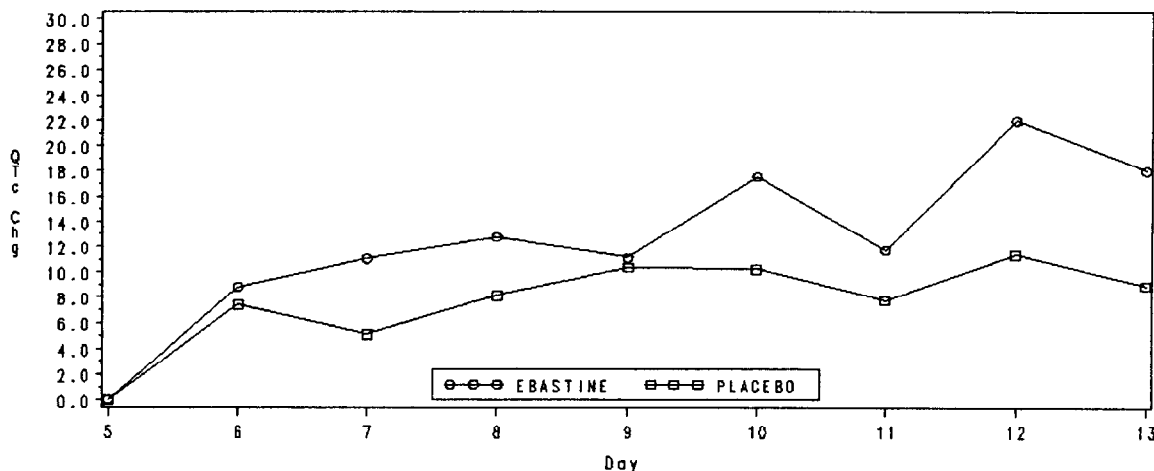
Figure 7. EBA 137, Mean QTcB changes of ebastine + ketoconazole and placebo + ketoconazole groups at different days of treatment as compared to day 5 of treatment
Figure created from applicant's submitted data

Table 156. EBA 137, Corrected and uncorrected mean QT results (multiple QTc analyses)

	Treatment	Day -1 Baseline mean*	Day 5 Ebastine	Day 13 Ebastine + Ketoconazole	Day 13 - 5 Change with ketoconazole	p-value[†]
Mean Heart	Ebastine	63.6 (27)	64.6 (27)	67.4 (26)	2.5 ± 0.9 (26)	<0.020
Rate (bpm)	Placebo	64.1 (28)	64.9 (26)	64.4 (26)	-0.5 ± 0.8 (26)	
Mean QT[‡]	Ebastine	375.7 (27)	371.3 (27)	381.5 (26)	11.1 ± 2.8 (26)	>0.600
(msec)	Placebo	373.3 (28)	370.3 (26)	379.8 (26)	9.5 ± 2.1 (26)	
Mean QTcB[‡]	Ebastine	383.8 (27)	383.0 (27)	401.2 (26)	18.1 ± 2.5 (26)	0.0023
(msec)	Placebo	384.0 (28)	383.5 (26)	391.4 (26)	8.0 ±2.3 (26)	
Mean QTcF[‡]	Ebastine	380.8 (27)	378.9 (27)	394.2 (26)	15.6 ± 2.3 (26)	0.0104
(msec)	Placebo	380.2 (28)	378.9 (26)	387.3 (26)	8.4 ±1.9 (26)	
QTc regress.	Ebastine				15.4 ± 11.5	
(msec)	Placebo				8.5 ± 9.4	
QTcM[‡]	Ebastine				13.0 ± 11.9	
(msec)	Placebo				7.1 ± 8.3	

* Results expressed as mean (n) or mean ± sem (n)
† p-value for one-sided test between ebastine and placebo treatment in day 13 minus day 5 change
‡ QTcB is Bazett's correction, QTcF is Fridericia's correction, QTcM is Malik's correction, QT is uncorrected QT interval

Source: v 1, p 5, 11/5/99 submission; QTc regression analysis from p 11, 1/5/00 submission; QTcM from p 7, section 18, 4/23/01 submission

13.1.8. Conclusion

In this study the addition of 400 mg QD of ketoconazole to a 20 mg QD regimen of ebastine at steady-state caused a significant mean QTc interval prolongation when compared to placebo (+18.1 msec vs 8 msec for QTcB). Addition of ketoconazole altered the PK parameters of ebastine, significantly elevating the ebastine concentration. PK/PD analysis demonstrated that there was significant prolongation of the QTc interval that correlated with increasing plasma ebastine concentration. The carryover effect of ebastine was not evaluated.

13.2. EBA 127: An open-label, interaction study between a single dose of ebastine and multiple doses of ketoconazole on cardiac function and pharmacokinetic profile in healthy adult male volunteers.

13.2.1. Investigator and center

The study was conducted at a single site in the US in 1994 (v 171, p 6).

Investigator: Stuart I. Harris, MD
                South Florida Bioavailability Clinic, Inc.
                11190 Biscayne Blvd
                Miami, FL 33181

13.2.2. Objectives

The objectives of this study were to determine the electrocardiographic effects and pharmacokinetic profile of a single dose of ebastine when co-administered after multiple doses of ketoconazole, and to examine the relationship between pharmacodynamic response and plasma ebastine and carebastine concentrations (v 171, p 243).

13.2.3. Study population

Study subjects were healthy male volunteers 18 to 40 years of age, with normal ECG and Holter (ECG and Holter exclusion criteria were similar to study EBA 132, page 95), and no relevant clinical, hematological, or biochemical abnormalities. Subjects were required not to have taken astemizole within 3 months, ketoconazole, itraconazole, or macrolide antibiotics within 4 weeks, and prescription or over-the-counter medications within one week of the study. (v 171, p 243-245)

13.2.4. Study design

This was a single-center, open-label drug interaction study between a single dose of ebastine and multiple doses of ketoconazole (v 171, p 239).

13.2.5. Study procedures

The study procedures are outlined in Table 157. A total of 12 subjects were recruited for the study. The subjects were admitted to the clinical unit for 15 days for the study. Each subject was given ketoconazole 400 mg QDAM on days 4 through 12, and a single dose of ebastine 20 mg was given in the morning on day 1 and day 9. ECG, PK sampling, and other measures were done at time points shown in Table 157. On admission day QTcB was calculated on leads II, aVF, and single precordial lead with the longest QT on 12-lead ECG. Thereafter, QTcB was calculated from the 3 leads chosen on admission day and each QTcB reported in the results is the mean of 3 intervals. The examining physician at the study site initially read the ECGs. All ECG tracings were finally interpreted in the central facility in Philadelphia. All QT correction was based on Bazett's method. (v 171, p 246-259)

Table 157. EBA 127, Plan of the study and schedule of observations

	Screen day -23	Admit day -2	Baseline (day -1)	1	2	3	4	5	6	7	8	9	10	11	12	End 13
Consent	x															
History	x																
Physical exam	x																x
Vital signs	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory*	x	x									x				x	
Ebastine				x								x				
Ketoconazole							x	x	x	x	x	x	x	x	x	
ECG†	x	x	x	x							x	x	x	x	x	x
Holter	x			x							x	x				
Telemetry				x								x	x	x	x	
PK sample‡				x	x	x	x					x	x	x	x	x
Adverse event	x	x	x	x	x	x	x	x	x	x	x	x	x	x		

*Same as study EBA 136, listed in Table 139 footnote (v 171, p 257).

Drug Interaction Cardiac Safety Studies, EBA 127

	Screen day -23	Admit day -2	Baseline (day -1)	Dosing days												End 13
				1	2	3	4	5	6	7	8	9	10	11	12	
✝ On days -1, 1, 8, and 9 serial ECG done at 0 (predose), 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours																
‡ On dosing days serial samples before dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours. On days 1 and 9 blood drawn at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, and 96 (for day 9 only) hours																
Source: v 171, p 272																

13.2.6. Results and conclusion

This study evaluated single doses of ebastine with multiple doses of ketoconazole. Therefore, ebastine levels were not at steady-state. The age range of the 12 enrolled subjects was from 18 years to 39 years. No subjects were discontinued, there were no serious adverse events, and there were no clinically relevant ECG changes or abnormal laboratory values. The maximum QTcB recorded in this study was 457 msec at 5 hours on day 5 of ketoconazole. No subject had detectable plasma ebastine concentrations after single dose of ebastine at day 1. In contrast, after co-administration of ebastine with ketoconazole at steady state (day 9), all subjects had measurable plasma ebastine concentration ranging from 20.3 ng/mL to 55.7 ng/mL. This study again supports ebastine-ketoconazole interaction, however, no significant QTcB changes were seen in this limited exposure. (v 171, p 24)

13.3. EBA 145: A double-blind, randomized, parallel group, placebo-controlled, loratadine-ketoconazole interaction cardiac safety study in healthy male volunteers.

13.3.1. Investigator and center

The study was conducted at a single site in France between May and August of 1997 (v 173, p 3).

Investigator: Thierry Duvauchelle, MD
                 Aster, 3-5 rue Eugene Millon
                 75015 Paris, France

13.3.2. Objectives

The objectives of this study were to compare the electrocardiographic effects of loratadine (10 mg QD) or placebo administered concomitantly with ketoconazole (400 mg QD), and to compare the disposition kinetics of loratadine before and after concomitant administration of ketoconazole. (v 173, p 76)

13.3.3. Study design

This was a single-center, randomized, double-blinded, placebo-controlled, parallel group study (v 173, p 65).

13.3.4. Study procedures

The study population and procedures were similar to the ebastine-ketoconazole interaction study EBA 137. A total of 60 subjects were recruited and 30 each were randomized into the

2 parallel treatment arms (loratadine + ketoconazole, and placebo + ketoconazole). The subjects were given loratadine 10 mg QDAM or placebo for 13 consecutive days (day 1-13), and for the last 8 days (day 6-13), ketoconazole 400 mg QDAM was added to the regimen. Serial ECG and PK sampling were done on day -1 to establish the baseline, and on day 5 and day 13 to reflect the loratadine steady-state and loratadine-ketoconazole steady state, respectively. ECG tracings were initially evaluated at the study site. Any tracings with QTc >500 msec (as calculated by the ECG machine) were hand calculated to confirm the results. Following preliminary safety evaluation at the study site, all ECG tracings were finally interpreted in the central facility in Philadelphia using the same criteria described for study EBA 136 (page 171) with the exception that the ECGs were not evaluated for QTc dispersion. Results reported in subsequent sections are from the central facility readings. All QT corrections were based on Bazett's method. (v 173, p 16-25, 77-93)

13.3.5. Study parameters and statistical considerations

The primary analysis were the mean changes from loratadine or placebo steady-state QTcB measurements (day 5) to loratadine + ketoconazole or placebo + ketoconazole steady-state (day 13) QTcB measurements in the mean QTcB, maximum QTcB, and AUC_{0-12hr}. The statistical analysis was an ANOVA with the model containing treatment as the main effect and subject as an error term. One-sided t-test at 5% level of significance was done to compare the loratadine and placebo groups. A sample size of 30 subjects per treatment arm was chosen to provide 90% power to detect a mean difference of 17 msec change from baseline QTcB between the two groups at a one-sided test. These assumptions were based on alpha level of 0.05 and a standard deviation of 20 msec derived from EBA 126 ebastine study. (v 173, p 76, 106, 107)

13.3.6. Results

A total of 62 subjects were enrolled in the study. The age range was from 18 to 38 years, and all were Caucasians. Two subjects, one from each group, discontinued for personal reasons. No serious adverse event was reported and no relevant changes were noted in any of the clinical or laboratory parameters. Results of the PK parameters are shown in Table 158. The co-administration of ketoconazole with loratadine resulted in significantly changes in loratadine disposition kinetics compared to loratadine alone. Cmax increased about 3.5 fold, Cmin increased about 8 fold, and AUC_{0-24} of increased about 4.5 fold. The PK parameters of the loratadine metabolite descarboethoxyloratadine were less affected. Results of the primary analysis are shown in Table 159. The addition of 400 mg QD of ketoconazole to a 10 mg QD regimen of loratadine caused a significant mean QTcB interval prolongation when compared to placebo. On cardiac telemetry, 3 subjects in the placebo group and 2 subjects in the loratadine group had rhythm abnormalities. None of these were clinically relevant. (v 173, p28-50)

Table 158. EBA 145, Mean (%CV) steady-state pharmacokinetic parameters of loratadine and DCL

Parameter	Loratadine			descarboethoxyloratadine (DCL)		
	Day 5 Loratadine	Day 13 Lora + Keto	p-value	Day 5 DCL	Day 13 DCL+ Keto	p-value
AUC$_{0-24}$ (ng*hr/mL)	12.32 (84.3)	54.93 (58.8)	0.0001	45.94 (61.5)	89.15 (67.6)	0.0001
Cmax (ng/mL)	2.99 (88.6)	10.41 (50.1)	0.0001	3.50 (48.4)	6.37 (47.5)	0.0001
Cmin (ng/mL)	0.052 (190.3)	0.430 (82.8)	0.0001	1.00 (94.5)	2.21 (100.1)	0.0001
Tmax (hrs)	1.92 (28.3)	2.28 (29.1)	0.0336	3.37 (72.4)	3.25 (47.6)	0.2661
Source: v 173, p 6						

Table 159. EBA 145, Summary of primary analysis of QTcB results

Variable	Treatment	Day -1 Baseline mean*	Day 5 Loratadine	Day 13 Loratadine + Ketoconazole	Day 13 - 5 Change with ketoconazole	p-value[†]
Mean QTcB (msec)	Loratadine	374.35 ± 2.98	374.80 ± 2.83	391.11 ± 2.43	16.31 ± 2.52	0.0462
	Placebo	378.63 ± 2.57	377.98 ± 2.73	387.58 ± 2.82	9.60 ± 2.12	
Max QTcB (msec)	Loratadine	391.40 ± 3.63	392.47 ± 2.96	409.03 ± 2.45	16.57 ± 2.98	0.0051
	Placebo	395.90 ± 2.54	395.27 ± 2.80	400.57 ± 3.11	5.30 ± 2.48	
AUC QTcB (msec*hr)	Loratadine	4487.38 ± 36.1	4512.73 ± 33.0	4697.33 ± 30.2	184.60 ± 30.65	0.0846
	Placebo	4544.18 ± 31.5	4536.94 ± 31.9	4653.73 ± 34.4	116.78 ± 23.53	
* Results expressed as mean ± sem, n=30						
† p-value for one-sided test between loratadine and placebo treatment in day 13 minus day 5 change						
Source: v 165, p 36						

13.3.7. Conclusion

In this study the addition of 400 mg QD of ketoconazole for 8 days to a 13 day regiment of 10 mg QD of loratadine caused a mean QTcB interval prolongation when compared to placebo (16.3 msec vs 9.6 msec), and altered the PK parameters of loratadine. The observed QTcB prolongation in this study is in contradiction to the loratadine package insert and a published abstract, however, the PK interaction between loratadine and ketoconazole is consistent with the abstract (Brannan et al., J Clin Pharmacol 1994; 34:1016). The magnitude of alteration pharmacokinetics of loratadine by ketoconazole as observed in this study was about 5-10 fold less compared to the alteration of ebastine kinetics by ketoconazole (Study EBA 137, page 187).

13.4. EBA 138: A pharmacokinetic and electrocardiographic evaluation of the interaction between multiple doses of ebastine and erythromycin in healthy adult male volunteers.

13.4.1. Investigator and center

The study was conducted at a single site in the US between March and May of 1996 (v 176, p 126).

Investigator: Robert Pyke, MD
                   Phoenix International Life Science, Inc.

5642 Hamilton Avenue
Cincinnati, OH 45224

ECG re-analysis: Marek Malik, MD, PhD, DSc (Med), FAAC, FESC
Dept. of Cardiological Services
St. Georges Hospital Medical School
London SW17 ORE
UK

13.4.2. Objectives

The objectives of this study were to compare the electrocardiographic effects of ebastine (20 mg QD) administered concomitantly with erythromycin (800 mg TID) to ebastine alone and to erythromycin alone, and to compare the disposition kinetics of ebastine to ebastine administered with ketoconazole (v 176, p 91).

13.4.3. Study population

Study subjects were healthy male volunteers 18 to 40 years of age, with normal ECG (ECG criteria were similar to study EBA 132, page 95), and no relevant clinical, hematological, or biochemical abnormalities. Subjects were required not to have taken astemizole within 3 months, ketoconazole, itraconazole, or macrolide antibiotics within 1 month, and prescription or OTC medications within 2 weeks of the study. (v 176, p 98)

13.4.4. Study design

This was a single-center, randomized, investigator-blinded, placebo-controlled, three-way crossover study (v 176, p 13).

13.4.5. Study procedures

The study procedures are outlined in Table 160. A total of 30 subjects were recruited and assigned in random sequence to 3 treatment periods (ebastine 20 mg QDAM with erythromycin 800 mg TID, ebastine 20 mg QDAM with placebo, and placebo with erythromycin 800 mg TID) with 10 days of dosing in each period separated by a washout of at least 14 days. In each treatment period, subjects were admitted to a monitored facility 2 days prior to dosing for 12 consecutive nights. Each subject was administered study medication for 10 days to attain steady-state conditions. Baseline serial ECG was done on day -1 and compared to steady-state serial ECG done on day 10. Subjects were discharged on day 11 and returned to the investigative site on an outpatient basis on days 12 to 16 for ECGs and timed PK blood sampling. Subjects were to be discontinued according to predetermined ECG criteria (same as study EBA 136) and monitored until they revert to baseline. The examining physician at the study site read the ECGs at the site for implementing the discontinuation criteria. All ECG tracings were finally interpreted in the central facility in Philadelphia using the same criteria as described for study EBA 136 (page 171) with the exception that the ECGs were not evaluated for QTc dispersion. (v 176, p 17-30, 100-113)

Table 160. EBA 138, Plan of the study and schedule of observations

| | Screen day -28 | Inpatient | | | Outpatient | | End day 16 | Washout >14 days |
		Admit day -2	Baseline day -1	Dosing day 1-10	day 11	day 12-15		
Consent	x							
History	x	x						
Physical exam	x						x	
Vital signs	x	x		x			x	
Laboratory	x*	x†			x†		x*	
Dosing				x				
Serial ECGs			x‡	x‡				
Safety ECGs	x			x§	x	x	x	
Telemetry			x	x				
PK sample**			x	x	x	x	x	
Distribute diary	x							
Collect diary		x					x	

* Same as study EBA 136, listed in Table 139 footnote (v 176, p 116).
† Serum chemistry only
‡ On day -1 and day 10 at -0.5, 1, 2, 4, 6, 8, and 12 hours relative to the dose (v 176, p 91)
§ On day 1-5 at 6 hours after dose; On day 6-9 at predose and 6 and 12 hours after dose
** Single PK on day -1, days 6-9, and days 11-16; Serial PK on day 10 at predose, 1, 2, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, and 144 hours relative to the dose (v 176, p 91)

Source: v 176, p 93-95

13.4.6. Statistical considerations and analysis of QT interval

A sample size of 30 was chosen in order to complete 24 evaluable subjects. A total of 24 subjects would provide 90% power to detect a mean difference of 15 msec change from baseline QTc between the ebastine + erythromycin group and the placebo + erythromycin groups at a one-sided test. These assumptions were based on alpha level of 0.05 and a standard deviation of 20 msec derived from EBA 126 ebastine study (v 176, p 33-36).

The statistical calculation and the initial analysis were based on QT corrected for heart rate by Bazett's method (QTcB). The primary analysis were the mean changes from baseline QTc measurements (day -1) to steady-state QTcB measurements (day 10) in mean QTcB, maximum QTcB, and AUC between the ebastine + erythromycin group versus ebastine + placebo group, and ebastine + erythromycin group versus placebo + erythromycin group. The calculations were made using QTcB measurements from -30 minutes to 12 hours postdose. The principal analysis was an ANOVA for a crossover study with the model containing main effects for treatment. One-sided test at 5% level of significance was done for all comparisons. The PK/PD relationship was examined by linear regression analysis.

Subsequent analyses (post-hoc) corrected QT by various other methods, including Fridericia's method (QTcF), QTc by linear regression, and an individual patient correction method called Malik's correction (QTcM). In the results section below, initially the results based on QTcB are presented, followed by results based on other correction methodology.

13.4.7. Results

A total of 30 subjects were enrolled in the study. The age range was from 19 years to 40 years, and there were 18 Caucasians, 9 blacks, 2 Hispanics, and one oriental. Seven subjects discontinued from the study - 4 subjects (00006, 00022, 00027, 00028) withdrew consent, and 3 subjects had protocol violations (00017 tested positive on urine drug screen, and 00018 and 00024 had unauthorized alcohol use, all in period 3). No serious adverse event was reported and no subjects were discontinued due to adverse event or due to the ECG discontinuation criteria.

On PK measurement, ebastine and erythromycin combination treatment caused a 2-3 times greater bioavailability of ebastine and carebastine compared to ebastine alone (Table 161). The PK/PD linear regression analysis demonstrated that there was significant relationship between increasing ebastine and carebastine plasma concentrations and QTc interval prolongation compared to baseline. Of the laboratory parameters, a higher incidence of mild transient elevations in liver enzymes were seen in the two ebastine containing treatment groups as shown in Table 162. (v 176, p 37-67)

QTc analysis results based on Bazett's correction (the primary analysis) are shown in Table 163. Mean QTcB change for the different treatment groups is shown in Figure 8. The co-administration of ebastine 20 mg QD with erythromycin 800 mg TID for 10 days caused a significant mean QTcB prolongation when compared to ebastine alone or erythromycin alone. A total of 30 subjects were ECG outliers (defined as 444 msec prolongation of QTcB and at least 10 msec prolongation of QTcB over baseline) - 12 were from ebastine plus erythromycin group, 8 were from ebastine plus placebo group, and 10 were from erythromycin plus placebo group. On cardiac telemetry no clinically significant arrhythmia was seen. One patient during placebo plus erythromycin treatment was noted to have second degree AV block. (v 176, p 37-67)

Subsequent analyses of QT by other methods, including QTcF, QTc by linear regression, and QTcM are shown in Table 164. The conclusion that ebastine given along with erythromycin causes a prolongation of QTc as compared to erythromycin alone was borne out by all methods of QTc correction. Although the magnitude of the effect was lower when correction methods other than Bazett's was used, all showed a prolongation of QTc when compared to placebo when erythromycin was added to ebastine at steady-state.

Table 161. EBA 138, Mean (%CV) pharmacokinetic parameters of ebastine and carebastine on day 10

Parameter	Ebastine			Carebastine		
	Ebastine + Placebo	Ebastine + EES	p-value	Ebastine + Placebo	Ebastine + EES	p-value
AUC$_{0-24}$ (ng*hr/mL)	42.8 (53.1)	113.0 (60.1)	0.0001	5033 (32)	13237 (20)	0.0001
Cmax (ng/mL)	8.5 (59.4)	18.6 (48.3)	0.0001	315.6 (40)	688.3 (20)	0.0256
Cmin (ng/mL)	0.41 (63.2)	1.2 (89.9)	NA	132 (44.3)	456.2 (25)	NA
Tmax (hrs)	2.2 (0.5)	2.3 (0..4)	0.6556	5.1 (0.8)	6.8 (1.4)	0.0397
Source: v 176, p 65, 66						

Table 162. EBA 138, Subjects with >50% elevation of transaminases

	SGOT	SGPT	GGTP
Ebastine + placebo	6 (20 %)	10 (33 %)	4 (13 %)
Ebastine + erythromycin	6 (20 %)	10 (33 %)	4 (13 %)
Placebo + erythromycin	3 (10 %)	7 (23 %)	3 (10 %)
Results expressed as number of subjects (% of total)			
Source: v 176, p 52-54			

Table 163. EBA 138, Summary of primary analysis of QTcB results for all treated subjects

Variable	Treatment	N	Baseline mean	Adjusted* mean change from baseline (SEM)	One-sided p-value vs. Eba+EES	Two-sided p-value vs. EES+pbo	Two-sided p-value vs. Baseline
Mean QTcB (msec)	Eba+EES	25	389.8	19.6 (2.1)		0.2983	
	Eba+Pbo	27	387.9	6.1 (2.0)	0.0001		0.0015
	EES+Pbo	28	391.6	8.9 (1.9)	0.0001		0.0000
Max QTcB (msec)	Eba+EES	25	408.8	22.3 (3.5)		0.1304	
	Eba+Pbo	27	411.1	2.4 (3.2)	0.0001		0.2291
	EES+Pbo	28	412.2	9.4 (3.2)	0.0035		0.0021
AUC QTcB (msec*hr)	Eba+EES	25	4660.5	242.6 (25.4)		0.6955	
	Eba+Pbo	27	4634.8	96.6 (23.7)	0.0001		0.0001
	EES+Pbo	28	4686.5	109.4 (23.1)	0.0001		0.0001
*Adjusted for imbalance of primary population (subjects with at least placebo and ebastine 100 mg) in each treatment							
Source: v 176, p 57							
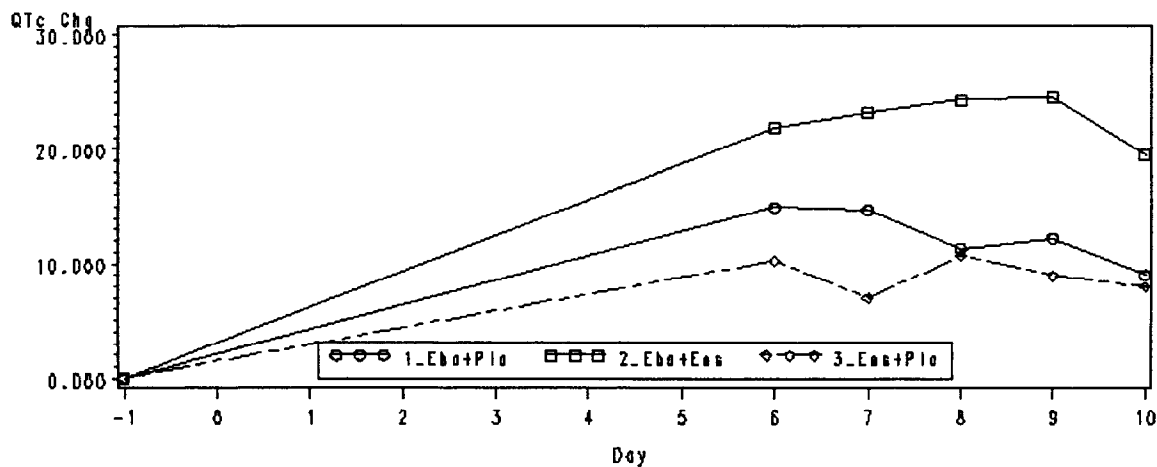
Figure 8. EBA 138, Mean QTcB change of the different treatment groups as compared to the baseline
Figure created from applicant's submitted data

Table 164. EBA 138, Corrected and uncorrected mean QT results (multiple QTc analyses)

	Treatment	N	Baseline mean	Adjusted[*] mean change from baseline (SEM)	One-sided p-value vs. Eba+EES	Two-sided p-value vs. EES+pbo	Two-sided p-value vs. Baseline
Mean Heart Rate (msec)	Eba+EES	25	67.2	7.6 (1.7)		0.2343	0.0004
	Eba+Pbo	27	65.0	5.6 (1.6)	0.2004		
	EES+Pbo	28	65.5	2.8 (1.5)	0.0212		0.0370
Mean QT[†] (msec)	Eba+EES	25	371.1	-2.8 (3.9)		0.0491	0.9966
	Eba+Pbo	27	376.0	-10.2 (3.6)	0.0956		
	EES+Pbo	28	377.3	0.5 (3.5)	0.7257		0.4489
Mean QTcB[†] (msec)	Eba+EES	25	389.8	19.6 (2.1)		0.2983	0.0015
	Eba+Pbo	27	387.9	6.1 (2.0)	0.0001		
	EES+Pbo	28	391.6	8.9 (1.9)	0.0001		0.0000
Mean QTcF[†] (msec)	Eba+EES	25	383.2	11.7 (1.8)		0.3509	0.0838
	Eba+Pbo	27	383.6	2.4 (1.7)	0.0000		
	EES+Pbo	28	386.5	4.4 (1.6)	0.0008		0.0055
QTc regress. (msec)	Eba+EES	25		12.0			
	Eba+Pbo	27		4.6			
	EES+Pbo	28		2.8			
QTcM (msec)	Eba+EES	25		9.3			
	Eba+Pbo	27		-0.35			
	EES+Pbo	28		4.3			

[*] Adjusted for imbalance of primary population in each treatment
[†] QTcB is Bazett's correction, QTcF is Fridericia's correction, QTcM is Malik's correction, QT is uncorrected QT interval

Source: v 1, p 8, 11/5/99 submission; QTc regression analysis from p 11, 1/5/00 submission; QTcM from p 8, section 18, 4/23/01 submission

13.4.8. Conclusion

Co-administration of ebastine 20 mg QD with erythromycin 800 mg TID caused a significant mean QTc interval prolongation (19.6 msec by Bazett's correction) when compared to ebastine alone (6.1 msec by Bazett's correction) or erythromycin alone (8.9 msec by Bazett's correction), and the addition of erythromycin to ebastine markedly altered the PK parameters of ebastine. PK/PD analysis demonstrated that there was significant prolongation of the QTc interval that correlated with increasing plasma ebastine concentration.

13.5. EBA 130: An open-label, interaction study between a single dose of ebastine and multiple doses of erythromycin stearate on the cardiac function and pharmacokinetic profile in healthy adult male volunteers.

13.5.1. Investigator and center

The study was conducted at a single site in the US in 1994 (v 180, p 6).

Investigator: Stuart I. Harris, MD
                South Florida Bioavailability Clinic, Inc.
                11190 Biscayne Blvd
                Miami, FL 33181

13.5.2. Objectives

The objectives of this study were to determine the electrocardiographic effects and pharmacokinetic profile of a single dose of ebastine when co-administered after multiple doses of erythromycin in healthy adult male volunteers, and to examine the relationship between QTc interval prolongation response and plasma ebastine and carebastine concentrations (v 180, p 10).

13.5.3. Study population

Study subjects were healthy male volunteers 19 to 40 years of age, with normal ECG and Holter (ECG and Holter exclusion criteria were similar to study EBA 132, page 95), and no relevant clinical, hematological, or biochemical abnormalities. Subjects were required not to have taken astemizole within 3 months, ketoconazole, itraconazole, or macrolide antibiotics within 4 weeks, and prescription or over-the-counter medications within 1 week of the study (v 180, p 300-302).

13.5.4. Study design

This was a single-center, open-label drug interaction study between a single dose of ebastine and multiple doses of erythromycin (v 180, p 295).

13.5.5. Study procedures

The study procedures are outlined in Table 165. A total of 15 subjects were recruited. The subjects were admitted to the clinical unit for 15 days for the study. Each subject was given erythromycin 500 mg every 6 hours on days 4 through 12, and a single dose of ebastine 20 mg in the morning on day 1 and day 9. ECG, PK sampling, and other measures were done as shown in Table 157. QTc was calculated on leads II, aVF, and single precordial lead with the longest QT on 12-lead ECG done on admission day. Thereafter, QTc was calculated from the 3 leads chosen on admission day and each QTc is the mean of 3 intervals. The examining physician at the study site initially read the ECGs for safety. All ECG tracings were finally interpreted in the central facility in Philadelphia. All QT correction was based on Bazett's method. (v 180, p 302-317)

Table 165. EBA 130, Plan of the study and schedule of observations

	Screen day -23	Admit day -2	Baseline day -1	1	2	3	4	5	6	7	8	9	10	11	12	End 13
Consent	x															
History	x															
Physical exam	x															x
Vital signs	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory*	x	x								x				x		
Ebastine				x								x				
Erythromycin							x	x	x	x	x	x	x	x	x	
ECG†	x	x	x	x							x	x	x	x	x	x
Holter	x			x							x	x				
Telemetry				x							x	x	x	x		
PK sample‡				x	x	x	x				x	x	x	x		x
Adverse event	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

* Same as study EBA 136, listed in Table 139 footnote (v 180, p 315).
† On days -1, 1, 8, and 9 serial ECG done at 0 (predose), 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours
‡ On days 1 and 9 blood drawn at 0 (predose) 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, and 96 (for day 9 only) hours

Source: v 180, p 330

13.5.6. Results and conclusion

This study evaluated single doses of ebastine with multiple doses of erythromycin. Therefore, ebastine levels were not at steady-state. The age range of the 15 enrolled subjects was from 18 to 39 years. No subjects were discontinued, there were no serious adverse events, and no clinically relevant ECG changes or abnormal laboratory values were seen. No subject had detectable plasma ebastine concentrations after single dose of ebastine at day 1. After co-administration of ebastine with erythromycin at steady state (day 9), 10 out of the 15 subjects had measurable plasma ebastine concentration ranging from 21.0 ng/mL to 43.6 ng/mL. This study supports ebastine-erythromycin interaction, however, no significant QTcB changes were seen in this limited exposure (v 171, p 24).

13.6. EBA 148: A comparative interaction study between multiple doses of ebastine ± ketoconazole and loratadine ± ketoconazole on cardiac function and pharmacokinetic profile in healthy adult male volunteers.

13.6.1. Investigator and center

The study was conducted at a single site in US between November, 1998 and February, 1999 (v 2.76, p 11).

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ECG re-analysis: Marek Malik, MD, PhD, DSc (Med), FAAC, FESC
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                  UK

13.6.2. Objectives

The objectives of this study were to compare the electrocardiographic effects of a therapeutic dose of ebastine (20 mg QD) and loratadine (10 mg/day) when administered with and without ketoconazole (400 mg QD) in healthy adult male volunteers, and to evaluate the pharmacokinetic profiles of ebastine/carebastine and loratadine/descarboethoxyloratadine when administered with and without ketoconazole.(v 2.76, p 17)

13.6.3. Study population

Study subjects were healthy, nonsmoking male volunteers 18 to 40 years of age, with normal ECG, and no relevant clinical, hematological, or biochemical abnormalities. ECG exclusion criteria were similar to study EBA 132 (page 95) except that QTc exclusion criterion was >440 msec rather than >444 msec. Patients were required not to have taken astemizole within 3 months, ketoconazole, itraconazole, or macrolide antibiotics within 2 months, and prescription or over-the-counter medications within 2 weeks of the study. (v 2.76, p 115-6)

13.6.4. Study design

This was a single-center, double-blinded, two-period crossover electrocardiographic and pharmacokinetic comparative drug interaction study between ebastine (20 mg once daily on days 1-13) plus ketoconazole (400 mg once daily on days 6-13) and loratadine (10 mg once daily on days 1-13) plus ketoconazole (400 mg once daily on days 6-13). There was a minimum of a 3-week washout period between study periods. (v 2.76, p 19)

13.6.5. Study procedures

The study procedures are outlined in Table 166. A total of 43 male subjects were recruited. The subjects were admitted to the clinical unit from day -2 to day 1, and again from the evening of day 4 through day 14 of the study. On days 2, 3, and 4, subjects returned as outpatients. Each subject was given double-blinded ebastine 20 mg or loratadine 10 mg (depending upon the study period) daily in the morning on day 1 through day 13, and open-label ketoconazole 400 mg daily in the morning on days 6 through 13 during both study periods. ECG, PK sampling, and other measures were done as shown in Table 166. However, blood levels of the comparator drug were not evaluated in the alternate treatment periods. The examining physician at the study site initially read the ECGs for safety, with machine calculation of QTc, followed by manual calculation of QTc if the automatic QTc was >500 msec. All ECG tracings were finally interpreted at a central facility in Philadelphia using digitized Jandel Sigmascan technology. QTcB was calculated on lead II. (v 2.76, p 19-32, 130).

Table 166. EBA 148, Plan of the study and schedule of observations for each study period

	Screen -23	Baseline -2	Baseline -1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Wash Out
Consent	x																	
History	x																	
Interim History		x																
Physical exam	x																	
Admitted		x-----------x					x--x										
Vital signs	x	x						x^7				x^7				x^7		
Laboratory	x^1	x^2						x^2				x^2				x^2		
Ebastine or Loratadine				X--X														
Ketoconazole								X-------------------------------X										
ECG	x			x^3				x^3	x^4	x^4	x^4	x^4	x^4	x^4	x^4	x^3	x	
Telemetry		x-----x						x------------------------------------x										
PK samples			x				x^5	x^5	x^6	x^5					x^5	x^5	x^6	x	
Adverse event				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

[1] Urinalysis (protein, glucose, blood), hematology (hemoglobin, hematocrit, WBC count, RBC count, and platelet count), and serum chemistry (creatinine, glucose, total cholesterol, triglycerides, total protein, total bilirubin, alkaline phosphatases, AST, ALT, GGT, sodium, potassium, C-reactive protein)
[2] Limited serum chemistry only (creatinine, AST, ALT, alkaline phosphatases, GGT, total bilirubin)
[3] 12-lead ECG serial measurements at -0.5 (predose), 0.5, 1, 1.5, 2, 3, 5, 8, 12, and 23.5 (pre-dose) hours
[4] 12-lead ECG serial measurements at 2, 5, and 12, hours post-dose
[5] Pharmacokinetic sample pre-dose
[6] Serial pharmacokinetic measurements following ECG measurements
[7] BP and pulse 5 hours post-dose

Source: v 2.76, p 21-2, 30, 110-1

13.6.6. Statistical considerations and analysis of QT

A total of 40 subjects would provide 90% power to detect a mean difference of 10 msec change from baseline QTc between the ebastine + ketoconazole group and the loratadine + ketoconazole groups with a two-sided test. These assumptions were based on alpha level of 0.05 and a standard deviation of 19 msec derived from EBA 137 and 145 ebastine study (v 2.76, p 33, 144). Therefore, the statistical calculation was based on studies in which QT was corrected for heart rate by Bazett's method (QTcB).

The initial safety analysis (primary analysis) was based on QT corrected for heart rate by both Bazett's (QTcB) and Fridericia's (QTcF) methods. The analyses included the mean changes from ebastine or loratadine steady-state QTc measurements (day 5) to ebastine + ketoconazole or loratadine + ketoconazole steady-state (day 13) QTc measurements in the mean, maximum, and AUC_{0-12hr} for QTc, QT, and heart rate. Also analyzed were the changes from baseline (day -1) to day 5 between the 2 treatment groups. The analysis was an ANOVA for a parallel design trial with the model containing treatment as the main effect. Subsequent analyses (post-hoc) corrected QT by various other methods, including QTc by linear regression, Framingham correction, and an individual patient correction method called Malik's correction (QTcM). In the results section below, initially the results based on QTcB are presented, followed by results based on other correction methodologies.

13.6.7. Results

A total of 43 subjects were enrolled and 40 completed the study. The age range was from 20 to 40 years. Thirty were Caucasians, 8 were Hispanic, 3 were Black, and 2 were classified as other. One subject (032) withdrew for personal reasons and one (036) was withdrawn for non-compliance. One subject (003) was discontinued on day -2 of period 2 due to elevated liver enzymes (ALT = 194 IU/l, AST = 110 IU/l, GGT 344 IU/l, and alkaline phosphatase = 170 IU/l). This subject had received the ebastine plus ketoconazole combination during the first treatment period. No serious adverse events were reported and no relevant changes were noted in any of the clinical parameters. (v 2.76, p 37-43, 55).

Co-administration of ketoconazole was shown to significantly alter the PK parameters of ebastine at steady state (Table 167). Cmax increased about 6 fold, Cmin increased about 45 fold, and AUC_{0-24} of ebastine increased about 16 fold. The PK parameters of carebastine were less affected (v 2.76, p 57-61). However, the applicant assumed that the washout period would be sufficient to avoid a carryover effect from the elevated blood levels and, during the second period, blood levels of the comparator drug were not evaluated. For study M/EBS/25, which employed a similar crossover design with a 2-week washout, a carryover effect was noted for ebastine [see M/EBS/25, page 213]. FDA analysis by Dr. Sandra Suarez did evaluate for an effect of treatment during period 1 with loratadine (plus ketoconazole) on the pharmacokinetic parameters for ebastine treatment in period 2, and none were found.

The PK/PD regression analysis demonstrated that there was a tendency toward increased QTc from baseline with increasing ebastine and carebastine plasma concentrations. Due to the limitations of inter- and intra-subject variability, no dose-response-QTc model could be defined to explain these relationships.

The primary QTc analyses results based on Bazett's correction are shown in Table 168 and the primary QTc analyses results based on Fridericia's correction are shown in Table 169. Outlier analyses for subject on day 13 shown in Table 170. The addition of 400 mg QD of ketoconazole to a 20 mg QD regimen of ebastine caused a significant mean QTcB and QTcF prolongation when compared to loratadine plus ketoconazole. A total of 13 subjects met the ECG outlier criteria of >440msec + >10 msec over corresponding baseline, of which 9 were from the ebastine plus ketoconazole group and 4 were from the loratadine plus ketoconazole group (Table 170).

Subsequent analyses of QT by other methods, including QTc by linear regression, and QTcM are shown in Table 171. The conclusion that ebastine given along with ketoconazole at steady-state causes a prolongation of QTc as compared to loratadine plus ketoconazole was borne out by all methods of QTc correction, although the magnitude of the effect was lower when correction methods other than Bazett's was used. In this study, the amount of QTc prolongation for ebastine plus ketoconazole was similar to the amount of QTc prolongation found in other studies, including study EBZ 137. Since this was a comparative study and placebo was not used, the exact effect size cannot be stated.

Table 167. EBA 148, Mean (%CV) steady-state pharmacokinetic parameters of ebastine and carebastine

Parameter	Ebastine			Carebastine		
	Day 5 Ebastine	Day 13 Eba + Keto	p-value	Day 5 Ebastine	Day 13 Eba + Keto	p-value
AUC_{ss} (ng*hr/mL)	55.8 (58)	869 (33)	0.0001	4229 (32)	7095 (27)	0.0001
Cmax (ng/mL)	9.45 (59)	61.0 (30)	0.0001	235 (33)	330 (29)	0.0001
Cmin (ng/mL)	0.488 (108)	17.1 (40)	0.0001	133 (32)	294 (25)	0.0001
Source: v 2.76, p 59, 60						

Table 168. EBA 148, Summary of analysis of QTcB results

Variable	n	Treatment	Day -1 Baseline mean*	Day 5 Ebastine or Loratadine	Day 13 + Ketoconazole	Day 13 - 5 Change with ketoconazole	p-value[†]
Mean QTcB	41	Ebastine	383.16 ±2.24	384.71 ±2.11	401.17 ±2.15	16.46 ±1.33	0.0081
(msec)	40	Loratadine	381.55 ±3.11	382.58 ±2.67	393.88 ±3.53	11.31 ±1.35	
Max QTcB	41	Ebastine	404.85 ±2.49	403.15 ±2.46	421.15 ±2.45	18.00 ±1.94	0.0056
(msec)	40	Loratadine	402.55 ±3.39	400.73 ±2.91	410.85 ±2.54	10.13 ±1.97	
AUC QTcB	41	Ebastine	4575.48 ±28.05	4618.74 ±28.12	4826.69 ±26.35	207.95 ±18.66	0.0577
(msec*hr)	40	Loratadine	4559.75 ±38.94	4595.95 ±31.85	4752.75 ±32.23	156.80 ±18.89	
* Results expressed as mean±sem							
† p-value for ANOVA between ebastine and loratadine treatment: day 13 minus day 5 (change when ketoconazole was added)							
Source: v 2.76, p 44 and v 2.77, p 88							

Table 169. EBA 148, Summary of analysis of QTcF results

Variable	n	Treatment	Day -1 Baseline mean*	Day 5 Ebastine or Loratadine	Day 13 + Ketoconazole	Day 13 - 5 Change with ketoconazole	p-value[†]
Mean QTcF	41	Ebastine	379.99 ±1.98	379.88 ±1.78	393.98 ±1.79	14.10 ±1.07	0.0022
(msec)	40	Loratadine	378.60 ±2.91	378.20 ±2.48	387.48 ±2.31	9.28 ±1.09	
Max QTcF	41	Ebastine	395.00 ±2.02	395.18 ±2.08	410.22 ±2.15	15.04 ±1.58	0.0031
(msec)	40	Loratadine	394.54 ±3.10	392.30 ±2.45	400.49 ±2.51	8.19 ±1.60	
AUC QTcF	41	Ebastine	4545.21 ±24.28	4558.73 ±23.32	4746.93 ±22.51	188.21 ±14.95	0.0167
(msec*hr)	40	Loratadine	4530.28 ±36.48	4542.03 ±29.39	4678.22 ±28.13	136.19 ±15.14	
* Results expressed as mean±sem							
† p-value for ANOVA between ebastine and loratadine treatment: day 13 minus day 5 (change when ketoconazole was added)							
Source: v 2.76, p 45							

Table 170. EBA 148, Outlier analysis of QTcB and QTcF results for Day 13

Variable		n	30-60 msec over mean baseline	>60 msec over mean baseline	>15% over mean baseline	>440msec + >10 msec over corresponding baseline	>440msec + >10 msec over mean baseline
QTcB							
Ebastine + ketoconazole	# Subjects	41	35 (85%)	4 (10%)	12 (29%)	9 (22%)	9 (22%)
	#ECGs	1941	238 (12.3%)	10 (0.5%)	22 (1.1%)	16 (0.8%)	16 (0.8%)
Loratadine + ketoconazole	# Subjects	40	26 (65%)	5 (13%)	6 (15%)	4 (10%)	4 (10%)
	#ECGs	1880	147 (7.8%)	8 (0.4%)	10 (0.5%)	5 (0.3%)	6 (0.3%)
QTcF							
Ebastine + ketoconazole	# Subjects	41	26 (63%)	0	0	1 (2.4%)	1 (2.4%)
	#ECGs	1941	132 (6.8%)	0	0	1 (0.1%)	1 (0.1%)
Loratadine + ketoconazole	# Subjects	40	19 (48%)	0	0	0	0
	#ECGs	1880	72 (3.8%)	0	0	0	0
Source: v 2.76, p 50							

Table 171. EBA 148, Corrected and uncorrected mean QT results (multiple QTc analyses)

	Treatment	Day -1 Baseline mean*	Day 5 Eba/Lora	Day 13 Eba/Lora + Ketoconazole	Day 13 - 5 Change with ketoconazole	p-value[+]
Mean Heart Rate (bpm)	Ebastine	63.5	65.2	67.4	2.2	0.6971
	Loratadine	63.3	64.8	66.6	1.8	
Mean QT[‡] (msec)	Ebastine	374.0	370.7	380.4	9.7	0.0595
	Loratadine	373.0	369.9	375.5	5.7	
Mean QTcB[‡] (msec)	Ebastine	383.2	384.7	401.2	16.5	0.0081
	Loratadine	381.6	382.6	393.9	11.3	
Mean QTcF[‡] (msec)	Ebastine	380.0	379.6	394.0	14.1	0.0022
	Loratadine	378.6	378.2	387.5	9.3	
QT regressn. (msec)	Ebastine				13.3	
	Loratadine				8.6	
QTcM (msec)	Ebastine				11.9	
	Loratadine				7.8	
* Results expressed as mean, n=30 [+] p-value for one-sided test between loratadine and placebo treatment in day 13 minus day 5 change [‡] QTcB is Bazett's correction, QTcF is Fridericia's correction, QTcM is Malik's correction, QT is uncorrected QT interval						
Source: v 1, p 14, 11/5/99 submission; QTc regression analysis from p 11, 1/5/00 submission; QTcM from p 8, section 18, 4/23/01 submission, v 2.76, p 52-3						

13.6.8. Conclusion

The study design for this study was very similar to the study design for study EBA 137 (page 187), except that this study was a comparative study with loratadine used instead of placebo. The addition of 400 mg QD of ketoconazole to a 20 mg QD regimen of ebastine at steady-state caused significant mean QTcB and QTcF interval prolongation when compared to loratadine (+16.5 msec vs 11.3 msec for QTcB). Loratadine was noted to have had about the same effect on QTcB and QTcF as placebo had in previous drug interaction studies (see EBA 137, page 187), and ebastine had similar effects on QTc as noted in other studies. The

addition of 400 mg QD of ketoconazole to a 20 mg QD regimen of ebastine altered the PK parameters of ebastine, significantly elevating the ebastine plasma levels. PK/PD analysis demonstrated that there was significant prolongation of the QTc interval that correlated with increasing plasma ebastine concentration. The carryover effect of ebastine was not evaluated.

13.7. M/EBS/24: A randomized, double-blind, placebo-controlled, 3-way crossover cardiac safety and pharmacokinetic interaction study between ebastine 20 mg, loratadine 10 mg, or placebo QD plus ketoconazole 200 mg BID, followed by open label ebastine 20 mg plus ketoconazole 400 mg QD, followed by open-label ketoconazole 400 mg QD in healthy adult male volunteers.

13.7.1. Investigator and center

The study was conducted at a single site in the United Kingdom between September and December of 2000 (v 2.83, p 1a).

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13.7.2. Objectives

This was a pilot study, with the primary objective to explore if there is a difference between the electrocardiographic effects and pharmacokinetic profile of ebastine (20 mg QD) compared to loratadine (10 mg QD) when co-administered with ketoconazole (200 mg BID or 400 QD) in healthy adult male and female volunteers (v 2.83, p 16).

13.7.3. Study population

The study sought to enroll healthy, nonsmoking male and female volunteers, 18 to 65 years of age, with normal ECG, and no relevant clinical, hematological, or biochemical abnormalities. ECG exclusion criteria were similar to study EBA 132 (page 95) except that QTc exclusion criterion was >440 msec for females and >430 msec for males. However, only males were enrolled. Subjects were required not to have taken astemizole within 3 months, ketoconazole, itraconazole, or macrolide antibiotics within 2 months, and

prescription or over-the-counter medications within 2 weeks of the study (v 2.83, p 24-5, 106-7).

13.7.4. Study design

This was a single-center, 3-phase (5-period), electrocardiographic and pharmacokinetic comparative drug interaction study between ebastine, loratadine, or placebo when co-administered with ketoconazole in different dosages. The first phase was a double-blind, placebo-controlled, 3-way crossover study between ebastine (20 mg once daily), loratadine (10 mg once daily), or placebo co-administered with ketoconazole (200 mg twice daily). The second phase was an open label study of ebastine (20 mg once daily) with and without ketoconazole (400 mg once daily). A third phase was an open label administration of ketoconazole alone (400 mg once daily). (v 2.83, p 18)

13.7.5. Study procedures

The study procedure is outlined in Table 172. [*Note: For simplicity, the third phase with ketoconazole alone is not included in the table, but the events are similar to open label phase 2. Note also that in phase 2 the days are discontinuously represented.*] A total of 6 subjects were recruited. The subjects were admitted to the clinical unit for each study phase and period. There was a 6-day washout between phases 1 and 2, and between each study period within phase 1, but there was about 2.5 weeks washout between phases 2 and 3. Each subject was given double-blinded ebastine 20 mg or loratadine 10 mg or placebo daily in the morning plus open-label ketoconazole 200 mg twice daily on day 1 through day 7 during one of the phase 1 study periods. During phase 2, each subject was given open label ebastine 20 mg daily in the morning on days 1 to 12, plus open-label ketoconazole 400 mg daily in the morning from day 6 to day 12. During phase 3, each subject received open label ketoconazole 400 mg daily in the morning on days 1 to 7. ECG, PK sampling, and other measures were done as shown in Table 172. A Hewlett Packard Pagewriter XL1 set at 25mm/sec and 10 mm/mV obtained 2 ECG tracings for each recording. The examining physician at the study site initially read the ECGs for safety, with machine calculation of QTc, followed by manual calculation of QTc if the automatic QTc was >500 msec. All ECG tracings were finally interpreted at a central facility (eResearch), with a blinded QTcB and QTcF calculated on lead II (v 2.83, p 14-36). The QTc was subsequently recalculated by QTcM and other methodology (v 2.84, p 4-16).

Table 172. M/EBS/24, Plan of the study and schedule of observations

	Screen -10 to -3	Base-line		Experimental phase (1): periods 1-3								Wash Out	Base-line		Open-label phase* period 4				
		-2	-1	1	2	3	4	5	6	7	8		-2	-1	1	5	6	12	13
Consent	x																		
History	x													x						
Admitted		x---x											x----------------------------------x						
Physical exam	x													x						
Vital signs	x	x			x					x	x			x			x	x	x	x
Screening tests§	x	x												x						
Laboratory#	x	x								x				x			x		x	

	Screen -10 to -3	Base-line		Experimental phase (1): periods 1-3								Wash Out	Base-line		Open-label phase* period 4				
		-2	-1	1	2	3	4	5	6	7	8		-2	-1	1	5	6	12	13
Ebastine, loratadine or placebo				x------------------------x															
Ebastine															x-------------x				
Ketoconazole				x------ 200 mg BID ------x													400 QD		
ECG†	x	x	x	x							x		x	x	x	x	x	x	x
PK sampling‡			x	x	x					x	x								
Adverse event	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

* Note that the days shown in this section of the table are discontinuous
† ECGs. For Phase 1, periods 1-3: D-1: -0.5, 1, 2, 4, 8, 12, and 23.5 (0.5h predose D1) hours. D7: -0.5 (predose), 0.5, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 12, and 23.5 hours post-dose.
For phase 2: D-1: -0.5, 1, 2, 4, 8, 12, and 23.5 (0.5h predose D1) hours. Days 5 and 12: -0.5 (predose), 1, 2, 4, 8, 12, 23.5 hours.
For phase 3: D-1: -0.5, 1, 2, 4, 8, 12, and 23.5 (0.5h predose D1) hours. D7: -0.5 (predose), 1, 2, 4, 8, 12, 23.5 hours.
‡ Pharmacokinetic sampling in phase 1. D-1: -0.5h. Days 1 and 7: -0.5 (predose), 1, 2, 4, 8, 12, 23.5 hours.
§ Screening tests: Urine drugs of abuse and alcohol, β-HCG (at d-2 screen only, then urine pregnancy)
# Full hematology, chemistry, and urine at screening (same as EBA 148). Limited testing at other visits: creatinine, AST, ALT, alkaline phosphatase, GGT, total bilirubin.

Source: v 2.83, p 20-1, 35-6, 38, 41

13.7.6. Results and conclusion

A total of 6 subjects were enrolled and 6 completed all three phases of the study. The age range was from 23 to 64 years. While the entry criteria allowed for females to be enrolled, all six subjects were male. Five were Caucasians and one was Black. No serious adverse events were reported and no relevant changes were noted in any of the clinical or laboratory parameters. (v 2.83, p 45-53).

Summary results of QTcB and QTcM are presented in Table 173. The results of this pilot study are limited by the small number of subjects and the unusual study design. They were used primarily to aid the design of further studies (i.e. M/EBS/25).

Table 173. M/EBS/24, Summary of Delta QTcB and QTcM

Treatment	n	Delta QTcB	Delta QTcM
Placebo + Ketoconazole 200 BID	6	-1.2 ± 14.1	-3.3 ± 16.6
Ebastine 20 QD + Ketoconazole 200 BID	6	-0.1 ± 14.3	4.0 ± 15.0
Loratadine 10 QD + Ketoconazole 200 BID	6	-4.0 ± 12.6	-1.3 ± 13.4
Ebastine 20 QD	6	-6.7 ± 5.1	-1.4 ± 9.0
Ebastine 20 QD+ Ketoconazole 400 QD	6	3.9 ± 6.9	13.0 ± 9.7
Ketoconazole 400 QD	6	3.1 ± 4.8	9.5 ± 7.3
* Results expressed as mean±sem			
Source: v 2.84, p 14-5			

13.8. M/EBS/25: A randomized, double-blind, placebo-controlled, two-way crossover cardiac safety and pharmacokinetic interaction study of ebastine 20 mg QD and ketoconazole 400 mg QD in healthy adult female volunteers.

13.8.1. Investigator and center

The study was conducted at a single site in US between December, 2001, and March, 2002 (v 2.70, p 2, 14).

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13.8.2. Objectives

The objectives of this study were to determine the effects on ventricular repolarization of ebastine when co-administered with ketoconazole in healthy adult female volunteers, and to examine the relationship between QTc interval prolongation response as evaluated by various models of QTc correction and plasma ebastine, carebastine, and ketoconazole concentrations, and to estimate if ketoconazole alone modifies the relationship between QT and RR. (v 2.70, p 24).

13.8.3. Study population

Study subjects were 24 healthy, nonsmoking female volunteers 18 to 40 years of age, with menstrual cycles of 28 ± 3 days, BMI between 18-28 kg/m^2, normal ECG (ECG exclusion criteria are listed separately below), and no relevant clinical, hematological, or biochemical abnormalities. Subjects were required not to have taken astemizole within 3 months, ketoconazole, fluconazole, itraconazole, or macrolide antibiotics within 2 months, and prescription or over-the-counter medications within 2 weeks of study drug administration. (v 2.70, p 120-1)

13.8.4. ECG exclusion criteria at screening (v 2.70, p 29, 121)

Unlike many previous studies, there was no exclusion criterion based on QTc (i.e. subjects were not excluded if QTc >0.444 seconds)

1. Fixed second degree AV block, transient or fixed third degree AV block
2. Atrial fibrillation
3. Ventricular flutter or ventricular fibrillation
4. Sustained ventricular tachycardia >30 seconds
5. *Torsade de Pointes*

13.8.5. Study design

This was a single-center, randomized, double-blind, placebo-controlled, 2-way crossover drug interaction study between ebastine 20 mg QD and ketoconazole 400 mg QD. (v 2.70, p 27)

13.8.6. Study procedures

The study procedure is outlined in Table 174. A total of 24 subjects were recruited. The study included two 13-day treatment periods separated by a 15-day wash-out period. Subjects were sequestered in the clinical unit for each treatment period, spanning from day – 2 through day 14. All treatment periods followed menses, and the washout period was adjusted so that the second treatment period was coordinated to each subject's menses. Therefore, day 1 of each study period was considered the fifth day of the menstrual cycle. During each treatment period each subject was given ebastine 20 mg or placebo administered once daily just after breakfast for 13 days. From Day 6 through Day 13, all subjects were administered ketoconazole 400 mg once daily just after breakfast. (v 2.70, p 27)

The study was designed to use an individual correction factor for heart rate correction of the QT interval. The corrected QT using this individualized correction factor is called QTcM. To obtain this individualized correction factor, a large number of ECGs were necessary for each subject. In fact, to establish an adequate baseline, serial ECGs were necessary on two days (day –2 and day –1), and these two days were averaged to form the 'baseline.'

On study days 1, 5, 12, and 13 serial ECG and PK sampling were done post dosing to reflect the ebastine non-steady state (day1), presumed ebastine steady-state (day 5), and presumed ebastine-ketoconazole steady states (days 12 and 13), and compared to the 'baseline' (day –2 plus day –1). Subjects were to be discontinued according to predetermined ECG criteria and monitored until they revert to baseline. ECG discontinuation criteria included: QTcF >500 msec for two or more ECGs in a single day, or a single increase in QTcF over 30% [*Note: the study report states this number to be 25%*] from baseline mean QTc at day - 1, or sustained ventricular tachycardia, or *Torsades de Pointes*, or ventricular flutter, or ventricular fibrillation. The examining physician at the study site was responsible for reading the ECGs for implementation of the discontinuation criteria. (v2.70, p 30-1, 121-2)

Digital ECG recordings were made with a GE Marquette system set at 25 mm/sec and 1 cm/mV, and 50 mm/sec and 2 cm/mV to record up to 5 cardiac cycles of each lead in a 10-second recording, and evaluated on a Magellan Research Workstation with a time axis resolution of 500 Hz, or 2 msec per pixel. All ECG tracings were blindly and independently measured by two cardiologists. If there was a difference of more than 25 msec, the questionable ECGs were returned to the same observers for re-measurement, and those results accepted as final, except that leads that were still problematic were read by Dr. Malik together with another senior cardiologist for a final QT measurement, and that decision was final. ECG acceptance criteria are discussed below. (v 2.70, p 34-8, 121-5)

Table 174. M/EBS/25, Plan of the study and schedule of observations

| | Screen | Treatment periods 1 and 2 | | | | | | | | Follow-up | |
Days	-21 to –3	-2	-1	1	2-4	5	6-11	12	13	14	15-20
Consent	x										
History	x					-					
Sequestration		x--x									
Physical exam	x	x								x	
Vital signs	x	x	x	x	x		x	x	x	x	
Screening labs*	x	x	x								
Laboratory†	x	x				x			x		
Ebastine/placebo				x---x							
Ketoconazole							x---------------x				
ECGs	x	x‡	x‡	x‡		x‡		x‡	x‡	x‡	
PK sampling§				x		x		x	x	x	
Adverse events	x	x	x	x	x	x	x	x	x	x	x
Telephone follow-up											x

* Virology (HIV, HBV, HCV), urine drug screen, breath alcohol, and blood pregnancy during screening, Urine drug screen, blood alcohol, and urine pregnancy on Day –2.

† Labs: Urinalysis (Semi-quantitative [dipstick] pH, protein, glucose, urobilinogen, bilirubin, nitrites, ketones, blood, leukocytes. Microscopic exam only if dipstick positive), hematology (hemoglobin, hematocrit, WBC count, RBC count, differential, platelet count, MCV, MCH, MCHC), and serum chemistry (creatinine, BUN, fasting glucose, uric acid, total cholesterol, triglycerides, total protein, albumin, C-reactive protein, total bilirubin, alkaline phosphatase, AST, ALT, GGT, sodium, potassium) (v 2.70, p 128)

‡ Serial ECG measurements:
Day -2: At -1, 2, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, and 23.5 hours relative to the dose
Days –1, 21, 5, and 12: At –0.5 (pre-dose), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, and 23.5 hours
Day 13: At –0.5 (pre-dose), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 23.5, 36, and 48 hours

§ PK measurements:
Days 1, 5, and 12: At –0.5 (pre-dose), 0.5, 1, 2, 4, 8, 12, 16, and 23.5 hours
Day 13: At –0.5 (pre-dose), 1, 2, 4, 8, 12, 16, 23.5, 36, and 48 hours

Source: v 2.70, p 118

13.8.7. Statistical considerations, analysis of QT interval, and ECG acceptance criteria

The statistical calculation and the initial analysis were based on QT corrected for heart rate by Malik's method (QTcM). A sample size of 24 was chosen to provide 90% power to detect a mean difference of 7 msec change from baseline QTcM between ebastine + ketoconazole and placebo + ketoconazole groups at a two-sided test. These assumptions were based on alpha level of 0.05 and a standard deviation of 10 msec (v 2.70, p 133). The primary analysis was the change from baseline to ebastine + ketoconazole or placebo + ketoconazole steady-state (day 13) mean QTcM. Baseline was defined as both days –2 and –1 for each treatment period. (v 2.70, p 117, 133-8)

Secondary, variables included

- Change from baseline to day 12 in mean QTcM

- Change from baseline to days 12 and 13 for maximum QTcM for each subject

- Differences between baseline mean QTcM and maximum QTcM at days 12 and 13 for each subject

- Differences between baseline minimum QTcM and maximum QTcM at days 12 and 13 for each subject
- Normalized AUC QTcM versus time at days 12 and 13 for each subject
- Outlier analysis in mean QTcM at days 12 and 13
- The same variables as above using QT, HR and Bazett, Fridericia, linear regression and other QT correction methods
- Safety evaluations
- Pharmacokinetic parameters for ebastine, carebastine, and ketoconazole.

There were two Amendments to the protocol, on January 15, 2002, and March 11, 2002. The first added comparisons for day 5 (change from baseline to day 5 when ebastine was at steady-state). The second limited the QT calculation and correction methodology to heart rate, uncorrected QT, Bazett (QTcB), Fridericia (QTcF), and individual correction methods (QTcM). Several additional methods were also used for the primary analysis of change from baseline to day 13 as outlined in the original protocol, and also for the secondary analysis of change from baseline to day 5 as outlined in the first Amendment. (v 2.70, p 27)

All analyses were based on the Per Protocol population (see ECG acceptance criteria below), with principle and secondary analyses (as appropriate) using the Wilcoxon Signed Rank Test with a significance of 0.05. This analysis did not take into account any treatment sequence carryover effects. (v 2.70, p 133-8)

ECG acceptance criteria for analysis of QT interval included (v 2.70, p 127):

- At least 3 cardiac cycles (3 complete images of sinus rhythm cycles that do not follow an atrial or ventricular premature beat or a fusion beat, and which do not have an apparent intraventricular conduction abnormality)
- At least 6 of the 12 leads are measurable
- The slope of the RR trend is either not statistically different from 0 or is within the interval between −5 msec and +5 msec per RR interval.

13.8.8. Results

A total of 24 female subjects were enrolled, and 23 subjects completed the study. One subject (#18) withdrew consent on day 5 of the first treatment period of ebastine. The age range of the study subjects was from 23 years to 40 years. There were 3 Caucasians (13%), 1 Black (4%), and 20 Hispanics (83%) enrolled. There were several protocol violations, but all were minor. No serious adverse events or deaths were reported. No subject was discontinued due to the ECG discontinuation criteria. Four subjects (17.4%) reported nausea when on the ebastine plus ketoconazole combination, with none during ebastine alone, and one when on the placebo plus ketoconazole combination. There were no significant changes in laboratory, vital sign, or physical examination parameters. Two subjects had ALT plus AST values that were considered elevated on day 13 of ebastine + ketoconazole, but neither had elevations at other time points. (v 2.70, p 52-5; 70 2; v 2.71, p 224-233)

Of significance, of the 4090 ECG recordings, 539 (13.2%) did not meet the ECG evaluable criteria. Therefore the number of Per Protocol evaluable ECGs were 3551 (86.8% of the

total). The study report states that the primary reason for exclusion of ECGs was the detection of a significant RR interval trend. Other ECGs were excluded due to the use of less than 6 measurable leads or due to a combination of the two exclusion criteria. Visual examination of a table showing the excluded ECGs reveals that they were scattered throughout the study, with no discernable pattern, except that somewhat more were excluded during baseline days than on other days. Rates of excluded ECGs were the same for both treatment sequences. One single patient (#15) was responsible for 72 of the excluded ECGs, of which 24 were during the baseline periods. (v 2.70, p 52-5; v 2.72, p 2)

Even though the study report stated that the number of Per Protocol evaluable ECGs were 3551, the electronic dataset submitted with the complete study report (submitted as part of the complete response) included 3516 ECGs. Therefore, on October 15, 2002, the Agency requested an explanation of the missing ECGs. Almirall submitted a response on October 24, 2002, stating that the difference of 35 ECGs were the ECGs from the subject who withdrew from the study on day 5, and therefore the ECGs from this subject were not included in the dataset used for the analysis.

Pharmacokinetic parameters for ebastine and carebastine are listed in Table 175. The concentration-time profiles of ebastine and carebastine measured on each treatment days 1, 5, 12, and 13 are shown in Figure 9 and Figure 10, respectively. Ebastine AUCt ($AUC_{0-23.5}$) and Cmax were similar on days 1 and 5, and the concentration dropped to near zero over a 23.5 hour period. Co-administration of ketoconazole was shown to significantly alter the pharmacokinetic parameters of ebastine (Table 175). Cmax, AUCt, and $AUC_{0\rightarrow\infty}$ of ebastine increased about 16-, 44-, and 52-fold, respectively. After treatment was stopped, the mean ebastine concentration (Cmax) dropped from about 69 ng/mL to 6.7 ng/mL over 50 hours on days 13 to 14. The Cmax of carebastine more than 55 times higher than the Cmax of the parent drug, and accumulated in the body due to its long half-life (24.6 hours at steady-state) compared with the dosing interval. While co-administration of ketoconazole did not significantly alter Cmax or AUCt of carebastine, and carebastine plasma levels remained constant throughout the dosing interval on day 12, and for 48 hours after dosing on day 13 (Figure 10).

While only two subjects had a complete concentration-time profile characterized on days 1, 5, 12, and 13 of the second treatment sequence, all the subjects had concentrations determined two hours post ebastine dosing on those days. Of significance, there was a carryover of plasma levels for ebastine after subjects received ebastine during the first treatment period, such that the ebastine AUCt on Day 1 of period 2 (17.4 ng/mL) were comparable to the ebastine AUCt on Day 5 of period 1 (17.9 ng/mL) (Table 176). However, the ebastine Cmax on Day 1 of period 2 was 20% of the ebastine Cmax observed on Day 5 of period 1, and the carebastine Cmax and AUCt on Day 1 of period 2 were 8% and 10% respectively of those levels observed on Day 5 of period 1. (v 2.70, p 88-9)

The applicant's QTc analysis results based on Malik's individual correction method (the primary analysis) are shown in Table 177. Results calculated from the 3516 ECG dataset by the FDA statistician are shown in Table 178. Results of FDA analyses were quite similar to the applicant's results (primary analysis results shown in **bold**). Supplementary analyses of QT by other methods, including QTcB, QTcF, and QTc individual log-log are shown in Table 179 and Figure 11 along with heart rate and QT results. On Day 5, when ebastine was

at steady-state, the resting heart rate increased by 3.90 msec over baseline compared to placebo, and the mean QTcM, as calculated by the applicant, increased by 0.78 msec over baseline (Table 179). The addition of 400 mg QD of ketoconazole increased the resting heart rate on day 13 by 4.60 msec over baseline compared to placebo, and caused a significant ($p = 0.0000$) mean QTcM prolongation of 10.71 msec from baseline when compared to placebo (primary variable; shown in **bold** in Table 177 and Table 179). Most of the effects of ebastine on heart rate are seen to occur by day 5 at which time ebastine is at steady state, with little further changes (0.70 msec) when ketoconazole is added despite the large increases in ebastine levels by days 12 and 13. Differences between ebastine and placebo for changes from baseline in mean QT results using multiple QTc correction methods are shown graphically in Figure 11. While there was some variation between different QTc analyses, and QTcM was the lowest, all showed a positive correlation between changes in QTc on all treatment days, including days 5, 12, and 13. (v 2.72, p 112)

The applicant's data was reanalyzed by FDA statisticians and clinical pharmacologists. Figure 12 shows the baseline, day 5 and day 12 mean QTcM for each treatment group and treatment sequence. A clear effect with ebastine plus ketoconazole, but not with placebo plus ketoconazole, is seen for each treatment group. There was no effect on QTcM seen when ketoconazole was added to placebo. Analyses showed that despite the carryover of plasma levels for ebastine to the beginning of the next treatment period after subjects received ebastine plus ketoconazole during the first treatment period, there was no pharmacodynamic carryover of QTcM prolongation at baseline of the next treatment period (Figure 12). Baseline also varied between the two baseline days and between the two treatment sequence groups, but baselines for each treatment sequence group remained quite similar between treatment sequences for both groups, implying that there was no regression to the mean for baseline QT interval over time. Previous studies employed an entry criteria limiting subjects to a QTc < 444 msec. The applicant has argued that the study entry criteria for ECG for the other cardiac safety studies predisposed to enrollment of individuals at the low end of natural rhythm of the individual QT variability, thus explaining the rise in QT over time for both the placebo and ebastine treatment groups in the other cardiac safety studies. However, since baseline did not change over the treatment sequences in this study, this argument for why QTc increased is no longer applicable.

ECG outlier criteria were defined as at least one ECG with >30 msec increase from mean baseline QTc, or QTc >450 msec and >10 msec increase from mean baseline QTc. Table 180 shows all QTc outliers based on Malik's correction. The QTcM outlier results for all subjects on days 12 and 13 are also represented graphically in Figure 13 as change from individual baseline for each subject. Eleven subjects met the ECG outlier criteria. Ten (10) of the 11 subjects had outlier ECGs on days 12 or 13 of ebastine plus ketoconazole; one (1) subject (#16, P+K to E+K) had outlier ECGs on baseline days –2 and -1, and on day 5 of placebo during the first treatment period (i.e. this was not related to a carryover from previous ebastine treatment). Of the 10 ebastine plus ketoconazole subjects who had ECGs that were outliers, 8 subjects had at least one ECG with a >30 msec increase (range = 30-49 msec), 3 subjects had at least one ECG with a >450 msec and >10 msec increase, and one had at least one ECG which met both outlier criteria. Several subjects had ECGs that met outlier criteria more than once. One subject (#2) on ebastine plus ketoconazole had a QTcM of 450 with a 48.76 increase from baseline on day 13. The one outlier subject (#16) on

placebo plus ketoconazole had a QTcM of 472 on day –2 and 477 on day –1 of the first treatment period, while the mean baseline for this subject was 459.6. (v 2.72, p 119-120)

The relationship between ebastine/carebastine blood concentrations and QTcM was explored in-depth by Dr. He Sun at the FDA. Pharmacokinetic/pharmacodynamic analysis was limited by the number of patients (23) who were enrolled and completed the study. The QTcM change was analyzed when subjects received ebastine plus ketoconazole and compared with when they received placebo plus ketoconazole. Figure 14 shows the median and distribution of ECGs, with both ebastine and placebo treatment groups plotted side-by-side, and with individual subject numbers. The closed box represents the 25th to 75th quintiles, brackets represent the whisker (1.5 time the hinge) intervals, and isolated lines outside the brackets represent outliers. The center line within the box represents the median. The use of a box plot shows both the central tendency and the data distribution. While most individual subjects are not discernable, it may be seen that several subjects consistently were either high (#16) or low (#9). In addition, the data suggest that there is ~5 msec increase in median QTcM between days 1 and 5 for the ebastine group, and again another ~10 msec increase between days 5 and 12 when ketoconazole is added. This comes to a non-baseline-corrected ~15 msec increase from day 1 to day 12 for ebastine at steady-state plus ketoconazole.

QTcM was analyzed under both ebastine and placebo treatment conditions. QTcM distribution for all reported ECGs were plotted by treatment for days –2, –1, 1, 5, 12, and 13, and are shown in Figure 15. The analysis by treatment group demonstrated that there was a significant correlation between increasing ebastine plasma concentrations and QTcM changes from baseline for the ebastine plus ketoconazole treatment group (Figure 14 and Figure 15) while QTcM remained constant for the placebo plus ketoconazole treatment group on all days. This relationship between ebastine treatment and QTcM held true for both periods on days 12 and 13 (Figure 12), with a small but evident relationship on day 5 (steady-state ebastine alone). Both the median, upper, and lower whisker limits increased with ebastine plus ketoconazole treatment, but there were no individual outliers seen on either day 12 or 13 (Figure 15).

Since significant inter-subject variability masks the QTcM versus ebastine concentration relationship, individual QTcM for each subject across different treatment days were analyzed. Figure 16 shows individual QTcM for each subject across different treatment days, and Figure 17 shows the same information presented as the individual QTcM versus exposure. For each subject, the blue boxes are ebastine treatment and red boxes are placebo treatment for the same treatment day at period 1 or 2, respectively. As in other studies (and as expected), there was significant intra- and inter-individual variability in QTc. The box and whisker limits for a particular day and individual indicate the intra-subject variability of repeated within-day QT measures, and the difference between the median of one subject and another demonstrates the inter-subject variability. There appeared to be more inter- than intra-individual variability, as shown in the analysis by individual subjects. Inter-subject variability of average QTcM was about 100 msec (range from 370 msec to 470 msec), and intra-subject within-day variability was about 10-30 msec at baseline and during placebo treatment. In Figure 16, it may bee seen that no general separation of the two colored boxes occurred at either baseline day or during the ebastine/placebo treatment days (days 1 and 5).

However, on days 12 and 13 (at the top of the figure) there is a clear separation of QTcM median value and quintiles with ebastine plus ketoconazole treatment from placebo plus ketoconazole treatment for all but two subjects (#3 and #11). This analysis further confirmed that not only were the means increased due to the co-administration of ebastine plus ketoconazole on days 12 and 13, but also nearly all individual QTcMs were as well.

QTc-time profiles (not shown) over 24 hours do not follow the significant fluctuations of ebastine or carebastine concentrations on any of the treatment days, either on days 1 and 5 when ebastine was given alone, or on days 12 and 13, when ebastine was given with ketoconazole. These analyses suggest that QTc prolongation does not acutely follow plasma concentration.

Since individual acute QTc change with drug concentration change was not apparent within a treatment day, an analysis of within-day mean QTc versus total drug exposure was conducted. Analysis by individual subjects (figure not shown) also showed a clear relationship between QTcM and treatment on days 12 and 13 when ebastine was given with ketoconazole. Mean individual within-day QTcM for baseline day −2 tended to be lower than baseline day −1 by an average of 4 msec. The mean individual within-day QTcM at treatment day 5 was always greater than on day 1, which suggested a delayed QTcM prolongation effect, considering that the ebastine AUC remained constant and the carebastine AUC increased by less than 2-fold between days 1 and 5. Mean individual within-day QTcM at treatment day 12 was always greater than on day 5 by an average of 10 msec, which suggests an ebastine exposure-related QTc prolongation effect, considering that the mean ebastine AUCt is increased by more than 40-fold and $AUC_{0 \to \infty}$ increased ~6-fold compared to day 5.

PK/PD modeling using individualized, group-wised, and mixed-effect methods with linear, exponential, and Emax models were evaluated (data not shown). The regression analysis demonstrated that there was a tendency toward increased QTc from baseline with increasing ebastine and carebastine plasma concentrations or AUC. Nevertheless, due to the limitations of inter- and intra-subject variability, goodness of fit analysis did not support any single exposure-response-QTc model. The applicant's conclusion that there is a plateau of QTc prolongation with increasing doses, concentrations, or exposure (AUC) is not supported by PK/PD modeling.

The conclusion that ebastine given along with ketoconazole at steady-state causes a prolongation of QTc as compared to ketoconazole alone was borne out by all methods of QTc correction including QTcM. The magnitude of effect was 10.71 msec for the primary analysis by QTcM on Day 13 (p = 0.000) (Table 177). These results are in accordance with the results seen in previous studies in males (EBA 137, EBA 148 and others).

**Table 175. M/EBS/25, Mean single-dose and steady-state pharmacokinetic parameters of ebastine and carebastine**

Parameter	Day 1 (EBA)	Day 5 (EBA)	Day 12 (EBA + KET)	Day 13 (EBA + KET)
Ebastine (n = 23)				
Cmax (ng/mL)	4.8 (3.3)	4.3 (2.7)	65.1 (14.8)	69.12 (13.9)
Cmin (ng/mL)	0.06	0.12	13.12	13.96
AUCt (ng*hr/mL)	17.9 (13.6)	17.9 (10.44)	736.5 (141)	792.8 (141)
AUCinf (ng*hr/mL)	19.4 (13.7)	19.5 (11.4)	945.9 (200.8)	1009 (194)
Carebastine (n=23)				
Cmax (ng/mL)	264.2 (67.8)	398.2 (94.1)	311.7 (72.4)	325 (76)
AUCt (ng*hr/mL)	3806.7 (866)	6250.6 (1125.2)	6700.7 (1582)	6958.7 (1757)
Source: Dr. Sandra Suarez, Office of Clinical Pharmacology and Biopharmaceutics, FDA				
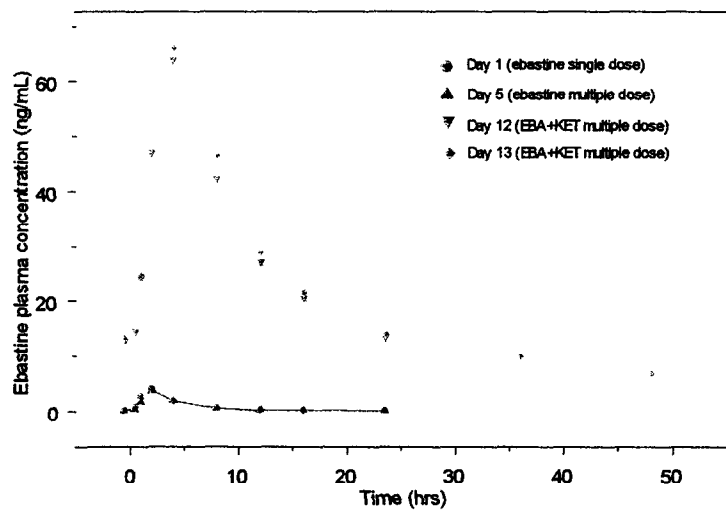
Figure 9. M/EBS/25, Mean ebastine concentrations over time, all treatment days
Source: Dr. Sandra Suarez, Office of Clinical Pharmacology and Biopharmaceutics, FDA
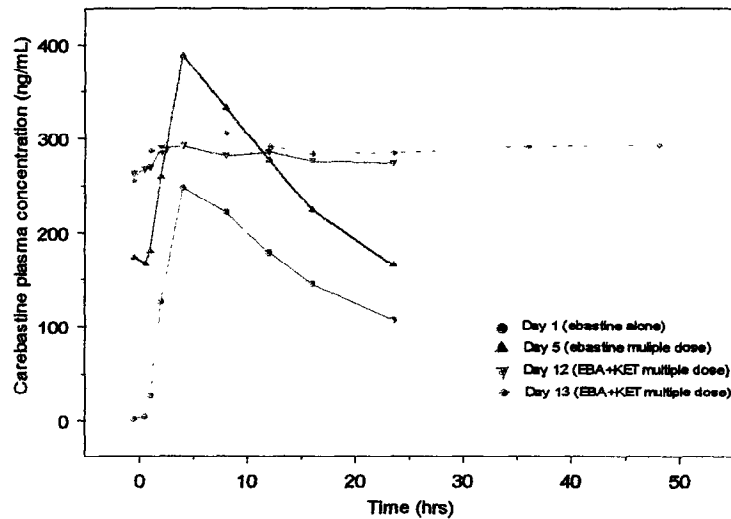
Figure 10. M/EBS/25, Carebastine concentrations over time, all treatment days
Source: Dr. Sandra Suarez, Office of Clinical Pharmacology and Biopharmaceutics, FDA

Table 176. M/EBS/25, Cmax and AUC ebastine and carebastine carry-over values for subjects who received ebastine plus ketoconazole in Period 1

Parameter	Period 2 Carryover			
	Ebastine (n=1)		Carebastine (n=1)	
Cmax (ng/mL)	Day 1	0.9	Day 1	31.6
	Day 5	0.71	Day 5	23.8
	Day 12	1.89	Day 12	10
	Day 13	1.81	Day 13	9.4
AUCt (ng*hr/mL)	Day 1	17.4	Day 1	640.25
	Day 5	14.3	Day 5	484
	Day 12	36.6	Day 12	215
	Day 13	37.6	Day 13	185
AUCinf (ng.hr/mL)	Day 1	-	Day 1	2685
	Day 5	-	Day 5	3006
	Day 12	111.26	Day 12	1185
	Day 13	142.7	Day 13	4779
Note: PK samples from only two subjects were analyzed over the entire period of sample collection. Data comes from only one subject who received ebastine + ketoconazole in period 1 followed by placebo + ketoconazole in period 2.				
Source: Dr. Sandra Suarez, Office of Clinical Pharmacology and Biopharmaceutics, FDA				

Table 177. M/EBS/25, Summary of primary analysis of QTcM results (msec)

Variable	Treatment (n = 23)	Baseline mean*	Day 13 + Ketoconazole	Change from baseline with ketoconazole	Delta Day 13	p-value[†]
Mean QTcM	Ebastine	410.01	421.09	11.09	10.71	0.0000
	Placebo	410.17	410.55	0.38		
Min QTcM	Ebastine	380.00	387.92	-17.77	-2.88	
	Placebo	379.73	379.67	-15.28		
Max QTcM	Ebastine	466.04	448.27	25.84	28.60	
	Placebo	459.36	444.08	10.50		
[†] p-value for 2-sided test between ebastine and placebo treatment in day 13 minus baseline (day –1 and day -2) change						
Source: v 2.70, p 58						

Table 178. M/EBS/25, FDA analysis of Mean QTcM (msec)

| Period	Treatment (n)	Baseline mean	Day 5	Day 12	Day 13	Day 5 - Base	Day 12 - Base	Day 13 - Base	p-value
1	Ebastine (11)	407.165	408.932	419.827	417.445	1.767	12.662	10.280	
	Placebo (12)	413.146	416.010	414.288	412.433	2.864	1.141	-0.714	
2	Ebastine (12)	412.396	414.998	424.369	422.943	2.601	11.973	10.547	
	Placebo (11)	406.647	406.477	408.885	406.847	-0.170	2.238	0.201	
Both periods	Ebastine (23)					2.202	12.302	10.419	
	Placebo (23)					1.413	1.666	-0.276	
Difference between Ebastine and Placebo (Delta)						0.789	10.636	10.695	0.0002
Source: Table created from data provided by Dr. Ted Guo, Division of Biometrics II, FDA									

Table 179. M/EBS/25, Corrected and uncorrected mean QT results (multiple QTc analyses)

Variable	Treatment (n = 23)	Baseline mean*	Day 5	Delta Day 5	Day 12	Day 13	Change from baseline to Day 13 *	Delta Day 13	p-value†
Heart Rate	Ebastine	70.01 (7.320)	77.10	3.90	77.61	77.54	7.53 (4.165)	4.60	0.0001
	Placebo	70.10 (7.231)	73.29		73.15	73.03	2.93 (3.733)		
QT	Ebastine	393.60 (21.523)	384.07	-5.49	394.12	392.57	-1.03 (12.276)	2.93	0.0826
	Placebo	393.01 (19.988)	388.96		389.77	389.04	-3.96 (9.263)		
Mean QTcM	Ebastine	410.01 (18.090)	411.77	0.78	422.44	421.09	11.09 (9.403)	10.71	0.0000
	Placebo	410.17 (17.164)	411.15		411.47	410.55	0.38 (6.817)		
Mean individualized log-log	Ebastine	410.27 (18.097)	411.99	0.64	423.38	421.87	11.60 (9.596)	11.33	0.0000
	Placebo	410.46 (17.340)	411.54		411.73	410.73	0.27 (6.975)		
Mean QTcB	Ebastine	423.21 (15.641)	433.68	5.25	446.35	444.69	21.49 (7.093)	16.88	0.0000
	Placebo	422.94 (14.710)	428.16		428.45	427.54	4.60 (8.053)		
Mean QTcF	Ebastine	412.92 (14.338)	416.31	1.42	428.05	426.45	13.53 (7.437)	11.92	0.0000
	Placebo	412.53 (12.566)	414.51		414.96	414.14	1.61 (6.629)		

* Results expressed as mean (SD) in milliseconds. For HR, QT, QTcB, and QTcF, the baseline pooled values were derived from baseline data of each subject separately. Delta = comparison between ebastine and placebo change from baseline.

† p-value for 2-sided test between ebastine and placebo treatment in day 13 minus baseline (day −1 and day -2 change

Source: v 2.70, p 59; v 2.72, p 112, 123, 131, 137, 148, 175
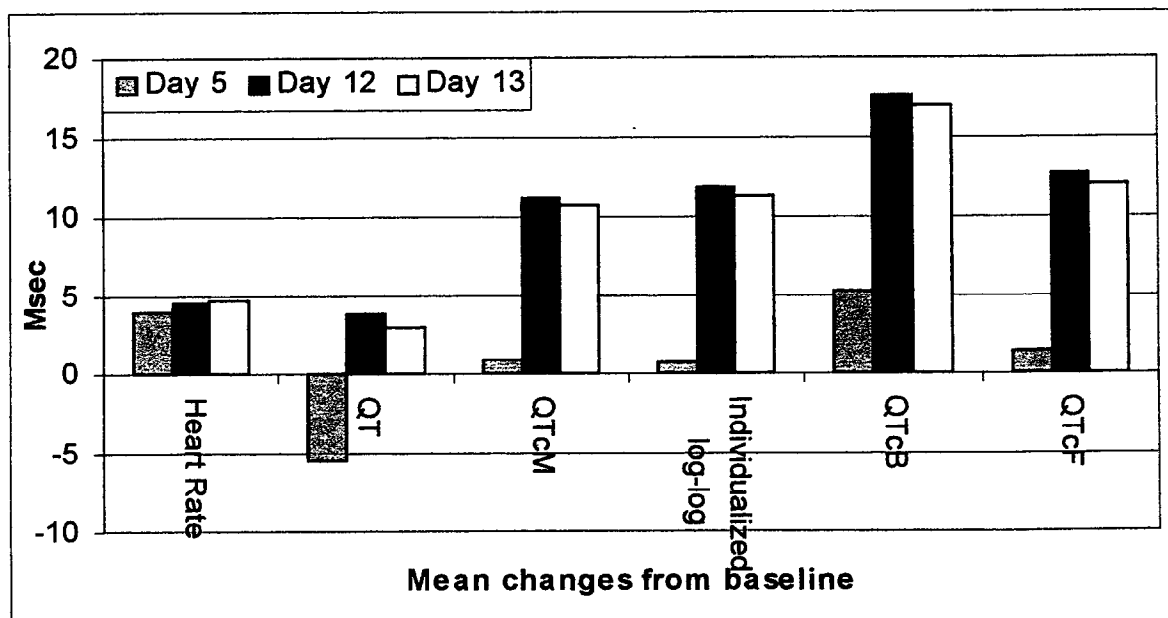
Figure 11. M/EBS/25, Differences between ebastine and placebo for changes from baseline in mean QT results (multiple QTc analyses)
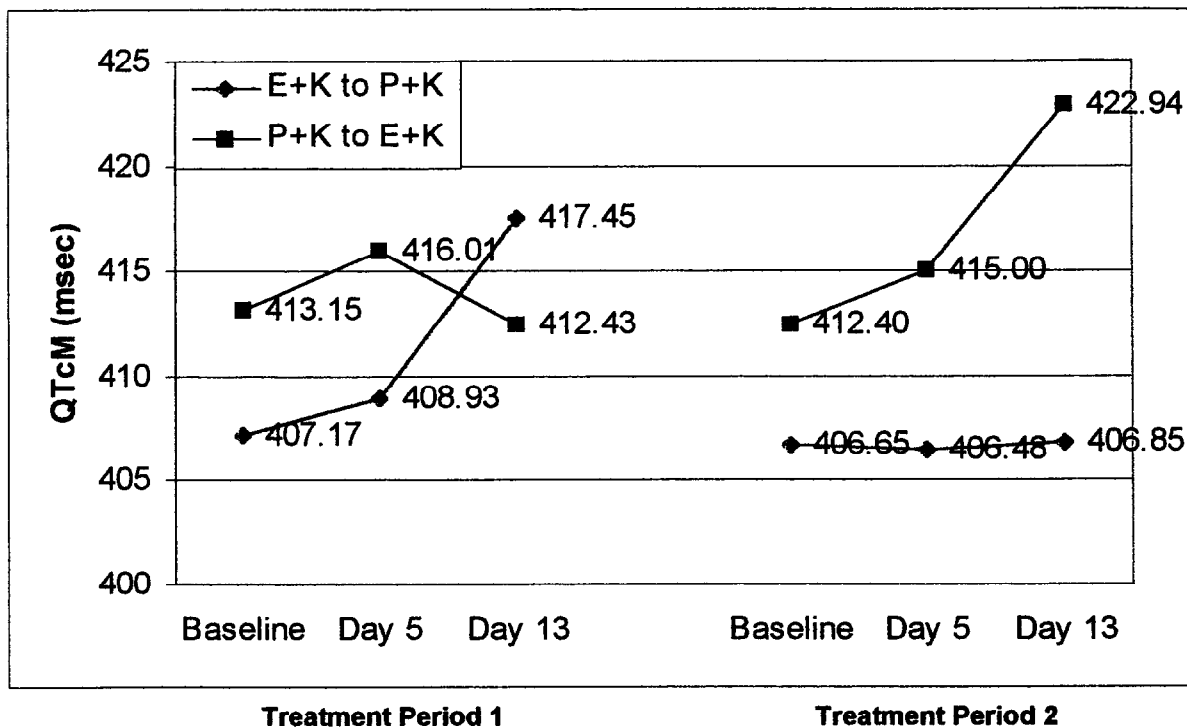Source: Data derived from tables in v 2.72, p 112, 123, 131, 137, 148, 175

Figure 12. M/EBS/25, Mean QTcM changes of ebastine + ketoconazole and placebo + ketoconazole groups on Days 5 and 13 of treatment as compared to baseline for each treatment period

E+K = Treatment period with ebastine 20 mg QD in AM from days 1-13, plus ketoconazole 400 mg QD in AM from days 6-13

P+K = Treatment period with placebo QD in AM from days 1-13, plus ketoconazole 400 mg QD in AM from days 6-13

Baseline = Days –1 and –2 combined

Source: Figure created from data provided by Dr. Ted Guo, Division of Biometrics II, FDA

Table 180. M/EBS/25, Outlier analysis of QTcM results

Patient	Mean baseline QTcM (msec)	Day	Time	QTcM	Difference QTcM - Baseline	Outlier qualification	
						30-60 msec over mean baseline	>440msec + >10 msec over mean baseline
Ebastine + Ketoconazole							
2	401.24	12	3.0	433	31.76	X	
			6.0	434	32.76	X	
			14.0	432	30.76	X	
		13	2.0	436	34.76	X	
			6.0	450	48.76	X	
6	394.68	12	6.0	427	32.32	X	
13	389.37	12	4.0	423	33.63	X	
			16.0	420	30.63	X	
14	431.38	12	5.0	454	22.63		x
			6.0	453	21.63		x
		13	6.0	452	20.63		x
15	418.95	12	23.5	449	30.05	X	
17	424.95	12	6.0	459	34.05	X	x
			7.0	451	26.05		x
			8.0	454	29.05		x
			14.0	463	38.05	X	x
		13	5.0	454	29.05		x
19	405.43	12	7.0	437	31.57	X	
			8.0	436	30.57	X	
			23.5	436	30.57	X	
21	411.05	13	6.0	448	36.95	X	
22	432.78	12	23.5	451	18.22		x
24	406.61	12	8.0	443	36.39	X	
			16.0	439	32.39	X	
Placebo + Ketoconazole							
16	459.36	-2	4.0	472	12.64		x
		-1	-0.5	477	17.64		x
		5	-0.5	472	12.64		x
Source: v 2.72, p 119-120							