ANTIVIRAL DRUGS ADVISORY COMMITTEE
BRIEFING DOCUMENT

PICOVIR™ (PLECONARIL)

NDA 21-245

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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1. INTRODUCTION AND SCIENTIFIC RATIONALE

Pleconaril is the first of a new class of antiviral agents designed to treat infections caused by picornaviruses, the primary etiologic agents of the "common cold." It was hypothesized that inhibition of picornavirus replication would reduce the severity and shorten the duration of cold symptoms. Pleconaril was rationally designed based on atomic resolution structures of drug/virus complexes, analyses of structure-activity relationships, screens for metabolic stability in liver microsomes, and extensive nonclinical safety testing. The pleconaril New Drug Application (NDA), submitted July 31, 2001, is the result of sustained efforts to design and conduct successful clinical safety and efficacy trials.

2. REGULATORY HISTORY AND PROPOSED INDICATION

2.1 U.S. Regulatory History of Pleconaril

Pleconaril was synthesized by Sterling Winthrop, Inc. in the early 1990s. This milestone was followed by nonclinical drug development and early Phase I clinical trials. In 1995, the IND was transferred to VIROPHARMA, where nonclinical tests and clinical pharmacology studies continued and additional Phase I tests were undertaken.

In 1996, a proof-of-concept coxsackievirus A21 challenge study in normal volunteers was conducted. Following demonstration of the antiviral and clinical benefit of pleconaril in this model, Phase II studies were undertaken to investigate the safety and efficacy of pleconaril for the treatment of viral meningitis. Because of difficulties in enrolling and conducting trials in an epidemic illness, and the inability to demonstrate a consistent treatment benefit, further pursuit of the viral meningitis indication was deferred indefinitely in 2000.

In 1997-1999, a series of Phase II clinical studies were conducted in patients with colds to evaluate the benefit of pleconaril for this indication. On November 22, 1999 and April 27, 2000, VIROPHARMA met with the Division of Antiviral Drug Products (DAVDP) at FDA to discuss the design of the Phase III cold studies, which were conducted during the fall of 2000. Positive results in both of these studies provided the basis for preparation of the NDA, which was submitted to FDA on July 31, 2001, following several pre-NDA meetings with DAVDP. The NDA was accepted for filing on September 24, 2001.

2.2 Proposed Indication

VIROPHARMA is seeking approval in NDA 21-245 of pleconaril for the following indication:

Pleconaril is indicated for the treatment of acute picornaviral upper respiratory illness (common cold) in adults. Treatment with pleconaril should be initiated as soon as possible after onset of symptoms.

3. THE COMMON COLD

3.1 Incidence of the Common Cold

There are approximately 1 billion colds per year in the U.S. (National Institute of Allergy and Infectious Diseases, 2001). The age distribution of patients with the common cold skews toward younger persons (Fox et al., 1975). Adults average two to four colds a year, although the range varies widely. Women, especially those aged 20 to 30 years, have more colds than men, probably because of their closer contact with children. On average, individuals older than 60 years experience fewer than one cold per year (Gwaltney et al., 1966). Colds are most prevalent among younger children, who experience about six to ten colds per year (Turner, 1997).

3.2 Picornaviruses and Their Role in the Common Cold

The principal viral pathogens associated with the common cold are picornaviruses (rhinoviruses and enteroviruses). Coronaviruses, adenoviruses, parainfluenza viruses, influenza viruses, and respiratory syncytial viruses are less frequent causes of the cold syndrome (Kirkpatrick, 1996). The prevalence of these pathogens varies by season, geography, host susceptibility, and exposure (Makela et al., 1998).

Picornaviruses, in particular the rhinoviruses, cause more human illness than any other microorganism and are isolated more frequently than other pathogens in cases of acute respiratory infections (Hendley, 1999; Winther, 1997). Picornaviruses cause approximately 50% of colds on an annual basis (Arruda et al., 1997; Makela et al., 1998; Monto and Ullman, 1974; Monto and Sullivan, 1993). In the northern hemisphere, rhinoviruses cause 60%-80% of all episodes of colds in fall months; in addition, a second peak occurs in the late spring.

Enteroviruses also cause colds. Enterovirus-induced respiratory infections are seen throughout the year, although the most common respiratory syndrome occurs during the summer months (Chonmaitree and Mann, 1995; Kepfer et al., 1974). Approximately 4% of

all respiratory illnesses and 6%-10% of colds are associated with enteroviruses (Gwaltney, 2000).

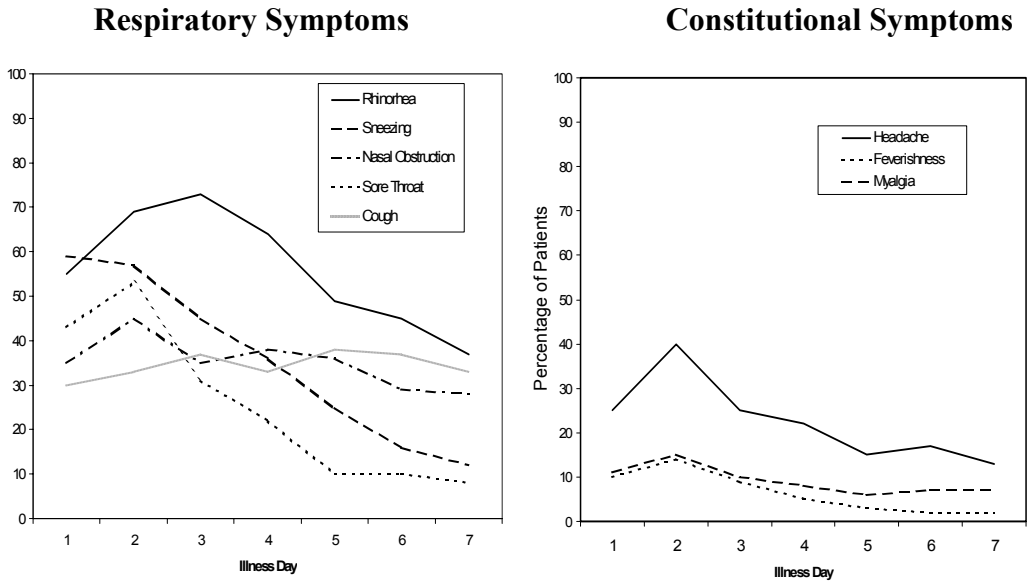
3.3 Symptoms and Clinical Sequelae of the Common Cold

The initial symptoms of the common cold — typically, sore throat, nasal congestion, and rhinorrhea — are quickly recognized by cold sufferers (Arruda et al., 1997). The morbidity associated with colds is substantial. Most (70%-88%) rhinovirus infections result in symptomatic colds, usually manifested by sneezing, rhinorrhea, nasal obstruction, sore throat, cough, and hoarseness (Kirkpatrick, 1996). Headache, malaise, and myalgia may also be present. Sinus abnormalities, frequently involving the maxillary and ethmoid sinuses, are present in most individuals with clinical symptoms of a cold, as demonstrated by CT scan (Gwaltney et al., 1994). Middle ear involvement is common, manifested in adults as middle ear pressure abnormalities and in children as middle ear pressure abnormalities, effusions, and otitis media (Chonmaitree et al., 1992; Elkhatieb et al., 1993). The common cold may also have significant effects on daytime alertness, reaction time, and sleep disturbance (Smith et al., 1998; Drake et al., 2000).

The duration of a cold is generally assessed by the duration and severity of the most common symptoms. In adults, a cold usually lasts about one week, although in approximately 25% of cases a cold lasts 2 weeks or longer (Gwaltney, 1995; Turner, 1997). Studies of experimentally induced rhinovirus colds showed that rhinovirus can be recovered from the nasopharynx for up to 3 weeks after inoculation of virus (Winther et al., 1986; Douglas et al., 1966). One of these studies indicated that clinical illness occurs when the titer of virus in nasal mucus is highest, most commonly 2-3 days after inoculation; in the same study, virus was observed to persist at low levels for up to 17 days after inoculation, well beyond the period of clinical illness (Douglas et al., 1966). Symptoms of rhinovirus infection and clearance of virus are thought to be mediated by cytokines released by the infected cells (Noah et al., 1995; van Kempen et al., 1999). The final step in immune clearance of rhinovirus is marked by the appearance of specific neutralizing antibodies in serum and nasal secretions approximately 2 to 3 weeks after infection (Barclay et al., 1989; Turner, 1997).

The typical time course of symptoms is illustrated in Figure 1.

Figure 1. Rhinovirus Cold Symptoms in 139 Adults With Natural Infections (Rao et al., 1995)



In a study of naturally acquired, self-diagnosed colds contracted by adults in the fall, rhinovirus infection was confirmed in 83% by virus culture or reverse transcriptase-polymerase chain reaction (RT-PCR) assay. Sore throat was the most frequent symptom initially reported in patients with a confirmed picornavirus cold (Arruda et al., 1997). Rhinorrhea and nasal congestion were the most bothersome symptoms in these patients. Sixty-nine percent (69%) of patients in this study were able to self-diagnose their cold within 8 hours of symptom onset.

Although the symptoms of picornavirus colds have a consistent pattern, there are wide variations in the presence and severity of individual symptoms among individuals and cold episodes (Gwaltney, 1995). In addition, the course of a typical cold varies from the norm in certain patient populations. Cigarette smokers experience both more severe symptoms and a longer duration of symptoms, particularly rhinorrhea and frequency of cough (Bensenor et al., 2001; Gwaltney et al., 1967; Turner, 1997; Tyrrell et al., 1993). In patients with asthma, colds due to picornaviruses may promote some components of allergic inflammation and lead

to increased lower respiratory symptoms (Johnston et al., 1995; Johnston et al., 1996; Kim and Hodinka, 1998; Nicholson et al., 1993).

3.4 Current Treatment Options for Colds

Approximately 75% of adults seek some type of treatment to relieve the symptoms of the cold and to allow them to continue their normal activities (McIssac et al., 1998). Most adults purchase an over-the-counter medication (OTC) for symptom relief rather than visit a physician. Two-thirds of families possess one or more OTC cold medications in their medicine cabinet (Maiman et al., 1982). Nevertheless, colds result in more physician contacts than any other respiratory illness (Monto and Sullivan, 1993).

When a physician contact occurs, the patient with a cold often receives a prescription, usually for a cough/cold product and/or an antibiotic. A recent survey of physicians indicated that approximately 35% of patients presenting with a non-influenza cold would receive a prescription for a cough/cold medication (McCaig and Hughes, 1995).

High rates (30%-50%) of antibiotic prescription for the common cold have been reported (Stone et al., 2000; Gonzalez et al., 1997; Nyquist et al., 1998; Mainous et al., 1996). Nearly one-third of all antibiotics prescribed by ambulatory care physicians are for colds, upper respiratory tract infections, and bronchitis (Adamovic et al., 1999). A recent clinical practice guideline noted that the common cold, among other nonspecific respiratory infections, must be targeted for reduction of unnecessary antibiotic use. Antibiotics are unlikely to provide clinical benefit to patients with these predominantly viral illnesses (Gonzales et al., 2001).

There are limited data on the efficacy of cold symptom relief medications in the setting of naturally occurring colds, generally based on evaluation of peak effects in one or a limited number of related symptoms such as nasal congestion, sneezing, and/or rhinorrhea (Taverner et al., 2001). While these agents in some cases provide transient symptom relief, none has been shown to possess antiviral activity or reduce the duration of a cold.

In contrast, the side effects of cough and cold medications are well documented (Hoffman and Lefkowitz, 1995; Serafin and Babe, 1995). The mechanisms of action of these products

involve relatively non-specific interference with normal physiological pathways, resulting in predictable side effects based on the known pharmacological actions. For example, the alpha-adrenergic activity of pseudoephedrine, which is responsible for its decongestant activity, also causes its cardiovascular and central nervous system side effects. The removal of phenylpropanolamine from OTC status is a recent illustration of concern regarding side effects of a sympathomimetic agent that had been used as a nasal decongestant (Anon., 2000).

To obtain relief of multiple symptoms, patients often take combination drug products. The label for a typical combination cold/cough OTC product is included in Appendix A, along with additional information on the major classes of cough/cold symptom relief medications in common use.

4. MICROBIOLOGY

4.1 Summary of Key Points

- Pleconaril is a novel antiviral drug designed to act by a virus-specific mechanism that has been investigated at the atomic level. Pleconaril inhibits virus capsid function by integrating into a drug-binding pocket within the virion capsid and interacting with amino acids of capsid protein VP1. As a consequence, pleconaril prevents attachment of most rhinoviruses to susceptible cells and prevents uncoating of both rhinoviruses and enteroviruses.

- Pleconaril exhibits broad-spectrum antiviral activity specific for rhinoviruses and enteroviruses in *in vitro* cell culture tests at drug concentrations that are non-toxic to cells. Pleconaril is not active against viruses from unrelated virus groups, including influenza virus, respiratory syncytial virus, coronavirus, parainfluenza virus, adenovirus, herpes simplex virus, measles virus, mumps virus, and reovirus.

- Pleconaril was effective at reducing mortality in three laboratory animal models of lethal picornavirus infection when administered orally. The animal model data provided a firm nonclinical efficacy basis for investigation of the compound in humans.

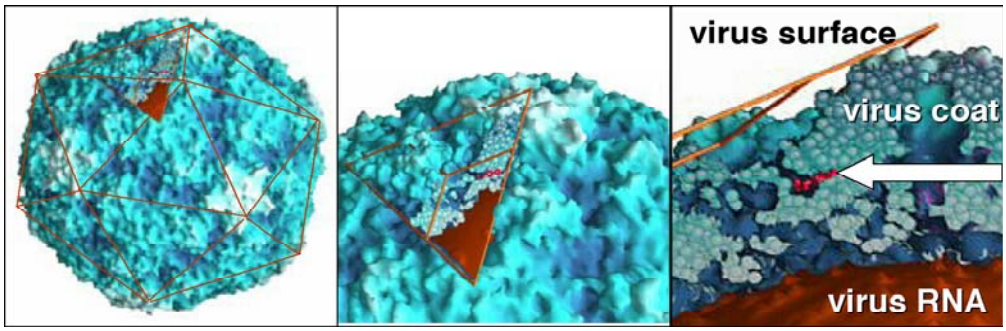
- Emergence of viruses with reduced susceptibility to pleconaril occurs at a low frequency. Viruses no longer inhibited by pleconaril in cell culture possess specific amino acid changes in the drug-binding pocket of VP1. The changes required to confer pleconaril resistance reduce virus fitness.

4.2 Mechanism of Action

Pleconaril inhibits picornavirus replication by direct interaction with the viral capsid and by inhibition of essential virus functions associated with the capsid (Figure 2). The picornavirus infection cycle begins with virus attachment to susceptible cells, followed by virus penetration into the cell. Once in the cell, the virus particle is disassembled, or uncoated, allowing for the release of viral RNA for subsequent viral protein production and RNA replication. Viral proteins and progeny RNA genomes are then assembled into new virus particles. Finally, mature virions are released typically by destruction (lysis) of the infected cell. The picornavirus capsid is critically important in the virus attachment, uncoating, and maturation phases of the infection cycle.

The antiviral effects of pleconaril can be observed in the early stages of virus replication and upon maturation of progeny virions. Specifically, by interfering with the capsid, pleconaril prevents attachment of the majority of rhinoviruses to host cells and inhibits the uncoating of viral RNA of both rhinoviruses and enteroviruses. Further, when infected cells are exposed to pleconaril after the uncoating stage, the drug blocks the infectivity of progeny virions upon virus assembly.

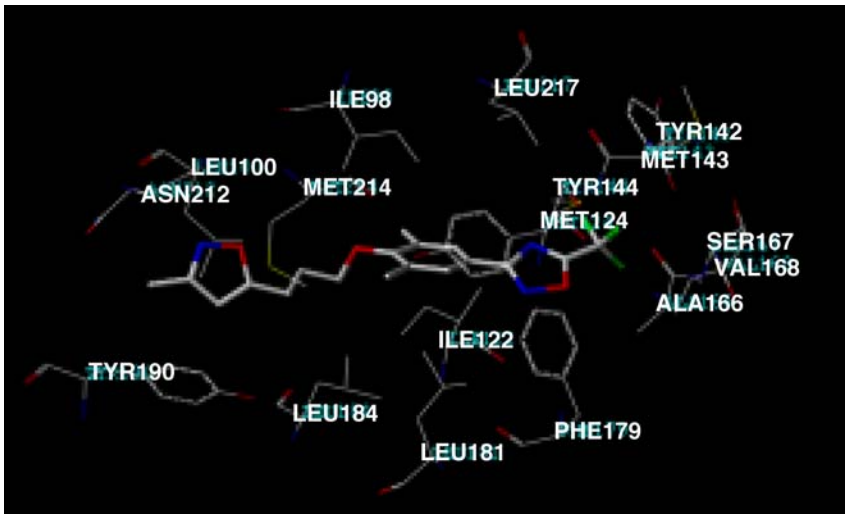
Figure 2. Pleconaril Bound in the Drug-Binding Pocket of a Human Picornavirus



Depictions, based on X-ray crystallographic data, of a picornavirus with a protomer cut away, revealing a capsid function inhibitor (red at end of arrow) integrated in the drug-binding pocket.

Pleconaril inhibits capsid function by integrating into a drug-binding pocket within the capsid. Pleconaril binds principally through hydrophobic interactions with a number of amino acids of VP1 that line the pocket. X-ray crystallographic studies of pleconaril bound to human rhinovirus (HRV) 16 indicate there are 17 amino acids of VP1 in the drug-binding pocket within 4 Å of bound pleconaril. Most of the 17 amino acids have aromatic or aliphatic side chains (Figure 3). Integration of pleconaril into the drug-binding pocket results in: (1) conformational changes in the capsid that prevent virus binding to the ICAM-1 cellular receptor (used by 90% of rhinovirus serotypes) and (2) increased capsid rigidity, which prevents virion disassembly and viral RNA release upon cell uptake, thus aborting the infection.

Figure 3. VP1 Amino Acids in the Drug-Binding Pocket of HRV16 with Atomic Interactions with Pleconaril



4.3 Spectrum of Antiviral Activity

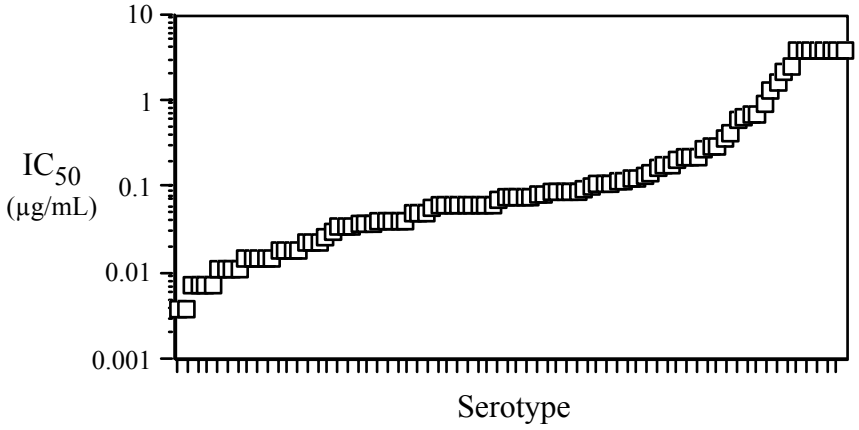
Pleconaril exhibits broad-spectrum antiviral activity against rhinoviruses and enteroviruses in *in vitro* cell culture tests at drug concentrations that are non-toxic to cells.

- Pleconaril inhibits 92% (93 of 101) of all prototypic rhinovirus serotypes (Figure 4A).
- Pleconaril inhibits 83% (44 of 53) of culturable prototypic enterovirus serotypes (Figure 4B).
- Pleconaril is specific for rhinoviruses and enteroviruses, and is not active against viruses from unrelated virus groups, including influenza virus, respiratory syncytial virus, coronavirus, parainfluenza virus, adenovirus, herpes simplex virus, measles virus, mumps virus, and reovirus.

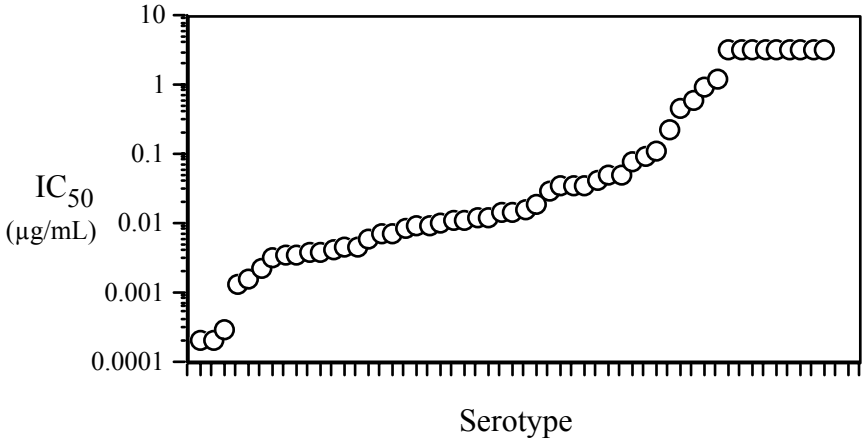
The minimum inhibitory concentrations for 50% and 90% of the prototypic rhinovirus serotypes (MIC_{50} and MIC_{90}) are 0.08 µg/mL and 1.6 µg/mL, respectively. For the culturable prototypic enteroviruses, MIC_{50} and MIC_{90} values are 0.02 µg/mL and >3.8 µg/mL, respectively.

Figure 4. Distribution of Susceptibility to Pleconaril (IC_{50} values) of Prototypic HRV Serotypes (Panel A) and Culturable Enterovirus Serotypes (Panel B)

A. HRV prototypic serotypes (n = 101)



B. Culturable enterovirus serotypes (n = 53)



4.4 Effectiveness in Animal Models of Lethal Picornavirus Infection

Because HRVs are highly host-specific, laboratory animal models are not available for these viruses. However, there are well-established laboratory animal models for enterovirus infections. Three murine models of lethal enterovirus infection were used to demonstrate the effectiveness of pleconaril *in vivo*: coxsackievirus A9 in suckling mice, coxsackievirus A21 in weanling mice, and coxsackievirus B3 (CVB3) in adult mice. In all three models, orally administered pleconaril increased animal survival rate.

In coxsackievirus A9-infected suckling mice, a single oral dose of 200 mg/kg of pleconaril given 2.5 days after subcutaneous virus challenge protected 80% of animals from lethal infection. In contrast, 10% of placebo-treated mice survived virus challenge.

Pleconaril administered orally 2 hours prior to intraperitoneal infection of weanling mice with coxsackievirus A21 and then 2 hours postinfection on Day 1, followed by twice daily (BID) dosing through Day 5, resulted in 100% survival at a dosage of 75 mg/kg/day, compared to less than 15% survival in placebo-treated animals.

In adult mice infected intraperitoneally with a myocarditic strain of CVB3, 15% of placebo-treated animals survived. Using the same dosing regimen as described above in the coxsackievirus A21 model, 90% of animals survived infection when treated with 200 mg/kg/day pleconaril. These animal model data established the oral bioavailability of pleconaril and provided a firm preclinical efficacy basis for investigation of the compound in humans.

4.5 Characteristics of Picornaviruses Selected for Resistance to Pleconaril

The susceptibility of picornaviruses to pleconaril was determined in an *in vitro* cell culture assay that measured picornavirus-induced cytopathic effect after 3 days of virus replication. In this cell culture assay, antiviral activity can be assessed properly only at drug concentrations below the level of drug toxicity for the cultured cells. For pleconaril, this concentration was 3.8 μg/mL. If replication of a virus was not inhibited by pleconaril at or below 3.8 μg/mL (i.e., IC_{50} >3.8 μg/mL), the virus was considered not susceptible to pleconaril.

Picornaviruses that are not susceptible to inhibition by pleconaril at concentrations ≤ 3.8 μg/mL can be isolated at low frequency from drug susceptible virus populations. Due to the error-prone nature of RNA virus replication, RNA viruses, including picornaviruses, exist in the host as a dynamic distribution ("quasi species") of nonidentical but related viruses. Therefore, drug-susceptible virus populations contain pre-existing virus variants that are not susceptible to pleconaril. In cell culture experiments using CVB3, variants not

susceptible to pleconaril were isolated by virus propagation in the presence of pleconaril at a frequency of approximately 1 in 20,000.

In the Phase III clinical studies of a 5-day treatment course, the frequency of emergence of virus isolates with reduced susceptibility to pleconaril *in vitro* (defined as a >10-fold increase in IC_{50} value relative to pretreatment susceptibility) in patients with susceptible viruses at baseline was 0.7% (2 of 294) for placebo- and 10.7% (28 of 263) for pleconaril-treated patients.

Genotype was evaluated for picornaviruses with reduced susceptibility to pleconaril following exposure to the drug (both cell culture and clinical isolates). In all cases examined, the molecular basis of the reduced susceptibility involved amino acid changes in the drug-binding pocket of capsid protein VP1. Of 10 independently derived CVB3 variants isolated in cell culture for reduced susceptibility to pleconaril, all differed from the wild-type virus at amino acid residue 92 (CVB3 numbering; equivalent to residue 98 in HRV16 numbering; Figure 3) in the drug-binding pocket of VP1 (Ile to Met [9 cases], Ile to Leu [1 case]). A second residue change was observed in one case at VP1 residue 207 (Ile to Val).

Thirteen post-baseline virus isolates from eight pleconaril-treated patients in the Phase III clinical studies were no longer susceptible to pleconaril. Eleven of these 13 post-baseline virus isolates had an amino acid change in the VP1 drug-binding pocket at position 98 (HRV16 numbering; Ile to Met [7 cases], Ile to Phe [4 cases]). The remaining two post-baseline viruses had a change at residue 122 in the drug-binding pocket (Ile to Phe or Val to Leu; Figure 3).

Amino acid residues of the picornavirus drug-binding pocket are important for virion stability (Phelps and Post, 1995; Phelps et al., 1998; Lewis et al., 1998). The amino acid changes in capsid protein VP1 that confer resistance to pleconaril also affect virion stability. For the CVB3 resistant variants isolated in cell culture and for the resistant-virus isolates from patients in the Phase III clinical studies, all but one showed reduced capsid stability (heat and/or pH lability) relative to its corresponding parental (baseline) virus.

The virulence of pleconaril-resistant viruses derived in cell culture was studied in a Balb/c mouse lethal infection model. Pleconaril-resistant CVB3 variants caused significantly lower mortality and showed a delayed time to death compared to wild-type drug-susceptible virus (Groarke and Pevear, 1999). Reduced lethality of the resistant viruses in mice was correlated with reduced virus replication *in vivo*. Virus levels in tissues of mice infected with resistant viruses were 2 to 3 orders of magnitude lower than those found in tissues of animals infected with wild-type drug-susceptible virus.

The virulence of human clinical virus isolates that are no longer susceptible to pleconaril *in vitro* has not been assessed directly because no accepted laboratory animal models for HRV disease exist. However, in the Phase III clinical studies, there were no indications that the emergence of pleconaril-resistant viruses in patients was associated with diminution of clinical benefit (See Section 8.4, Clinical Virology, for further discussion of these patients).

The findings of attenuated virulence of pleconaril-resistant HRV are consistent with a report of drug resistance with another capsid inhibitor, Ro 09-0410. Ro 09-0410 is a chalcone capsid inhibitor that binds in the same VP1 drug-binding pocket of picornavirus as pleconaril. An HRV2 variant selected for resistance to Ro 09-0410 in cell culture was shown to be significantly less virulent in humans than its wild-type drug-susceptible parental virus (Yasin et al., 1990). In that study, wild-type HRV2 or a cell culture-derived variant that was no longer susceptible to Ro 09-0410 was inoculated into the nose of human volunteers at the Medical Research Council Common Cold Unit in Salisbury, UK. The frequency of infection of the volunteers (as determined by seroconversion) was significantly lower with the resistant virus compared to the drug-susceptible wild-type virus. Of those with signs of a cold, there were no significant differences in the clinical scores between volunteers challenged with the resistant or wild-type viruses. However, volunteers infected with the drug-resistant virus shed significantly less virus than those infected with the drug-susceptible wild-type virus.

Thus, available *in vitro* and *in vivo* data show that picornaviruses with reduced susceptibility to pleconaril have specific amino acid changes in the VP1 drug-binding pocket, and that these changes result in attenuated viruses that are less stable than wild-type drug-susceptible viruses.

5. NONCLINICAL DEVELOPMENT

5.1 Safety

5.1.1 Summary of Key Points

- The nonclinical safety profile of pleconaril has been characterized in general pharmacology studies, acute and subchronic safety studies in rats and dogs, reproductive toxicology studies in rats and rabbits, and genotoxicity tests. Because of the short dosing schedule (5 days) proposed for humans, carcinogenicity studies are not required for the proposed clinical indication. However, carcinogenicity studies will be conducted to support a future clinical prophylaxis indication.

- Results of general pharmacology studies, single- and multiple-dose safety studies, reproductive studies, and genotoxicity studies with pleconaril were consistent with the following conclusions:
  - No significant safety issues;
  - No evidence of convulsant activity, adverse motor activity, hemodynamic or cardiovascular changes;
  - Low acute toxicity potential;
  - Minimal risk for an increase in adverse effects in humans due to repeat dosing with pleconaril;
  - No effects on reproductive performance, including spermatogenesis;
  - No evidence of teratogenicity;
  - Exposure to pleconaril *in utero* and during nursing does not affect the viability or the normal development, including reproductive performance, of the offspring;
  - No mutagenic or clastogenic potential.

- Pleconaril has a nonclinical safety profile that supports its use as an antiviral agent in patients with the common cold.

5.1.2 General Pharmacology

Three general pharmacology studies were conducted with pleconaril prior to the initiation of clinical trials. In a rat study, oral administration of pleconaril at single oral doses up to 300 mg/kg did not produce any evidence of a proconvulsant liability or any drug-related effects on motor activity. In a dog study, the acute hemodynamic effects of pleconaril were studied in pentobarbital-anesthetized animals at intravenous (IV) doses of 0.3 to 10.0 mg/kg. Pleconaril did not produce any changes in cardiac output or stroke volume, and no cardiac arrhythmias were observed during the course of the study. Cardiovascular effects were also assessed in 1-month and 6-month dog safety studies. In these studies, there were no changes in cardiovascular parameters as monitored by electrocardiogram (ECG) evaluations, including QT intervals, at doses up to 200 mg/kg/day administered for 1 month or 100 mg/kg/day for 6 months of pleconaril treatment. Based on the results of these general pharmacology studies, the potential for pleconaril to induce convulsant activity, adverse motor activity, hemodynamic or cardiovascular changes in humans is very low.

5.1.3 Acute Toxicity

Pleconaril has a low acute toxicity potential. Single-dose toxicity studies were conducted in mice and rats. At the highest oral doses of 2000 mg/kg, no signs of systemic or local toxicity were noted in either mice or rats. For mice and rats, the oral maximum tolerated dose (MTD) is greater than 2000 mg/kg.

5.1.4 Repeated-Dose Toxicity

Oral 1-month and 6-month repeated-dose toxicity studies utilizing methylcellulose suspensions of pleconaril were conducted in rats and dogs. Chronic carcinogenicity studies with pleconaril have not been conducted, since the proposed dosing schedule for pleconaril use in humans is 400 mg three times daily (TID) for 5 days. However, carcinogenicity studies will be conducted to support a future prophylaxis indication.

In the 1-month studies, both rats and dogs were given pleconaril orally at daily doses of 0, 12.5, 50, or 200 mg/kg. In both species, the liver was the primary organ affected by pleconaril treatment. In rats, changes in clinical chemistries were observed in the 200 mg/kg

group (the highest dose tested) as follows. Cholesterol increased 30%; alkaline phosphatase increased 22%; glucose values decreased 8%-16%. Slight increases of mean liver weights of 3% and 10% in the 50 and 200 mg/kg groups, respectively, and minimal to mild diffuse centrilobular hepatocellular hypertrophy was observed in both the 50 and 200 mg/kg groups. These effects have minimal toxicological significance. A less than dose-proportional increase in plasma drug concentrations with increasing dose was observed, with moderate accumulation at the end of the study.

In the 1-month dog study, decreases in body weights (10%) and feed consumption were observed in dogs that received the high dose of 200 mg/kg. In addition, slight increases in liver weights (10%) were observed in the 200 mg/kg group and centrilobular hepatocellular hypertrophy was observed in the 50 and 200 mg/kg groups. These changes in the liver have minimal toxicological significance. Plasma concentrations of pleconaril were similar in males and females. T_{max} occurred 1 to 2 hours post-dosing, and the C_{max} and AUC increased with increasing doses but was less than dose proportional.

Long-term daily exposure to pleconaril was assessed in rat and dog 6-month studies where pleconaril was administered orally at 0, 10, 25, or 50 mg/kg BID, for a daily dose of 0, 20, 50, or 100 mg/kg/day for 6 months. In both studies, additional animals remained on study for a 2-month non-dosing period to assess the recovery of any adverse effects detected during the 6 months of treatment. In the rats, no treatment-related effects were detected in appearance, behavior, food consumption, body weights, ophthalmoscopic evaluations, clinical chemistries, and macroscopic or microscopic evaluations. In addition, no adverse effects were detected in the recovery animals. The systemic exposure to pleconaril over the dosing period was approximately dose proportional, and time- and gender-independent.

In the dog study, no treatment-related effects were detected, after 6 months of dosing, in appearance, behavior, food consumption, body weights, ophthalmoscopic evaluations, ECGs, and macroscopic or microscopic evaluations. However, slight increases in liver weights (approximately 20%) were observed in females in the 50 and 100 mg/kg/day groups. While there were no microscopic changes detected in the livers, alanine aminotransferase was increased in one female in the 100 mg/kg/day group at the 6-month evaluation. The minor

changes in the liver weight of female dogs have minimal toxicological significance. The effects of pleconaril upon the liver were reversible, as indicated by the absence of findings at the end of the 2-month recovery period. The systemic exposure to pleconaril, as measured by C_{max} and AUC, was approximately dose proportional, and time- and gender-independent.

The results of the 1-month and 6-month nonclinical studies demonstrate that pleconaril has an excellent safety profile when administered orally to rats and dogs for extended dosing durations up to 6 months. Animals that received daily doses of pleconaril for 1 month had daily systemic exposures that were 1-2 times higher than humans receive over 5 days at 400 mg TID, the proposed dosing regimen. In addition, the daily maximum plasma concentrations (C_{max} values) achieved in the 1-month studies were approximately 2-5 times higher than maximum plasma concentrations in humans. In the 6-month studies, dogs and rats received daily exposures similar to or slightly lower than that of humans receiving 400 mg TID, with minimal or no adverse effects detected in the animals. The results of these studies support the daily oral administration of pleconaril to humans for 5-day courses of therapy and also suggest minimal risk for additional adverse effects in humans following repeated courses of therapy.

5.1.5 Reproduction Toxicity

Pleconaril was evaluated in a rat fertility study for effects on fertility and early embryonic development. In this study, rats were administered oral doses of up to 180 mg/kg/day, on a BID schedule. There were no treatment-related deaths and no effects on reproductive parameters. Spermatogenic endpoints were not adversely affected by pleconaril administration at any dose level. In addition, intrauterine survival of the F_1 embryos was not affected by test article administration. Results of the rat fertility study demonstrate that pleconaril has no effects on reproductive performance, including spermatogenesis.

Teratology studies were conducted in rats and rabbits. Doses were selected based on results of dose-ranging studies. The high dose selected for the definitive rat teratology study was 360 mg/kg. For the rabbit study, the high dose selected was 200 mg/kg. There were no malformations in fetuses attributed to pleconaril treatment. The results of the rat and rabbit

teratology studies indicate that pleconaril does not induce malformations in fetuses when exposed *in utero*.

A pre- and post-natal development study in rats was conducted to determine potential adverse effects of pleconaril on pregnancy, parturition and lactation of maternal animals when the drug was administered orally to pregnant F_0 rats from implantation to weaning. Growth, viability, development, and reproductive performance of the F_1 generation were also assessed. Based on the results of the dose-ranging study, the high dose of 180 mg/kg/day was selected for the definitive two-generation study of pleconaril in rats. The rats were dosed daily from gestation Day 6 through lactation Day 20. No adverse effects on F_0 pregnancy status, duration of gestation, or the process of parturition were observed at any dose. The F_1 postnatal survival and mean pup body weights were reduced in the 180 mg/kg/day group. Various indicators of physical and functional development, as well as behavioral responses, in the F_1 pups in the treated groups were comparable to the control group values. Intrauterine growth and survival of the F_2 fetuses were not affected by F_0 maternal treatment at any dose. These results indicate that exposure to pleconaril *in utero* and during lactation does not affect the normal development of offspring.

5.1.6 Genotoxicity

The following studies were conducted to assess the genotoxicity potential of pleconaril: (1) Reverse mutation assay (Ames test) in *S. typhimurium* and *E. coli*; (2) *In vitro* chromosomal aberration test in Chinese hamster ovary (CHO) cells; (3) *In vitro* HGPRT gene mutation assay in CHO cells; and (4) *In vivo* micronucleus test for chromosomal damage in mice. Concentrations and doses of pleconaril were selected, based on the current ICH and FDA guidelines for conducting these studies. Pleconaril was negative in all four studies. The results of the genotoxicity studies indicate that pleconaril does not have mutagenic or clastogenic potential.

5.2 Absorption, Distribution, Metabolism, and Excretion (ADME)

5.2.1 Summary of Key Points

The nonclinical ADME of pleconaril was evaluated in several *in vitro* and *in vivo* studies. The rat and dog were the primary species studied. The oral route was selected for the majority of the nonclinical disposition studies because the proposed dosing regimen in humans is via the oral route.

- Nonclinical pharmacokinetic and drug metabolism studies demonstrated that pleconaril has multi-exponential disposition profiles following both IV and oral administration, a long apparent terminal half-life of elimination, high plasma protein binding, low renal clearance, and slow but extensive metabolism (by both reductive and oxidative pathways).

- No significant induction of the cytochrome P450 (CYP450) drug metabolizing enzyme system was observed during repeated dosing for 6 months in nonclinical toxicology studies.

- The overall nonclinical drug disposition profile of pleconaril was sufficient to define the toxicology profile in nonclinical species.

- The pleconaril pharmacokinetic and metabolic profiles in animals are similar to those of humans. The nonclinical safety studies support the safety of pleconaril in humans.

5.2.2 Absorption and Pharmacokinetics

Nonclinical animal studies indicated that oral absorption of pleconaril in animals is influenced by the type and composition of the formulation used, the prandial state, and the dose administered. The absolute oral bioavailability in the fasted dog ranged from 12%-20%, which increased to 74% bioavailability in the fed state. Upon attainment of C_{max} after oral administration of [^{14}C]-pleconaril at 12.5 mg/kg, plasma concentrations of [^{14}C]-radioactivity declined in a biexponential fashion, falling rapidly from C_{max} through 12 and 36 hours post-dosing in the dog and rat, respectively, and then more slowly thereafter. The mean (± SD) terminal elimination half-life of [^{14}C]-radioactivity after oral administration was 33.1 ± 6.4 hours in the rat and 88.3 ± 5.8 hours in the dog. Evaluation of blood concentrations of [^{14}C]-radioactivity indicated minimal distribution of [^{14}C]-associated pleconaril into the cellular components of blood. Results demonstrated that pleconaril has a

steady-state volume of distribution, which was substantially larger (10 fold) than bodyweight in dogs, indicating extensive tissue distribution. The systemic plasma clearance of pleconaril in the dog was 0.73 L/h/kg.

5.2.3 Distribution

In vitro studies showed pleconaril to be highly bound (~99%) to plasma proteins in rat, dog and human plasma at concentrations ranging from 1 to 10 μg/mL. Studies of tissue distribution in Sprague-Dawley and Long-Evans rats following oral administration of [^{14}C]-pleconaril demonstrated that [^{14}C]-associated pleconaril was extensively distributed into most tissues, with highest concentrations in the liver, Harderian gland, brown fat, and the adrenal cortex. Significant concentrations of [^{14}C]-pleconaril were present in fat and the nasal epithelium. Concentrations of drug-derived radioactivity in the brain, sciatic nerve, and spinal cord remained substantially higher than those in plasma and cerebrospinal fluid from 2 to 24 hours post-dosing, suggesting a partitioning into tissues of the central nervous system for pleconaril and/or its metabolites. By 48 hours, most of the radioactivity had been cleared from the tissues. The overall distribution of [^{14}C]-pleconaril, and the prolonged association of radioactivity with lipid-rich tissues, was consistent with the lipophilic nature of this compound and its metabolites.

5.2.4 Metabolism and Excretion

The CYP450 induction potential of pleconaril was examined in microsomes prepared from rat and dog liver samples obtained following *in vivo* dosing of pleconaril in 6-month oral toxicity studies. No significant alterations in hepatic microsomal protein content, microsomal CYP450 concentration or the individual CYP450 enzyme activities of 1A, 2B, 2E, 3A, and 4A isoforms were observed. These results suggest that CYP450 induction in human subjects is unlikely.

The major route of pleconaril excretion in the rat and dog following IV or oral administration was via the feces. The high recoveries of pleconaril-related radioactivity in the feces following IV administration indicated extensive biliary secretion of the drug. Urinary excretion accounted for 17% and 12% of the oral dose and 37% and 19% of the IV dose, in

rats and dogs, respectively. The majority of the dose following oral and IV administration in the rat and dog was excreted within 48 to 72 hours of dosing, which was followed by a slower elimination phase. In the rat, pleconaril and/or metabolites have been shown to partition into lipid-rich tissues in the body. Slow release from these tissues may account for the slow terminal excretion phase observed in rats.

Pleconaril was slowly but extensively metabolized in the rat and the dog and has a similar metabolic profile in these two species. Two major sites of metabolism were identified as: 1) the reductive cleavage of the trifluoromethyloxadiazole ring to yield amidine derivatives, and 2) the opening of the isoxazole ring yielding alkyl acid derivatives of pleconaril. After IV and oral dosing, no unchanged pleconaril was detected in urine. After IV administration, the fecal metabolic profile of [^{14}C]-pleconaril showed that no unchanged drug was excreted. The determination that substantially higher amounts of certain metabolites were observed in both plasma and feces following oral compared to IV administration of [^{14}C]-pleconaril suggests a significant route-dependent metabolism. The observation that significantly less unchanged [^{14}C]-pleconaril was excreted in the feces than anticipated, based on estimates of oral absorption, suggests the potential for intestinal biotransformation of pleconaril.

In general, the metabolic pathways in the rat and dog were comparable, both qualitatively and quantitatively, to the metabolic pathway in humans. Thus, the exposures to pleconaril and its metabolite profile in nonclinical toxicology studies in the rat and dog following oral administration of pleconaril were similar to those of humans.

6. CLINICAL PHARMACOLOGY AND PHARMACOKINETIC PROFILE

6.1 Summary of Key Points

The clinical pharmacology and pharmacokinetic profile of pleconaril was well defined in a series of studies in healthy subjects and in patients. These studies characterized the safety and pharmacokinetics of pleconaril following single- and repeated-dose regimens and evaluated factors that may influence the pharmacokinetic behavior of pleconaril.

- The pharmacokinetic profile of pleconaril is dose proportional from 50 mg to 1000 mg.
- Pleconaril is a low clearance drug with a volume of distribution consistent with extensive tissue distribution, despite high binding (~99%) to plasma protein.
- The pharmacokinetic profile of pleconaril is affected by coadministration with food, which substantially increases its absorption. Thus, pleconaril was administered with food in all Phase II and III studies.
- *In vitro* and *in vivo* drug inhibition studies demonstrated that pleconaril has a low potential to affect the pharmacokinetics of other drugs via metabolic interactions (CYP450 enzyme inhibition) and albumin protein binding drug interactions in humans taking 400 mg TID for 5 days. Possible exceptions are very narrow therapeutic index drugs that are primarily metabolized by CYP 1A2 (e.g., theophylline).
- A drug interaction has been observed between pleconaril and oral contraceptive agents in women enrolled in a 6-week prophylaxis study in adults (pleconaril 400 mg BID or 400 mg QD) (Section 9.8). This interaction is under investigation for both the five-day and longer treatment regimens (Section 11.1).
- The potential of pleconaril to induce CYP450 enzymes in humans is being investigated and data will be available in March 2002.
- Coadministered drugs that are CYP450 substrates, inhibitors, or inducers are not expected to alter the pharmacokinetic profile of pleconaril. Although pleconaril is slowly but extensively metabolized to multiple products, the CYP450 drug metabolizing enzymes are not significantly involved in the primary biotransformation pathways of pleconaril.
- There were no clinically significant changes in the pharmacokinetic profile of pleconaril due to gender, age or smoking status. Renal or hepatic impairment (mild

or moderate) had no clinically significant effect on the pharmacokinetic profile of pleconaril. Therefore, no dosage adjustment of pleconaril is required in these special populations.

6.2 Absorption and Pharmacokinetic Profile

The single dose pharmacokinetic profile of pleconaril is summarized in Figure 5 and Table 1. Following oral absorption, pleconaril displays a biexponential disposition profile with a short alpha half-life (2–3 hours) and a long terminal half-life (approximately 180 hours).

Figure 5. Mean Plasma Concentrations After Single Dose Oral Administration of 400 mg Pleconaril with Food (Inset Plot Displays 0 – 12 Hour Interval) (N=24)

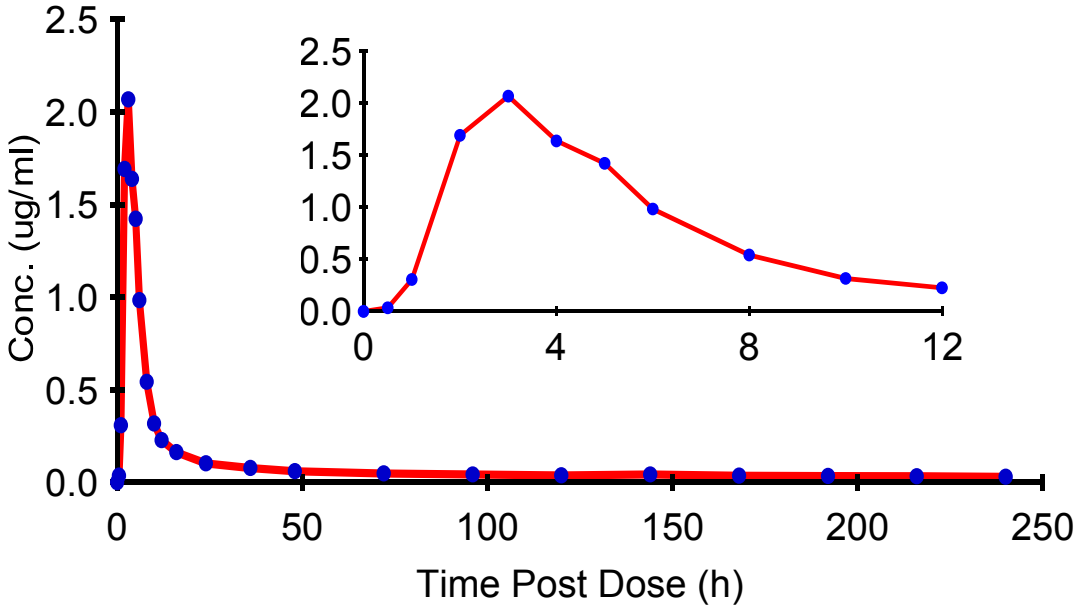


Table 1. Mean (SD) Pharmacokinetic Parameters of Pleconaril in Fed Healthy Young Subjects (N = 24) After Single Dose Oral Administration of 400 mg Pleconaril

T_{max} (h)	C_{max} (µg/mL)	$T_{1/2}$ (h)	$AUC_{0-\infty}$ (µg h/mL)	CL/F (L/h)	Vz/F (L)
3.0 (2.0 – 5.0)[a]	2.3 (0.8)	185.7 (116.6)	29.2 (14.0)	16.8 (7.9)	4113.7 (2393.7)

[a] (Minimum – Maximum)

Pleconaril was administered with food in all Phase II and III clinical studies. Pleconaril absorption is increased significantly (3- to 4-fold) when the drug is administered with food.

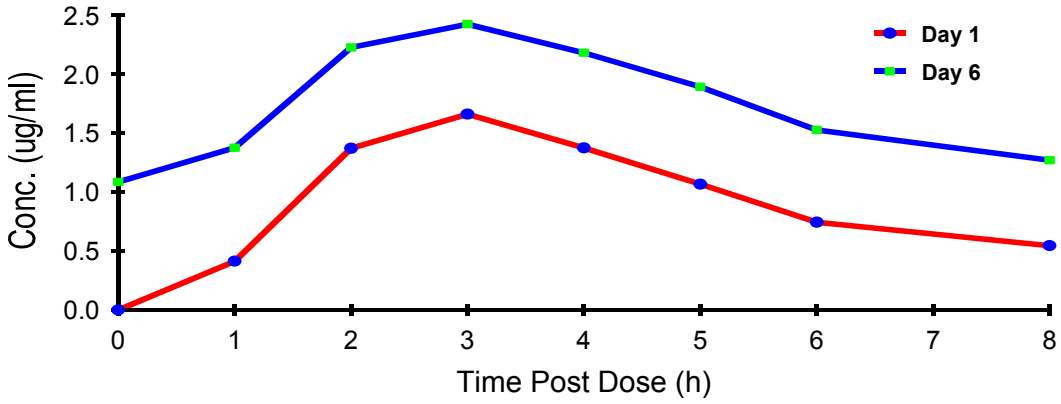
The pharmacokinetic profile of pleconaril is dose proportional and linear over a dose range of 50 mg to 1000 mg.

Pleconaril has a volume of distribution (Vz/F) that is consistent with extensive tissue distribution, despite the fact that pleconaril is highly bound (~99%) to plasma proteins. Pleconaril is a low systemic clearance drug. Renal clearance contributes insignificantly to the systemic clearance of pleconaril. Less than 1% of the dose is excreted unchanged as pleconaril in urine.

The clinical dosing regimen (400 mg TID) was designed to maintain antiviral concentrations throughout the dosing interval, considering the rate of absorption and the alpha disposition half-life. The alpha disposition phase half-life of pleconaril (~2.8 hours) is a relevant pharmacological half-life for the treatment of the common cold because it is most representative of the drug concentration profile in the targeted tissues of interest (e.g., nasal epithelium). This profile suggested that a TID dosing regimen of pleconaril would be most appropriate for the treatment of the common cold. It would also limit the peak-to-trough plasma concentration range, and thus minimize the total dose administered.

Plasma accumulation of pleconaril was modest (approximately 2 fold) when pleconaril was administered according to the proposed clinical dosing regimen (400 mg TID for 5 days, Figure 6). The long terminal half-life had only a modest influence on pleconaril plasma concentration-time profiles for the clinical dosing regimen.

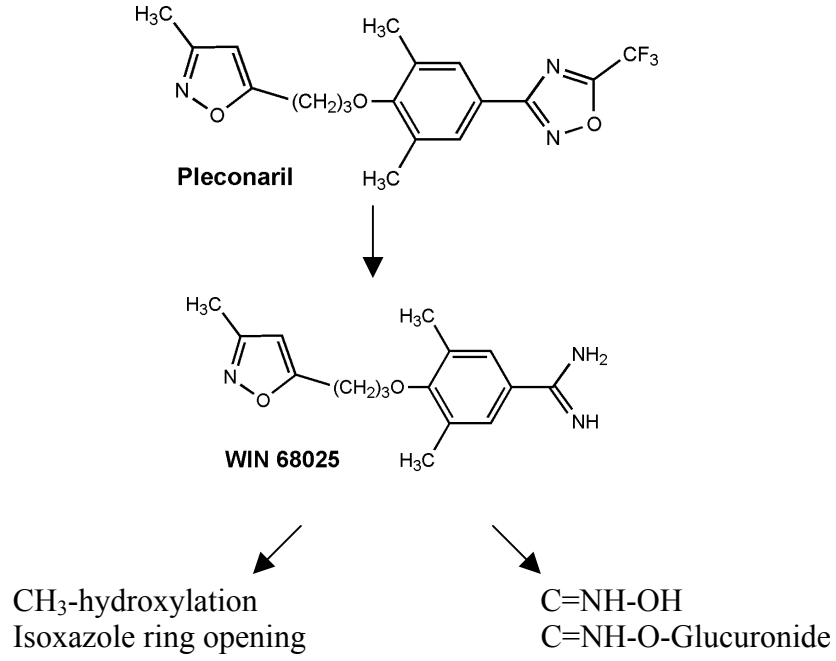
Figure 6. Mean Plasma Concentrations of Pleconaril Over a Dosing Interval on the First and Last Dose of a Repeat-Dose Regimen (400 mg, q8h) in Fed Subjects (N=16)



6.3 Biotransformation

Pleconaril is slowly but extensively metabolized. Pleconaril is converted to a benzamidine derivative by a reductive biotransformation pathway to yield WIN 68025. Further metabolism of the benzamidine derivative involves oxidation and conjugation of the amidine group, or isoxazole ring opening to give alkoxy keto-acid derivatives (Figure 7).

Figure 7. Major Metabolic Pathways of Pleconaril



The benzamidine metabolite (WIN 68025) is likely formed *in situ* from pleconaril in the gastrointestinal tract by human intestinal microflora. A portion of the WIN 68025 that is formed may then be absorbed from the gastrointestinal tract and metabolized systemically to yield other benzamidine metabolites. The formation of WIN 68025 by enzymes other than those in gut microflora (e.g., in the liver) has not been demonstrated under aerobic conditions *in vitro* with human drug-metabolizing systems (liver microsomes, S9 fraction, cytosol and individually expressed CYP450 isoenzymes).

Results from a Phase I study in healthy subjects following administration of [^{14}C]-pleconaril demonstrated that pleconaril is the only major circulating component (>50% of total radioactivity) in plasma at 2, 4, and 12 hours postdose. Although there are a number of circulating benzamidine metabolites in plasma, the levels are at or near the limit of quantification (~2% of circulating radioactivity). Pleconaril is the only known active antiviral component circulating in human plasma.

6.4 Drug Interaction Potential

6.4.1 The Effect of Other Drugs on Pleconaril

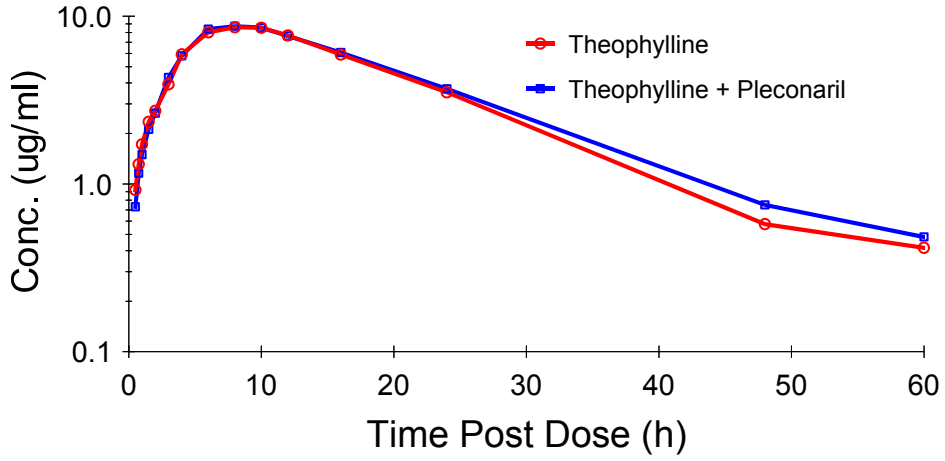
In vitro studies with pooled human liver microsomes and individually expressed human CYP450 isoforms have shown that the CYP450 drug metabolizing enzymes are not significantly involved in the primary biotransformation pathways of pleconaril. Thus, a clinically significant effect of coadministered drugs that are CYP450 substrates, inhibitors or inducers on the pharmacokinetics of pleconaril is not expected.

6.4.2 The Effect of Pleconaril on Other Drugs

Significant metabolic drug interactions involving inhibition by pleconaril of drugs metabolized by the CYP450 isoforms CYP 2A6, 2C8, 2D6, 2E1 and 3A4 (e.g., antihistamines, systemic and inhaled steroids, β-lactam and macrolide antibiotics) are not expected. Pleconaril showed no significant inhibition *in vitro* of these CYP450 isoforms (up to concentrations of ~35 µg/mL). The potential of pleconaril to induce these CYP450 enzymes in humans is currently being investigated and data will be available in March 2002.

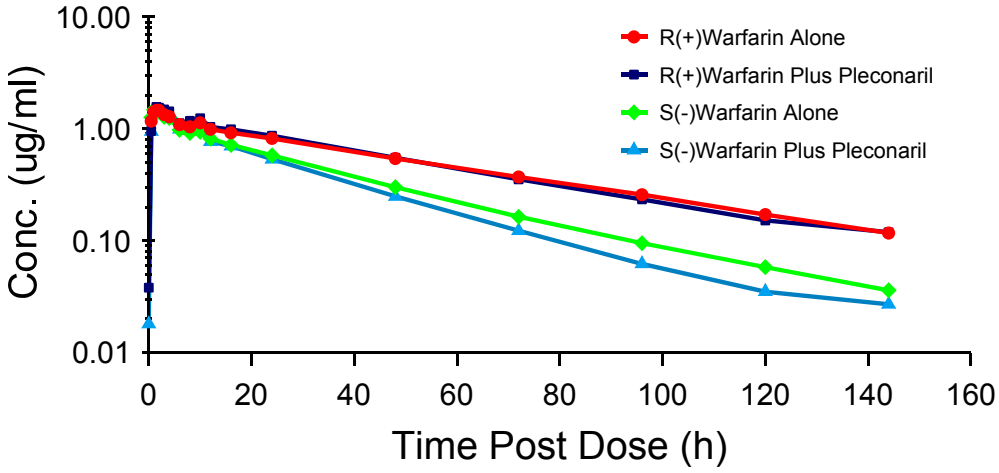
Pleconaril was a weak *in vitro* inhibitor of CYP 1A2, 2C9 and 2C19. An *in vivo* drug-interaction study with theophylline, a sensitive probe substrate for exploring potential metabolic drug interactions on CYP 1A2, demonstrated that the inhibitory effect of pleconaril on CYP 1A2 was small in a 5-day treatment regimen (Figure 8). In this study, theophylline clearance (Cl/F) decreased by 14% and half-life increased by 19.6%.

Figure 8. Mean Plasma Theophylline Concentrations Following Single Administration of Theophylline (450 mg) Alone and After Repeat Dosing of Pleconaril (400 mg TID for 5 Days): Semilog Plot



In addition, an *in vivo* drug-interaction study with the probe substrate, warfarin (specifically, S(-) warfarin, a sensitive probe substrate for examining the metabolic drug interaction potential on CYP 2C9), demonstrated no significant inhibitory effect of pleconaril on CYP 2C9 in a 5-day treatment regimen. In this study, no clinically significant change in S(-) and R(+) warfarin pharmacokinetic parameters was observed (Figure 9).

Figure 9. Mean Plasma S(-) and R(+)Warfarin Concentrations Following Single Administration of Warfarin (25 mg) Alone and After Repeat Dosing of Pleconaril (400 mg TID for 5 Days): Semilog Plot



No significant effect of pleconaril dosing on the warfarin anticoagulation parameters, prothrombin time or INR, was observed.

Clinically significant metabolic drug interactions of pleconaril on CYP1A2 substrates (e.g., quinolone antibiotics) and CYP 2C9 substrates (e.g., leukotriene receptor antagonists) are not expected on a 5-day treatment regimen. Possible exceptions are very narrow therapeutic index drugs that are primarily metabolized by CYP 1A2 (e.g., theophylline).

Clinically significant albumin protein-binding interactions, in which pleconaril displaces another drug from albumin (increasing free drug concentration), also are not expected. Although pleconaril is highly bound (~99%) to plasma albumin, the plasma concentrations of pleconaril are well below those concentrations typically required to displace other drugs, due

to the high capacity of albumin for drug binding. This expectation is consistent with the lack of an effect of pleconaril dosing on the anticoagulation parameters for warfarin, which also is highly bound (~99%) to plasma albumin.

6.5 Special Populations

Definitive Phase I studies in healthy subjects, and a population pharmacokinetic analysis in Phase III patients, demonstrated that there are no clinically significant changes in the pharmacokinetic profile of pleconaril due to gender, age, or smoking status. Renal or hepatic impairment (mild or moderate) also had no clinically significant effect on pleconaril pharmacokinetic parameters. Therefore, no dosage adjustment of pleconaril is required in these special populations.

6.6 Phase I/Ib Safety Results

Pleconaril was safe and well tolerated in doses up to 1000 mg. The most commonly observed adverse events in Phase I/Ib studies were headache and nausea. Increases in median cholesterol levels were the most common changes in laboratory parameters observed.

Cardiac electrophysiology data from adult Phase I studies were obtained from 12-lead ECG measurements at baseline and at the approximate time of maximum plasma concentration (C_{max}) of pleconaril. Evaluation of ninety adults who received either single (400 mg) or multiple (400 mg BID or TID for 7 days) doses of pleconaril revealed no clinically significant changes in median heart rate, PR interval, QRS interval, QT interval, or corrected QT interval (QT_c).

Review of QT_c intervals for each individual subject in these Phase I studies revealed that only 2 subjects developed a QT_c interval ≥450 msec after the start of study drug. One of these subjects, who received placebo for 7 days, had a QT_c interval of 451 msec on Day 4. One subject, who received a single dose of pleconaril 400 mg, had a prolonged QT_c interval at baseline (520 msec) and on Day 1 (467 msec).

Two subjects had QT_c intervals that increased from baseline values by ≥50 msec. One subject, who received pleconaril 400 mg TID for 7 days, had a baseline QT_c interval of

354 msec that increased to 411 msec on Day 6. One subject, who received pleconaril 400 mg BID for 7 days, had a baseline QT_c interval of 352 msec that increased to 413 msec on Day 4, but returned to lower values (364 to 384 msec by Day 7). Overall, these results indicate no clinically remarkable ECG findings.

7. CLINICAL EFFICACY

7.1 Summary of Key Points

Pleconaril reduces the duration and severity of colds caused by picornavirus. In the pivotal Phase III studies, treatment with pleconaril demonstrated the following benefits:

Primary Endpoint

- Reduction in the duration of illness, as measured by time from initiation of therapy to resolution of rhinorrhea and alleviation of other cold symptoms to mild or absent without the use of cold symptom relief medication.

Secondary Endpoints

- Reduction in time to resolution of each of six individual cold symptoms (rhinorrhea, nasal congestion, sore throat, cough, malaise, and myalgia).
- Reduction in the time to patient self-assessment of "no cold."
- Reduction in total symptom severity over the course of the illness.
- Reduction in use of tissues for rhinorrhea.
- Reduction in nights with sleep disturbance due to cold symptoms.
- Reduction in use of concomitant cold symptom relief medications.
- Reduction in the proportion of patients with picornavirus-positive cultures of nasal mucus beginning on the day after initiation of therapy.

Post Hoc Analyses

- Reduction in the proportion of patients with any symptom self-reported as bothersome (moderate or severe), beginning on the day after initiation of therapy.
- Reduction in severity of total symptom score and in the individual cold symptoms of rhinorrhea, cough, nasal congestion, and myalgia, with onset of clinical action within a day following initiation of therapy.
- Shortening of the time to reduce the total symptom severity score to one-half that of baseline.

7.2 Pre-Pivotal Cold Treatment Studies and Clinical Trial Design Considerations

The Phase II studies provided important insight into the clinical presentation of colds caused by picornaviruses and indicated that a meaningful primary endpoint would incorporate complete resolution of rhinorrhea and substantial improvement of the remaining symptoms. This endpoint reflects lessening the period of the illness in which symptoms are most prominent. The insights derived from the Phase II program were reflected in the design of the pivotal Phase III studies upon which this NDA is based. The Phase II and Phase III clinical studies provide a substantial database for evaluation of the safety of pleconaril for treatment of the common cold. Pleconaril is the first antiviral drug for treatment of the common cold to be evaluated in large Phase III field studies.

7.2.1 Coxsackie A-21 Challenge Study

Coxsackievirus infection was induced in 33 normal adult volunteers in an initial proof-of-concept study (Study 843-003). Administration of oral pleconaril initiated prior to virus inoculation reduced the severity of respiratory and systemic symptoms compared to placebo and resulted in fewer patients from whom virus could be cultured from nasal mucus. The study demonstrated that pleconaril was effective in reducing clinical respiratory illness caused by a picornavirus, presumably by reaching the target site of virus replication (i.e., nasopharyngeal epithelium) at concentrations capable of inhibiting virus replication.

7.2.2 Early Phase II Studies

After proof of concept, the clinical development program addressed treatment of naturally occurring, established respiratory illnesses. Two hundred twenty-one (221) otherwise healthy adults (≥14 years of age) with naturally acquired summer colds were randomly assigned to receive one of two doses of a coconut oil-based, liquid formulation of pleconaril (200 mg TID or 400 mg TID) for 7 days or matching placebo (Study 843-010). Eligible patients were required to have at least one respiratory symptom (rhinorrhea, nasal congestion, sore throat, or cough) and one systemic symptom (malaise or myalgia). RT-PCR testing by Enzyme Linked OligoSorbant Assay (ELOSA; see Section 8.2) of nasal wash specimens identified relatively few patients (29%) infected with a picornavirus. The illness profile of

the ELOSA-positive patients was more consistent with rhinovirus infection than enteroviral illness (e.g., low frequency of fever). Therefore, subsequent studies were designed to enroll patients with symptoms more typical of rhinovirus colds during a time of year (fall) when the number and proportion of rhinovirus colds are highest.

In Study 843-010, the primary endpoint was specified as time to reach a predefined numerical total symptom score that was thought to represent meaningful resolution of cold symptoms. The total symptom score was comprised of scores for multiple individual symptoms, including rhinorrhea, nasal congestion, sore throat, cough, malaise, myalgia, and fever. Although headache and sneezing are also common in patients with colds, they were not included in the primary endpoint because of their non-specific nature. In Study 843-010, patients treated with pleconaril experienced more rapid reduction in the severity and duration of illness as measured by time to resolution of all symptoms. The specific symptoms of rhinorrhea and cough were affected to the greatest extent; fever did not appear to be a prominent factor in the evaluation of a picornavirus cold.

Based on the results of Study 843-010, the time to complete resolution of all cold symptoms (rhinorrhea, nasal congestion, cough, sore throat, myalgia, and malaise) was selected as the primary endpoint for the next cold treatment study (Study 843-020); fever was neither an entry requirement nor a component of the primary endpoint. In Study 843-020, 1024 patients were randomly assigned to receive one of two doses of a coconut oil-based, liquid formulation of pleconaril (400 mg BID or 400 mg TID) for 7 days or matching placebo. Forty-one percent (41%) of patients were identified as infected with a picornavirus, based on RT-PCR testing (ELOSA) of nasal wash specimens. The results indicated that pleconaril had a beneficial impact on the time to resolution of all cold symptoms.

7.2.3 Late Phase II Study

The same primary efficacy endpoint (time to resolution of all symptoms) initially was incorporated into the design of Study 843-032. However, in a meeting prior to unblinding the data, the FDA encouraged VIROPHARMA to focus on the acute phase of the illness when morbidity from colds is greatest and to identify an endpoint of shorter duration. A new

endpoint, time to complete resolution of rhinorrhea and alleviation of other cold symptoms (to absent or of mild intensity) for a specified minimum period of time (i.e., two consecutive reporting periods, or 24 hours), was acceptable to FDA and similar to that applied to the evaluation of neuraminidase inhibitors in the treatment of influenza.

In Study 843-032, 875 patients were randomly assigned to receive pleconaril tablets, 400 mg TID (N=436), or matching placebo (N=439) for 7 days. Forty-three percent of patients tested positive for picornavirus by ELOSA in a swab of blown nasal mucus obtained at baseline.

Study 843-032 did not demonstrate a statistically significant difference between treatment and control groups for the prospectively defined primary endpoint. However, some secondary endpoints indicated a treatment benefit of pleconaril. A *post hoc* analysis of the primary endpoint, using a slight modification in which the endpoint was sustained for at least 48 hours, indicated a trend towards reduction in the duration of illness in patients with a cold due to a picornavirus who received pleconaril. This modified primary endpoint (complete resolution of rhinorrhea and alleviation of other cold symptoms [to absent or of mild intensity] sustained for 48 hours) was used in the design of the two Phase III adult studies. The Phase III studies had the added stipulation that patients would reach the endpoint only if not taking concomitant cold symptom relief medication.

Table 2 summarizes the key design changes from Study 843-032 to the pivotal studies 843-043 and 843-044. Changes in entry criteria and study conduct were made to increase the specificity for enrolling picornavirus-infected patients and to minimize the number of potentially confounding factors that would make detection of a treatment effect of pleconaril more difficult.

Table 2. Key Design Differences Between Studies 843-043 and 843-044 Compared to Study 843-032

Feature of Studies 843-043/44	Rationale
Moderate or severe rhinorrhea at baseline was required.	In Study 843-032, patients with moderate or severe rhinorrhea had approximately twice the proportion of RT-PCR positive nasal mucus samples than patients with mild to absent rhinorrhea.
A systemic symptom was not required.	The systemic symptoms of malaise and myalgia were monitored and contributed to total symptom score when present. However, they are not considered key symptoms of a picornavirus cold.
The use of cold symptom relief medications was discouraged and restricted to acetaminophen (Tylenol®) and dextromethorphan (Benylin®), which were supplied by the sponsor.	Use of cold medications may affect symptoms and influence assessment of treatment effect. These two commonly used medications are unlikely to affect rhinorrhea, the most common symptom of a cold.
The time from onset of first cold symptom to the first dose of study drug was limited to 24 hours.	Experience with acute self-limited viral respiratory infections suggests that early treatment results in better outcome.
Patients with active allergic rhinitis and asthma were excluded.	Both asthma and allergic rhinitis symptoms may confound the assessment of the primary endpoint, which is symptom-based.
Patients were required to answer "yes" to the question: "Do you have a cold?"	Observational studies suggest persons with self-diagnosed colds during the fall rhinovirus season have a high (>80%) incidence of picornavirus detectable in nasal mucus. Self-diagnosis may help exclude patients with symptoms of allergic rhinitis rather than a cold.
Patients were stratified at entry by recent smoking history and pre-enrollment use of cold symptom relief medications.	Analyses of Study 843-032 indicated that recent smoking history and concomitant use of cold medications may obscure the ability to detect a treatment effect of pleconaril using the designated primary endpoint. Therefore, stratification was used to balance the treatment groups regarding these factors.
The total blown nasal mucus sample was collected and tested using two RT-PCR methods.	Collecting the entire mucus sample and using two RT-PCR assays was intended to improve the sensitivity of the detection methods in identifying patients with picornavirus infections.
Patients 18 years of age and older were eligible, in contrast to greater than 14 years of age in Study 843-032.	For ease of enrollment, minors were excluded.

7.3 Phase III Studies

7.3.1 Design and Conduct

The Phase III clinical program consisted of two large, placebo-controlled clinical trials (Studies 843-043 and 843-044) that enrolled adults with typical cold symptoms within a day of onset of symptoms. These trials, considered pivotal, incorporated information derived

from the preceding studies (see Table 2 above), with recognition of the inherent challenges of establishing efficacy of a drug to treat an acute, self-limited viral illness, particularly a drug that represents the first in its class (antiviral) for an illness (the common cold) that has no specific treatment.

The two Phase III studies were randomized, double-blind, placebo-controlled clinical trials of identical design. Approximately 1050 patients were enrolled in each study from 197 investigative sites (divided between the studies) across the U.S. and Canada, from August through early November of 2000. The intended commercial tablet formulation of pleconaril (200 mg) was used in both studies.

Eligible patients were ≥18 years of age and presented with a constellation of symptoms consistent with picornavirus colds including:

- Moderate or severe rhinorrhea (i.e., using 2 or more tissues per hour for any 1 hour within 12 hours preceding study entry).
- At least one other respiratory symptom (cough, pharyngeal symptoms [sore throat], or nasal congestion) of moderate or severe intensity.
- Maximum duration of any cold symptom of ≤24 hours prior to the first dose of study drug.

Patients were excluded if they had fever >37.8 °C (100 °F), allergic rhinitis that required medication within 2 weeks prior to the start of the study, asthma that required treatment within 2 months prior to the start of the study, or known immune deficiency condition.

Qualified patients were randomly assigned to pleconaril 400 mg TID x 5 days or matching placebo in a 1:1 ratio within strata based on smoking status (current or recent smoker vs. non-smoker) and prestudy use of cold symptom relief medication. A patient was considered to be a smoker if he/she smoked or stopped smoking ≤3 months prior to enrollment. Patients were followed for 18 days, completing a study diary in which they recorded their assessments of their symptoms twice each day. At each assessment, patients rated each of six individual cold symptoms (rhinorrhea, nasal congestion, sore throat, cough, malaise, myalgia), according to the following severity scales:

Rhinorrhea

Severity	Definition
None	Rhinorrhea was not present
Mild	1 tissue used per hour
Moderate	2-5 tissues used per hour
Severe	>5 tissues used per hour

Nasal Congestion, Sore Throat, Cough, Malaise, Myalgia

Severity	Definition
None	Symptom was not present
Mild	Symptom was noticeable
Moderate	Symptom was bothersome
Severe	Symptom interfered with activity

The severity of each symptom was scored on a nominal scale of 0 to 3 (none=0, mild=1, moderate=2, severe=3). Thus, the maximum possible symptom severity score for all six symptoms at each assessment was 18.

7.3.2 Efficacy Endpoints

The prospective primary endpoint in the Phase III studies was the time to complete resolution of rhinorrhea and alleviation of five other cold symptoms (cough, nasal congestion, pharyngeal symptoms [sore throat], malaise, and myalgia) to absent or mild without the concomitant use of cold symptom relief medication for four consecutive reporting periods (~48 hours).

The primary efficacy endpoint was comprised of four components:

- Resolution of rhinorrhea (the primary symptom for defining illness duration).
- Alleviation of all other cold symptoms to absent or mild.
- Maintenance of the endpoint for at least four consecutive reporting periods (~48 hours).
- No use of concomitant cold symptom relief medication for the 48-hour period following initial attainment of the endpoint.

Rhinorrhea was chosen as the primary symptom for defining illness duration for the following reasons:

- Rhinorrhea is the predominant symptom of a picornavirus cold.
- Rhinorrhea symptom scores could be defined by tissue use in a given 12-hour period, allowing more objective scoring.
- Rhinorrhea could be supported by a secondary endpoint of total tissue use.
- Rhinorrhea was correlated with a higher likelihood of picornavirus colds in Phase II studies.

Alleviation of the other cold symptoms to absent or mild, rather than resolution of all cold symptoms, was selected to provide an outcome that more closely represented the typical duration of the early, more bothersome phase of a cold and to reflect the FDA's advice that unknown factors may affect the last symptom to resolve. The 48-hour period for maintenance of the endpoint was chosen to provide a sufficiently long observation period to ensure that the illness had resolved. The requirement that the achievement of the primary endpoint be in the absence of concomitant cold medication use reflects the possibility that a patient may achieve some symptom relief from concomitant use of cold symptom relief medication, thus artificially reducing the duration of the illness.

Prospectively specified secondary endpoints consisted of:

- Time to patient self-assessment of "no cold."
- Investigator assessment of the presence or absence of a cold at scheduled study visits.
- Time to resolution of individual cold symptoms.
- Sum of total symptom severity scores (during Days 1-18).
- Number of tissues used for rhinorrhea (during Days 1-6 and Days 1-18).
- Number of nights of sleep disturbance due to cold symptoms (during Days 1-18).
- Number of days during which cold symptom relief medication was used (during Days 1-6 and Days 1-18).
- Number of days of impaired patient activity level due to cold symptoms (during Days 1-18).
- Incidence of acute respiratory complications of colds (during Days 1-18).

- Proportion of patients with positive virus-culture results at Day 3 and Day 6 compared to baseline (during Day 1).
- Change in virus levels on Days 3 and 6 relative to baseline levels, as determined by TaqMan® RT-PCR assay.

Post hoc analyses, performed after the study was unblinded, further addressed severity of cold symptoms. *Post hoc* analyses consisted of:

- Proportion of patients with symptoms that were scored as moderate or severe vs. mild or absent on each study day.
- Change from baseline in total symptom severity scores by day.
- Time to ≥50% reduction from baseline in total symptom severity score.

7.3.3 Picornavirus RT-PCR Assays and Virus Cultures

Blown nasal mucus samples from patients enrolled in Studies 843-043 and 843-044 were obtained at baseline and on Days 3 and 6. All nasal mucus samples from a given patient were run in the same assay and tested by the automated TaqMan® assay to determine whether the patient was picornavirus-infected, and to assess the relative picornavirus levels in post-baseline samples relative to that individual's baseline level. If the baseline nasal mucus sample tested negative by the TaqMan® assay, an aliquot of the sample was tested using the manual ELOSA, which detects a broader spectrum of picornaviruses (Please refer to Section 8.2 for discussion of performance characteristics of the two experimental RT-PCR assays).

If a patient was unable to produce a nasal mucus sample on Days 3 or 6, a 0.5 cc sterile water bullet was used to stimulate production of a mucus sample. A patient was considered positive for picornavirus infection if a nasal mucus sample was positive by either RT-PCR assay (TaqMan® or ELOSA) on any sampling day.

Virus culture procedures were performed on all baseline samples that were RT-PCR positive by either assay; if baseline samples were positive for virus cultures, samples taken on Day 3 and Day 6 were also subjected to virus-culturing procedures.

7.3.4 Statistical Methodology for Efficacy

7.3.4.1 Power and Sample Size

The Phase III studies were designed initially to include all treated patients in the primary efficacy analysis dataset. Based on exploratory analyses of data from Study 843-032, power calculations indicated that each of the Phase III studies would require approximately 1000 patients to detect a 20% relative difference between the two treatment groups in the proportion of patients reaching endpoint at a 5% significance level with 90% power. This difference is equivalent to an approximately 2-day difference in the median time to reaching endpoint (assuming an illness duration of approximately 10 days in the placebo group).

Blinded review of the RT-PCR results from the Phase III studies indicated that the proportion of picornavirus-infected patients with picornavirus colds was approximately two-thirds in both studies. This high proportion of patients with picornavirus infection was sufficient to support a change in the primary population for analysis of efficacy from "all treated patients" to "picornavirus-positive patients." Sixty-five percent (1363/2096) of patients were RT-PCR positive on any study day. With fewer patients, a relative difference of 25% in the proportion of patients reaching endpoint is required to maintain 90% power.

The change in the primary efficacy analysis dataset was documented in a statistical analysis plan submitted to the FDA before the study blind was broken.

7.3.4.2 Randomization

Each patient was randomized to receive pleconaril or placebo (in a 1:1 ratio) on the basis of a computer-generated randomization schedule administered by an interactive voice response system (IVRS). Patients were randomized within strata based on smoking status (current or recent smoker vs. non-smoker) and pre-enrollment use of cold symptom relief medications (used vs. did not use). Randomization was not stratified by center because of the anticipated large number of participating centers with low enrollment.

7.3.4.3 Definition of Patient Populations for Analysis

7.3.4.3.1 Intent-to-Treat

All patients treated with at least one dose of study medication were included in the intent-to-treat (ITT) population.

7.3.4.3.2 Intent-to-Treat Infected

As specified in the statistical analysis plan and agreed to with DAVDP at the pre-NDA meeting on May 23, 2001, the primary analysis population included all treated patients with a picornavirus infection, as determined by RT-PCR testing of any nasal mucus sample (Days 1, 3, or 6). This primary analysis population is referred to as Intent-to-Treat Infected (ITT-I). Many infectious diseases present as syndromes that can be caused by more than one type of infectious agent, and empiric therapy is the norm. However, since organism-specific anti-infective agents do not affect other organisms that may cause the syndrome, it is customary and appropriate to evaluate the efficacy of a new anti-infective agent in the population of patients who subsequently are identified as infected with the specific organism of interest.

Patients with baseline samples that tested RT-PCR negative but who had a subsequent positive sample comprised 4.7% of the ITT-I population. Infection with a picornavirus post-baseline that was not present at baseline is unlikely during the treatment period.

7.3.4.3.3 RT-PCR Positive at Baseline

The RT-PCR positive at baseline population included patients whose baseline sample tested positive, regardless of the RT-PCR results of samples taken on Day 3 or Day 6. This population was not specified in the statistical analysis plan. The FDA asked VIROPHARMA to examine the efficacy of pleconaril in these patients.

7.3.4.3.4 RT-PCR Negative

The complement of the ITT-I population included all patients whose baseline, Day 3 and Day 6 nasal mucus samples were RT-PCR negative. There is no expectation of efficacy of a specific antipicornavirus agent in this population of patients without evidence of picornavirus infection, and none was seen.

The numbers of patients in each efficacy analysis population are shown in Table 3.

Table 3. Number of Patients in Each Efficacy Analysis Dataset

	Study 843-043		Study 843-044		Pooled	
Population	**Placebo**	**Pleconaril**	**Placebo**	**Pleconaril**	**Placebo**	**Pleconaril**
ITT	526	526	524	520	1050	1046
ITT-I	326 (62%)	337 (64%)	356 (68%)	344 (66%)	682 (66%)	681 (65%)
RT-PCR positive at baseline	297 (56%)	315 (60%)	333 (64%)	320 (62%)	630 (60%)	635 (61%)
RT-PCR negative	200 (38%)	189 (36%)	168 (32%)	176 (34%)	368 (35%)	365 (35%)

7.3.4.4 Definition of Primary Endpoint

The primary endpoint was defined as the time from initiation of therapy to alleviation of cold symptoms (complete resolution of rhinorrhea and alleviation of five other cold symptoms [cough, nasal congestion, sore throat, malaise, and myalgia]) to absent or mild without the concomitant use of cold symptom relief medication for four consecutive reporting periods (~48 hours). This endpoint was developed by VIROPHARMA in conjunction with FDA and a panel of experts in viral respiratory infections.

7.3.4.5 Statistical Methods for Analysis of the Primary Endpoint

The distribution of time to endpoint (resolution of rhinorrhea and alleviation of other cold symptoms) was estimated by the Kaplan-Meier method, and the Wilcoxon-Gehan statistic was used to test the difference in duration of illness between the placebo and pleconaril groups.

Duration of the cold was measured as the time from the first dose of study medication to the time of the first of the four consecutive reporting periods in which the endpoint was

maintained. Duration was measured and analyzed in hours and minutes, but is reported in days.

The statistical model included strata for smoking status (smoker vs. non-smoker) and pre-enrollment use of cold symptom relief medication (used vs. did not use).

Patients who did not reach endpoint had their data censored at the time of last recorded observation. Patients who dropped out of the study and had no recorded symptom scores after the start of study drug were censored at 12 hours after the first dose.

7.3.4.6 Pooled Data

The objectives of the analyses of pooled data from Studies 843-043 and 843-044 were:

- To provide more precise estimates of the effect of pleconaril in treating the common cold than available from each study separately, and
- To provide larger numbers of patients for the examination of interactions between treatment and stratification factors and between treatment and demographic characteristics.

There is no intent to draw inferences from the pooled analyses that are not supported by the individual studies. The p-values from the pooled data are intended only to suggest the strength of the total evidence of a treatment difference.

Pooled data were used to examine interactions between treatment and smoking history; between treatment and entry pre-enrollment use of cold symptom relief medications; and between treatment and demographic subgroups. In a *post hoc* analysis, the pooled data were also used to investigate the treatment-by-site interaction.

7.3.5 Patient Enrollment and Disposition

Nearly 2100 patients (1050 placebo and 1046 pleconaril) were enrolled in the two Phase III studies (1052 patients in Study 843-043 and 1044 patients in Study 843-044). Sixty-five percent (65%) were identified as picornavirus-infected (i.e., RT-PCR positive at some time during the study). Patient disposition for each study by treatment group and overall for all randomized patients (intent-to-treat [ITT]) is shown in Table 4. More than 90% of patients in

each treatment group completed the 5-day course of treatment with study drug (i.e., pleconaril 400 mg TID or matching placebo for 5 days).

Table 4. Patient Disposition, ITT

	Study 843-043		Study 843-044		Pooled	
	Placebo	**Pleconaril**	**Placebo**	**Pleconaril**	**Placebo**	**Pleconaril**
Number of patients	**526**	**526**	**524**	**520**	**1050**	**1046**
Number of patients completing treatment	487 (93%)	479 (91%)	493 (94%)	486 (93%)	980 (93%)	965 (92%)
Number of patients not completing treatment	39 (7%)	47 (9%)	31 (6%)	34 (7%)	70 (7%)	81 (8%)
Reasons for not completing treatment						
• Adverse event	15 (3%)	17 (3%)	13 (2%)	19 (4%)	28 (3%)	36 (3%)
• Noncompliance	5 (1%)	11 (2%)	1 (<1%)	6 (1%)	6 (1%)	17 (2%)
• Lost to follow-up	11 (2%)	8 (2%)	8 (2%)	4 (1%)	19 (2%)	12 (1%)
• Patient request	7 (1%)	6 (1%)	6 (1%)	3 (1%)	13 (1%)	9 (1%)
• Other	1 (<1%)	5 (1%)	3 (1%)	2 (<1%)	4 (<1%)	7 (1%)

7.3.6 Baseline Characteristics and Demographics

Table 5 presents demographic characteristics and time between onset of cold symptoms and first dose of study drug for ITT patients. Across the two studies, 69% of patients were female, 83% were white, and 73% were between the ages of 18 and 44 years. Treatment groups within each study and across both studies were well matched with respect to these characteristics.

Table 5. Demographics and Other Baseline Characteristics, ITT

	Study 843-043		Study 843-044		Pooled
	Placebo	Pleconaril	Placebo	Pleconaril	All Patients
Number of Patients	**526**	**526**	**524**	**520**	**2096**
Age (yrs)					
N	526	526	524	520	2096
Mean (SD)	36 (13.4)	36 (13.1)	37 (14.1)	36 (14.2)	36 (13.7)
Median	35	35	36	34	35
Min, Max	18, 79	18, 77	18, 86	18, 82	18, 86
Distribution of age (yrs)					
18 to 44	392	393	369	379	1533
45 to 64	115	117	133	118	483
>64	19	16	22	23	80
Gender					
Male	179 (34%)	173 (33%)	149 (28%)	154 (30%)	655 (31%)
Female	347 (66%)	353 (67%)	375 (72%)	366 (70%)	1441 (69%)
Race					
White	414 (79%)	397 (75%)	461 (88%)	467 (90%)	1739 (83%)
Black	55 (10%)	57 (11%)	25 (5%)	23 (4%)	160 (8%)
Hispanic	37 (7%)	50 (10%)	22 (4%)	16 (3%)	125 (6%)
Asian	9 (2%)	9 (2%)	6 (1%)	7 (1%)	31 (1%)
Other	11 (2%)	13 (2%)	10 (2%)	7 (1%)	41 (2%)
Time from onset of symptoms to first dose of study drug (hours)					
Mean (±SD)	17.7 (5.83)	17.4 (5.81)	17.2 (5.94)	17.4 (6.30)	17.4 (5.97)
Median	19.8	19.5	19.1	19.3	19.4

The proportion of patients who tested positive by RT-PCR for picornavirus RNA in any nasal mucus sample during the study was similar across the treatment groups and the two studies. Table 6 presents the demographic characteristics of the RT-PCR positive patients, which were very similar to those of the ITT patients.

Table 6. Demographics and Other Baseline Characteristics, ITT-I

	Study 843-043		Study 843-044		Pooled
	Placebo	Pleconaril	Placebo	Pleconaril	All Patients
Number of Patients	**326**	**337**	**356**	**344**	**1363**
Age (yrs)					
N	326	337	356	344	1363
Mean (SD)	36 (12.9)	35 (12.4)	36 (13.8)	35 (13.5)	36 (13.2)
Median	35	33	35	33	34
Min, Max	18, 73	18, 75	18, 86	18, 82	18, 86
Distribution of age (yrs)					
18 to 44	244	257	261	259	1021
45 to 64	73	74	82	74	303
>64	9	6	13	11	39
Gender					
Male	115 (35%)	107 (32%)	105 (29%)	113 (33%)	440 (32%)
Female	211 (65%)	230 (68%)	251 (71%)	231 (67%)	923 (68%)
Race					
White	270 (83%)	271 (80%)	321 (90%)	309 (90%)	1171 (86%)
Black	21 (6%)	21 (6%)	13 (4%)	15 (4%)	70 (5%)
Hispanic	20 (6%)	32 (9%)	11 (3%)	7 (2%)	70 (5%)
Asian	6 (2%)	5 (1%)	4 (1%)	7 (2%)	22 (2%)
Other	9 (3%)	8 (2%)	7 (2%)	6 (2%)	30 (2%)
Time from onset of symptoms to first dose of study drug (hours)					
Mean (±SD)	18.4 (5.31)	18.4 (5.18)	17.8 (5.70)	18.0 (5.94)	18.1 (5.55)
Median	20.0	20.2	19.6	20.0	20.0

Table 7 and Table 8 show the proportion of ITT and ITT-I patients, respectively, with each of the six individual cold symptoms at baseline. The most frequently reported symptoms at baseline were rhinorrhea, nasal congestion, malaise, and sore throat for both ITT and ITT-I patients. The median total symptom severity score at baseline was 9 (on a scale of 0-18) within each treatment group and across both studies.

Table 7. Proportion of Patients With Individual Cold Symptoms of Any Severity at Baseline, ITT

	843-043		843-044		Pooled	
	Placebo	Pleconaril	Placebo	Pleconaril	Placebo	Pleconaril
	526	526	524	520	1050	1046
Rhinorrhea[a]	525 (>99%)	525 (>99%)	523 (>99%)	520 (100%)	1048 (>99%)	1045 (>99%)
Nasal Congestion	495 (94%)	501 (95%)	488 (93%)	484 (93%)	983 (94%)	985 (94%)
Cough	400 (76%)	402 (76%)	375 (72%)	391 (75%)	775 (74%)	793 (76%)
Sore Throat	440 (84%)	437 (83%)	432 (82%)	432 (83%)	872 (83%)	869 (83%)
Malaise	457 (87%)	453 (86%)	444 (85%)	436 (84%)	901 (86%)	889 (85%)
Myalgia	287 (55%)	280 (53%)	263 (50%)	260 (50%)	550 (52%)	540 (52%)

[a] Patients were required to have moderate or severe rhinorrhea at entry.

Table 8. Proportion of Patients With Individual Cold Symptoms of Any Severity at Baseline, ITT-I

	843-043		843-044		Pooled	
	Placebo	Pleconaril	Placebo	Pleconaril	Placebo	Pleconaril
	326	337	356	344	682	681
Rhinorrhea[a]	325 (>99%)	337 (100%)	355 (>99%)	344 (100%)	680 (>99%)	681 (100%)
Nasal Congestion	308 (94%)	322 (96%)	334 (94%)	325 (94%)	642 (94%)	647 (95%)
Cough	244 (75%)	261 (77%)	244 (69%)	254 (74%)	488 (72%)	515 (76%)
Sore Throat	283 (87%)	289 (86%)	304 (85%)	290 (84%)	587 (86%)	579 (85%)
Malaise	279 (86%)	293 (87%)	303 (85%)	284 (83%)	582 (85%)	577 (85%)
Myalgia	172 (53%)	176 (52%)	169 (47%)	161 (47%)	341 (50%)	337 (49%)

[a] Patients were required to have moderate or severe rhinorrhea at entry.

7.3.7 Efficacy Results

Because pleconaril is an antiviral agent that specifically inhibits rhinoviruses and enteroviruses, it has potential for efficacy only in patients with an infection caused by these viruses. Therefore, as agreed by the FDA, if the performance characteristics of the experimental RT-PCR assays are determined to be valid and reliable, the subset of patients identified by RT-PCR assays as picornavirus-infected is the appropriate primary efficacy population.

In the discussion of the study results (below), analyses of the primary endpoint are shown for all relevant subpopulations. The RT-PCR negative patients were analyzed to provide clinical confirmation of the expected absence of treatment benefit from pleconaril. The secondary endpoints also were analyzed in all relevant subpopulations; results for the primary efficacy population (the ITT-I group) are discussed below and results for ITT can be found in Appendix C, Tables 1 through 14).

7.3.7.1 Primary Efficacy Endpoint

7.3.7.1.1 Analysis of the Primary Endpoint With Censoring

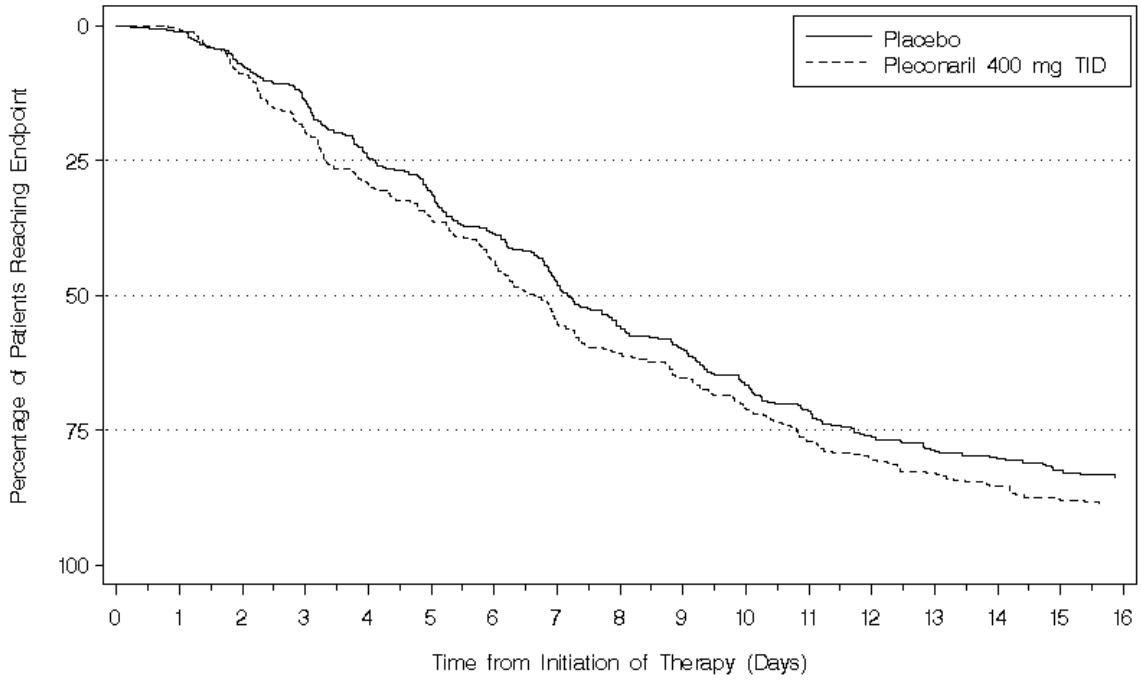
The results of the analyses of the primary endpoint in the ITT, ITT-I, RT-PCR positive at baseline, and RT-PCR negative populations of patients for both studies and the pooled data are presented in Table 9. Kaplan-Meier graphs of the results in ITT-I patients in Study 843-043 and Study 843-044 are shown in Figure 10 and Figure 11, respectively.

Table 9. Time to Alleviation of Illness (Primary Endpoint)

	Study 843-043		Study 843-044		Pooled	
Patient Populations	**Placebo**	**Pleconaril**	**Placebo**	**Pleconaril**	**Placebo**	**Pleconaril**
ITT	**526**	**526**	**524**	**520**	**1050**	**1046**
Patients reaching endpoint	417 (79%)	430 (82%)	411 (78%)	423 (81%)	828 (79%)	853 (82%)
Median (days)	6.9	6.4	7.1	6.2	7.0	6.3
p-value[a]		0.201		0.015		0.009
ITT-I	**326**	**337**	**356**	**344**	**682**	**681**
Patients reaching endpoint	258 (79%)	282 (84%)	286 (80%)	290 (84%)	544 (80%)	572 (84%)
Median (days)	7.2	6.6	7.7	6.2	7.3	6.3
p-value[a]		0.037		0.001		<0.001
RT-PCR positive at baseline	**297**	**315**	**333**	**320**	**630**	**635**
Patients reaching endpoint	234 (79%)	264 (84%)	267 (80%)	268 (84%)	501 (80%)	532 (84%)
Median (days)	7.2	6.5	7.8	6.2	7.4	6.3
p-value[a]		0.031		0.002		<0.001
RT-PCR negative	**200**	**189**	**168**	**176**	**368**	**365**
Patients reaching endpoint	159 (80%)	148 (78%)	125 (74%)	133 (76%)	284 (77%)	281 (77%)
Median (days)	5.9	6.1	5.9	6.0	5.9	6.0
p-value[a]		0.639		0.776		0.591

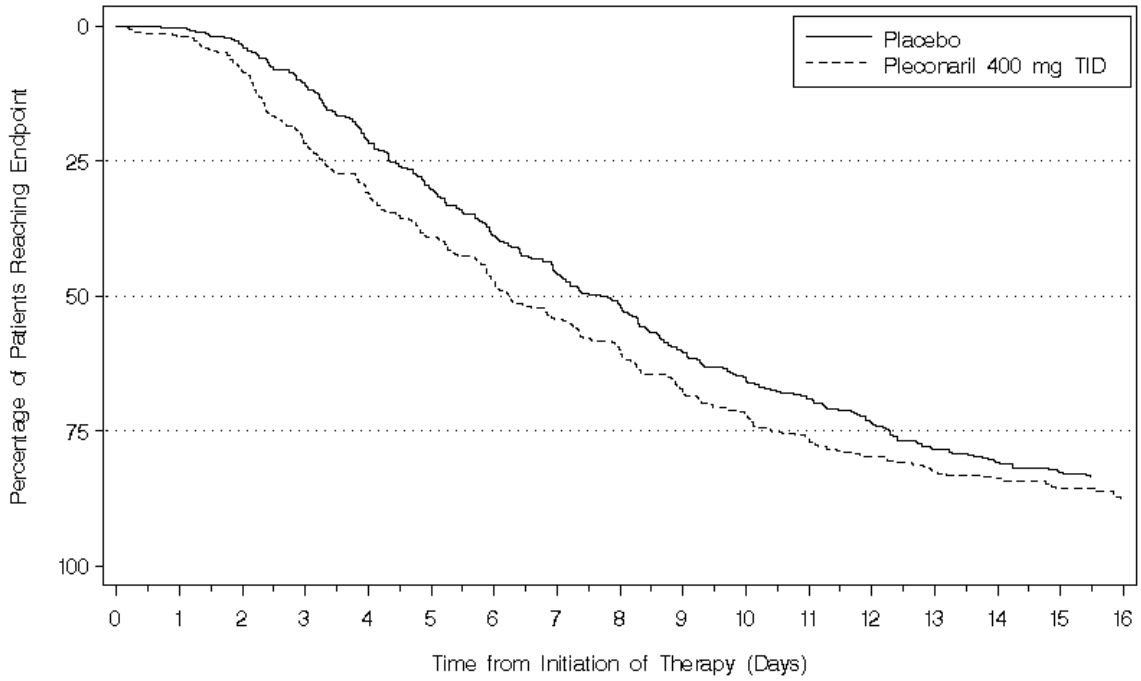
[a] p-values were calculated from a Wilcoxon test (strata: study, smoking status and pre-enrollment use of cold symptom relief medication).

Figure 10. Time to Primary Endpoint - ITT-I, Study 843-043



NOTE: Marks on the x-axis represent the time (days) to reaching endpoint.

Figure 11. Time to Primary Endpoint - ITT-I, Study 843-044



NOTE: Marks on the x-axis represent the time (days) to reaching endpoint.

The patients with a picornavirus cold who were in the placebo group experienced their cold for approximately 1 week. Based on the pooled data, the treatment benefit of pleconaril in reducing the duration of illness in the ITT-I group was 1.0 day (see Table 9), and 0.7 days in the ITT population. In the individual studies, the median treatment benefit ranged from 0.6 days to 1.5 days in the picornavirus-infected patients, using the prospectively identified primary endpoint.

To investigate differences in results for the primary endpoint in the two pivotal studies, the same data sets were analyzed using minor modifications of the primary endpoint. The modified primary endpoints shortened (to 24 hours) or lengthened (to 72 hours) the required minimum duration that the endpoint must have been sustained. These analyses of the modified endpoints in both studies indicated median treatment benefits that fell between 0.6 days and 1.5 days, as shown in Table 10. In Study 843-043, the modified endpoints indicated larger median benefits (1.0 day in both analyses with p-values ≤ 0.01) compared to the 0.6-day median benefit ($p=0.037$) using the prospectively defined endpoint. In Study 843-044, the modified endpoints indicated smaller median treatment benefits (0.6 and 1.1 days) than were seen with the prospectively defined endpoint (1.5 days), all with p-values <0.01. These additional analyses provide support for the robustness of the primary endpoint in estimating the treatment benefit based on duration of illness. They also indicate that the median benefits of 0.6 and 1.5 days observed using the prospectively defined endpoint represent the extremes of all analyses performed.

Table 10. Time to Alleviation of Symptoms Sustained for 24, 48, and 72 Hours, ITT-I

	834-043		843-044	
	Placebo	Pleconaril 400 mg TID	Placebo	Pleconaril 400 mg TID
ITT-I Patients	**326**	**337**	**356**	**344**
Alleviation of Cold Symptoms Sustained For 24 Hours				
Patients reaching endpoint	274 (84%)	295 (88%)	303 (85%)	304 (88%)
Median (days)	6.8	5.8	6.3	5.7
p-value[a]		0.008		0.002
Alleviation of Cold Symptoms Sustained For 48 Hours (per Statistical Analysis Plan)				
Patients reaching endpoint	258 (79%)	282 (84%)	286 (80%)	290 (84%)
Median (days)	7.2	6.6	7.7	6.2
p-value[a]		0.037		0.001
Alleviation of Cold Symptoms Sustained For 72 Hours				
Patients reaching endpoint	247 (76%)	266 (79%)	278 (78%)	276 (80%)
Median (days)	7.9	6.9	8.1	7.0
p-value[a]		0.011		0.007

[a] p-values were calculated from a Wilcoxon test (strata: smoking status and pre-enrollment use of cold symptom relief medication).

7.3.7.1.2 Analysis of the Primary Endpoint Without Censoring

Data were analyzed according to the prospectively defined statistical analysis plan, which included censoring patients who did not reach the primary endpoint for any reason immediately after the last recorded observation. The reasons for not reaching the primary endpoint were discontinuation from the study prior to the Day 18 visit or persistence of symptoms beyond 18 days. The proportions of patients in the pivotal studies who did not reach the prospectively defined primary endpoint during the 18-day study period in the pleconaril and placebo groups were 16% and 21%, respectively, in Study 843-043 and 16% and 19%, respectively, in Study 843-044.

At the request of the FDA, the analyses of the primary endpoint were repeated by assigning all patients who were censored to a time-to-endpoint equal to the longest time observed among patients (~16 days). The results of these analyses are shown in Table 11.

Table 11. Analysis of the Primary Endpoint With and Without Censoring, ITT-I

	843-043		843-044	
	Placebo	**Pleconaril**	**Placebo**	**Pleconaril**
	326	**337**	**356**	**344**
Analysis With Censoring (per Statistical Analysis Plan)				
Patients reaching endpoint	258 (79%)	282 (84%)	286 (80%)	290 (84%)
Median (days)	7.2	6.6	7.7	6.2
p-value[a]		0.037		0.001
Analysis Without Censoring				
Patients reaching endpoint	326 (100%)	337 (100%)	356 (100%)	344 (100%)
Median (days)	7.5	6.9	8.0	6.3
p-value[a]		0.046		0.002

[a] p-values were calculated from a Wilcoxon test (strata: smoking status and pre-enrollment use of cold symptom relief medication).

In comparing the results of the planned analyses (with censoring) to the results of the analyses without censoring, the following observations were made:

- The median durations of the time to reach endpoint were increased by ≤0.5 days in the pleconaril and placebo groups in both studies.
- The magnitudes of the median difference between the pleconaril and placebo groups in both studies were not affected.
- The overall inferential conclusions from the analyses were not affected.

7.3.7.2 Secondary Efficacy Endpoints

7.3.7.2.1 Patient Assessment of "No Cold"

In addition to the primary endpoint, the pivotal Phase III studies incorporated a self-assessment by each patient of recovery from his/her cold. This endpoint supports the clinical relevance of the primary endpoint, and it also provides a global assessment of the effects of pleconaril on the entire spectrum of cold symptoms, including those that may not have been captured as specific study assessments. As shown in Table 12, among ITT-I patients in both studies, the median times to patient assessment of "no cold" (approximately 7 days for placebo and 6 days for pleconaril) were similar to the duration of the illness as defined by the primary endpoint.

Table 12. Time to Patient Assessment of "No Cold," ITT-I

	Study 843-043		Study 843-044		Pooled	
	Placebo	Pleconaril	Placebo	Pleconaril	Placebo	Pleconaril
	326	337	356	344	682	681
Patient Assessment						
Patients reaching endpoint	275 (84%)	288 (85%)	310 (87%)	301 (88%)	585 (86%)	589 (86%)
Median (days)	6.8	6.0	7.0	6.0	6.9	6.0
p-value[a]		0.026		0.048		0.003

[a] p-values were calculated using a Wilcoxon test (strata: study, smoking status and pre-enrollment use of cold symptom relief medication).

7.3.7.2.2 Investigator Assessment of Presence or Absence of a Cold

Approximately 50% of the pleconaril patients and 60% of the placebo patients were assessed by the investigator as having a cold on Day 6 in both studies. Investigator assessments were less sensitive than the patient-recorded assessments in estimating the duration of illness for the following reasons: 1) investigator assessments were made twice, three days apart, in contrast to the twice-daily patient assessments; 2) investigator assessments were not always made by the same observer at each of the visits, as subinvestigators and study nurses made the assessment in the absence of the investigator; 3) symptom-based illnesses are inherently difficult to assess by an outside observer; and 4) investigator assessments did not factor in the use of concomitant cold symptom relief medications. As shown in Table 13, in Study 843-043, the analysis of the investigator's assessment of presence or absence of illness supports a treatment benefit of pleconaril on both Days 3 and 6, whereas analysis of Study 843-044 does not.

Table 13. Proportion of Patients With a Cold by Investigator Assessment, ITT-I

	Study 843-043		Study 843-044		Pooled	
	Placebo	Pleconaril	Placebo	Pleconaril	Placebo	Pleconaril
	326	337	356	344	682	681
Number of Patients with a Cold/Number of Patients Assessed						
Day 3	299/309 (97%)	279/316 (88%)	309/336 (92%)	300/325 (92%)	608/645 (94%)	579/641 (90%)
p-value[a]		<0.001		0.886		0.009
Day 6	188/304 (62%)	157/315 (50%)	197/338 (58%)	182/328 (55%)	385/642 (60%)	339/643 (53%)
p-value[a]		0.003		0.482		0.010

[a] p-values were calculated from a Fisher's exact test.
NOTE: The assessment windows were Days 2-4 for visit Day 3 and Days 5-9 for visit Day 6.

7.3.7.2.3 Resolution of Individual Cold Symptoms

The efficacy of pleconaril in shortening duration of multiple cold symptoms was confirmed by analyses of the time to resolution of six individual symptoms that were measured (rhinorrhea, nasal congestion, sore throat, cough, malaise, and myalgia). As shown in Table 14, in picornavirus-infected patients, the duration of each symptom was shorter in the pleconaril-treated patients compared to placebo-treated patients, although in a few instances these differences did not reach statistical significance in both studies.

Table 14. Time to Resolution of Individual Cold Symptoms, ITT-I

	843-043		843-044		Pooled Data	
	Placebo	Pleconaril	Placebo	Pleconaril	Placebo	Pleconaril
	326	**337**	**356**	**344**	**682**	**681**
Rhinorrhea						
Number of patients analyzed	326	337	356	344	682	681
Median (days)	6.9	6.0	7.1	5.9	7.0	6.0
p-value[a]		0.025		<0.001		<0.001
Nasal Congestion						
Number of patients analyzed	320	333	355	342	675	675
Median (days)	6.3	5.8	6.4	6.0	6.3	5.9
p-value[a]		0.005		0.152		0.003
Sore Throat						
Number of patients analyzed	299	304	324	307	623	611
Median (days)	3.8	2.8	3.8	3.0	3.8	2.9
p-value[a]		<0.001		0.004		<0.001
Cough						
Number of patients analyzed	304	304	327	303	631	607
Median (days)	6.1	5.9	6.8	5.4	6.3	5.4
p-value[a]		0.087		0.024		0.005
Malaise						
Number of patients analyzed	316	327	345	333	661	660
Median (days)	4.5	3.9	4.1	3.8	4.2	3.8
p-value[a]		0.022		0.193		0.011
Myalgia						
Number of patients analyzed	261	256	274	266	535	522
Median (days)	3.8	2.8	3.9	2.9	3.9	2.9
p-value[a]		<0.001		0.003		<0.001

[a] p-values are from a Wilcoxon test (strata: study, smoking status and pre-enrollment use of cold symptom relief medication).

7.3.7.2.4 Sum of Cold Symptom Severity Scores Over 18-Day Study

Because there are no established guidelines for the clinical evaluation of the common cold, VIROPHARMA adapted analyses that have been described for the evaluation of allergic rhinitis, another syndrome that is marked by prominent nasal symptoms. In the guidance from FDA for the clinical development of drugs to treat allergic rhinitis (Draft Guidance, April 2000), the preferred measures of effectiveness are patient self-rated composite symptom scores. The total nasal symptom score is a composite of the relevant symptoms of allergic rhinitis (rhinorrhea, nasal congestion, nasal itching, and sneezing), commonly scored using a 0-3 point scale, with 0 representing absence of symptoms and 3 representing severe symptoms (causing interference with daily activities). In the guidance, an appropriate primary efficacy endpoint for assessing efficacy in reducing symptoms of allergic rhinitis is the change from baseline in the total nasal symptom score for the entire double-blind treatment period.

The concept of evaluating the patient self-rated composite symptom scores over the study period is applicable to the assessment of an antiviral treatment for colds, since the individual symptoms of colds can be assessed using a similar 0-3 point scale. Because patients with a cold do not have a pretreatment baseline period of chronic underlying symptoms, it is appropriate to assess impact on total symptom severity over the study period relative to placebo. Therefore, to assess the impact of pleconaril in reducing overall symptom severity, a prospectively specified analysis of the sum of the total symptom severity scores throughout the 18-day study period was performed.

Table 15 shows the sum of cold symptom severity scores over the 18-day study for the individual studies and pooled data. In all cases, the severity of symptoms over the course of the illness was less in the pleconaril patients than in the placebo patients.

Table 15. Sum of the Twice-Daily Cold Symptom Severity Score Over the 18-Day Study Period, ITT-I

	Study 843-043		Study 843-044		Pooled	
	Placebo	Pleconaril	Placebo	Pleconaril	Placebo	Pleconaril
	326	337	356	344	682	681
Geometric mean (CV%)	33.7 (25.7)	28.4 (25.7)	33.2 (24.1)	27.8 (27.3)	33.4 (24.9)	28.1 (26.5)
Median	36.1	28.5	34.4	29.0	35.4	28.8
p-value[a]		0.006		<0.001		<0.001

[a] p-values were calculated using an ANCOVA of log-transformed data (model includes treatment, smoking status, and pre-enrollment use of cold symptom relief medication and covariate of baseline total symptom severity score).

NOTE: The last-observation-carried-forward approach was used to impute missing values.

7.3.7.2.5 Other Measures of Efficacy

Table 16 presents analyses of additional prospectively defined secondary endpoints: total tissue use, nights with sleep disturbance due to cold symptoms, days of cold symptom relief medication use, and days of impaired activity. Analyses of tissue use were intended as an objective measure of rhinorrhea. The other endpoints were evaluated to assess the effect of pleconaril on functional aspects of the illness.

These analyses show that pleconaril patients used fewer tissues for rhinorrhea, experienced fewer nights of sleep disturbance due to cold symptoms, and used cold symptom relief medications on fewer days than did placebo patients. Although the analysis of days of impaired activity did not reach statistical significance, there was a trend in favor of pleconaril in Study 843-043. Assessment of impairment of activity in these studies may have been a less sensitive measure of potential benefit than other endpoints because patients did not have the opportunity to record degrees of impairment.

Altogether, the secondary endpoints in these studies support the primary endpoint in demonstrating treatment benefits of pleconaril in reducing the duration and severity of picornavirus colds. Although the individual studies varied in the extent of the treatment benefit across these endpoints, the direction of the effect consistently favored pleconaril.

Table 16. Other Efficacy Endpoints, ITT-I

	843-043		843-044		Pooled Data	
	Placebo	Pleconaril	Placebo	Pleconaril	Placebo	Pleconaril
	326	337	356	344	682	681
Total Tissue Use During the Treatment Period (Days 1-6)						
Geometric mean (CV%)	72.8 (21.1)	69.9 (20.2)	84.1 (18.1)	66.5 (21.1)	78.4 (19.6)	68.2 (20.7)
Median	77.5	74.0	92.0	72.0	86.5	72.5
p-value[a]		0.566		<0.001		0.003
Total Tissue Use During the Study Period (Days 1-18)						
Geometric mean (CV%)	103.6 (22.1)	93.8 (21.4)	117.0 (18.3)	88.5 (22.1)	110.3 (20.2)	91.1 (21.8)
Median	115.0	96.0	131.5	91.0	122.0	93.0
p-value[a]		0.198		<0.001		<0.001
Number of Nights With Sleep Disturbance During the Study Period (Days 1-18)						
Mean (SD)	4.2 (4.35)	3.1 (3.12)	3.7 (3.59)	3.4 (3.70)	3.9 (3.98)	3.2 (3.43)
Median	3.0	2.0	3.0	2.0	3.0	2.0
p-value[b]		<0.001		0.270		<0.001
Number of Days With Cold Symptom Relief Medication Use During the Treatment Period (Days 1-6)						
Geometric mean (CV%)	0.91 (105.6)	0.75 (115.1)	1.04 (98.5)	0.82 (113.1)	0.98 (101.8)	0.79 (114.1)
Median	1.0	0.0	1.0	0.0	1.0	0.0
p-value[a]		0.058		0.028		0.004
Number of Days With Cold Symptom Relief Medication Use During the Study Period (Days 1-18)						
Geometric mean (CV%)	1.17 (104.5)	0.97 (112.4)	1.30 (99.4)	1.04 (115.1)	1.23 (101.7)	1.00 (113.8)
Median	1.0	1.0	1.0	1.0	1.0	1.0
p-value[a]		0.082		0.048		0.008
Number of Days With Impairment of Normal Activity Due to Cold Symptoms During the Study Period (Days 1-18)						
Mean (SD)	4.6 (4.51)	3.9 (3.72)	4.1 (3.97)	4.0 (3.99)	4.4 (4.24)	4.0 (3.86)
Median	3.0	3.0	3.0	3.0	3.0	3.0
p-value[b]		0.066		0.580		0.088

[a] p-values were calculated using an ANOVA of log transformed data (model included treatment, study, smoking status, and pre-enrollment use of cold symptom relief medication).

[b] p-values are calculated from an ANOVA of arcsine of square root transformed proportion of days (model includes treatment, study, smoking status, and pre-enrollment use of cold symptom relief medication).

7.3.7.2.6 Newly Diagnosed Acute Respiratory Complications Following a Cold

The incidence of newly diagnosed acute respiratory complications, including otitis media, bronchitis, sinusitis, and pneumonitis, was low in the placebo and pleconaril groups (<4% for any complication) in both Phase III studies (Table 17). Each of the clinically diagnosed acute respiratory complications was reported at similar rates in both treatment groups; the difference between the treatment groups was not statistically significant (Fisher's exact test; $p>0.05$) for any complication in either of the two studies.

Table 17. Newly Diagnosed Acute Respiratory Complications, ITT-I

	843-043		843-044		Pooled	
	Placebo	Pleconaril	Placebo	Pleconaril	Placebo	Pleconaril
	326	337	356	344	682	681
Number of patients with:						
Otitis media	3 (0.9%)	7 (2.1%)	1 (0.3%)	6 (1.7%)	4 (0.6%)	13 (1.9%)
Bronchitis	12 (3.7%)	11 (3.3%)	10 (2.8%)	10 (2.9%)	22 (3.2%)	21 (3.1%)
Sinusitis	8 (2.5%)	8 (2.4%)	11 (3.1%)	6 (1.7%)	19 (2.8%)	14 (2.1%)
Pneumonitis	0	2 (0.6%)	0	0	0	2 (0.3%)

Although the incidence of otitis media appears higher in the pleconaril patients, none of the differences reached statistical significance. In addition, review of the other Phase II adult and pediatric studies that collected these data indicated no differences between the treatment groups in the incidence of acute otitis media, except in Study 843-023 where the incidence was higher in the placebo group compared with the pleconaril group (see Table 18).

Table 18. Incidence of Otitis Media Reported in Studies 843-020, 843-023, 843-032 and 843-051 – ITT Patients

	Placebo	Pleconaril
Study 843-020 (adults):		
Number of patients	337	678
Number of patients with acute otitis media	1 (0.3%)	6 (0.9%)
Study 843-023 (children):		
Number of patients	45	38
Number of patients with acute otitis media	9 (20%)	3 (7.9%)
Study 843-032 (adults):		
Number of patients	439	436
Number of patients with acute otitis media	3 (0.7%)	1 (0.2%)
Study 843-051 (children):		
Number of patients	98	197
Number of patients with acute otitis media	8 (8.2%)	15 (7.6%)

Overall, adverse event data from 4447 patients treated in the adult cold studies showed comparable rates for the pleconaril and placebo groups in the incidence of adverse events reported as otitis media (placebo 16/1975, 0.8%; pleconaril 30/2472, 1.2%).

7.3.7.2.7 Antiviral Activity of Pleconaril

Using two independent methods to assess antiviral activity, it was determined that the proportion of patients with infectious picornavirus in nasal mucus declined earlier and more rapidly in the pleconaril group than in the placebo group. The antiviral activity of pleconaril

was assessed through analyses of serial virus cultures, the gold standard in testing for infectious virions, and by the experimental RT-PCR TaqMan® assay.

7.3.7.2.7.1 Virus Cultures

All patients in the pivotal studies provided a blown nasal mucus sample at baseline (pre-dosing) and on Days 3 (analysis window of Days 2 to 4) and 6 (analysis window of Days 5 to 9). All samples were tested for the presence of picornavirus material in the picornavirus-specific, RT-PCR TaqMan® assay. If the baseline sample was negative in the TaqMan® assay, baseline samples were tested in the ELOSA.

All RT-PCR positive baseline samples were sent to clinical diagnostic laboratories for picornavirus culture [see Section 8.3 for a more detailed discussion]. If a baseline sample was positive for picornavirus by virus culture, the Days 3 and 6 nasal mucus samples from the same patient were cultured. All culture-positive samples were outgrown, and virus sent to VIROPHARMA for testing for *in vitro* susceptibility to pleconaril.

As shown in Table 19, among those with positive virus cultures at baseline, fewer patients in the pleconaril group had a positive culture on Day 3 and Day 6 compared to the placebo group. Virus was cultured from a substantial proportion of patients in both groups on Day 6, although the TaqMan® assay indicated that the relative level of virus at this stage of illness was very low in comparison to baseline (see Table 20). The persistence of positive virus cultures on Day 6 is consistent with the literature regarding data from natural and experimentally induced rhinovirus infections (Fox et al., 1975; Winther et al., 1986). In both settings, rhinovirus remained detectable by culture in more than 40% of samples collected one week after onset of infection.

Table 19. Virus Culture Results on Days 3 and 6 in Patients With Positive Cultures at Baseline

	843-043		843-044		Pooled	
	Placebo	**Pleconaril**	**Placebo**	**Pleconaril**	**Placebo**	**Pleconaril**
Proportion (%) of Patients with Positive Virus Cultures/Patients with Positive Virus Cultures at Baseline						
Day 3 p-value[a]	132/182 (73%)	100/185 (54%) <0.001	150/212 (71%)	102/195 (52%) <0.001	282/394 (72%)	202/380 (53%) <0.001
Day 6 p-value[a]	94/180 (52%)	94/184 (51%) 0.835	102/207 (50%)	71/191 (37%) 0.016	196/387 (51%)	165/375 (44%) 0.070

[a] p-values were calculated from a Fisher's exact test.

NOTE: Table includes patients with both baseline and visit data. The analysis windows were Days 2-4 for visit Day 3 and Days 5-9 for visit Day 6.

7.3.7.2.7.2 Virus Levels in Nasal Mucus

Virus levels in nasal mucus samples were estimated relative to a standard series of known amounts of human rhinovirus 1B run in parallel, using the TaqMan® assay. All samples from a given patient were tested concurrently. The percent change in post-baseline (Days 3 and 6) virus levels relative to that patient's baseline level was then calculated. The median percent change values for each treatment group were then compared, as shown in Table 20.

Although virus levels declined rapidly in all groups, patients in the pleconaril group showed a larger percent reduction in virus levels on Day 3 compared with patients in the placebo group. By Day 6, the median percent reduction in virus levels was more than 99% in both treatment groups, near the lower limit of detection in most patients. Although virus was cultured from 37% to 52% of patients on Day 6, these results indicate that the amount of virus present in these samples was low.

Table 20. Change From Baseline in Virus Levels by RT-PCR TaqMan® Assay

	Study 843-043		Study 843-044		Pooled	
	Placebo	Pleconaril	Placebo	Pleconaril	Placebo	Pleconaril
Patients With TaqMan® Positive RT-PCR Results at Baseline	**262**	**276**	**301**	**290**	**563**	**566**
Day 3						
N	245	250	284	270	529	520
Median % change	-91.1	-98.1	-90.1	-97.4	-90.3	-97.7
p-value[a]		0.011		<0.001		<0.001
Day 6						
N	241	250	277	270	518	520
Median % change	-99.6	-99.8	-99.3	-99.9	-99.5	-99.8
p-value[a]		0.121		<0.001		<0.001
Overall antiviral effect (by repeated measures analysis)[b]		**0.010**		**<0.001**		**<0.001**

[a] p-values were calculated from an ANOVA for each day with treatment, study, smoking status, and pre-enrollment use of cold symptom relief medications as factors.

[b] p-values were calculated from a repeated measures ANOVA with treatment, patient (treatment), day, and treatment-by-day interaction as factors.

NOTE: Patients with baseline viral levels >0 but <10 pfu/mL were considered positive and assigned 10 pfu/mL for the analysis. Day 3 analysis window was Days 2 to 4; Day 6 analysis window was Days 5 to 9.

7.3.7.3 Post Hoc Analysis of Antiviral Onset of Action

Because a subset of patients had nasal mucus samples collected on Day 2, a *post hoc* assessment of the onset of the antiviral effect of pleconaril was performed. Although the proportion of patients with culture results on Day 2 was relatively small (13%) compared to the number with results in the Days 2 to 4 window, the pooled data revealed significantly fewer patients with positive picornavirus cultures on Day 2 in the pleconaril group compared to the placebo group (see Table 21). These results are consistent with a robust antiviral effect of pleconaril within a day of initiation of treatment.

Table 21. Virus Culture Results on Day 2

	Placebo	Pleconaril
Patients w/ culture results at baseline and between Days 2 and 4	**394**	**380**
Patients w/ culture results at baseline and Day 2	58	45
Number (%) of patients with positive culture results on Day 2	49 (85%)	27 (60%)
p-value[a]		0.007

[a] p-values were calculated from a Fisher's exact test.

7.3.7.4 Post Hoc Analyses of Symptom Severity

Several *post hoc* analyses were conducted in the ITT-I patients to support the prospective analyses regarding the effect of pleconaril on symptom severity.

To address the concern that the prospectively specified sum of the symptom severity scores over the course of the illness might confound severity with duration of illness, changes from baseline in total symptom severity and severity of the six individual symptoms were analyzed by day (twice daily reporting periods), as described in Sections 7.3.7.4.1 and 7.3.7.4.2.

Since the most bothersome and pronounced cold symptoms vary from patient to patient, time to ≥50% reduction from baseline in total symptom severity scores was analyzed. This endpoint reflects a clinically meaningful reduction in total symptoms without focusing on an individual symptom and is presented in Section 7.3.7.4.3. This approach is similar to that used by Canadian investigators in their attempt to evaluate the clinical significance of changes in symptom severity in acute respiratory and influenza illness in children (Jacobs et al., 2000).

Following discussions with the FDA (after submission of the NDA), analyses of the proportion of patients in each treatment group at each successive reporting interval who assessed at least one of their symptoms as moderate or severe were performed. These results are presented in Section 7.3.7.4.4. This binary approach to the symptom severity data (i.e., moderate or severe vs. mild or absent) addresses the criticism that the differences between adjacent scores on the severity scale (i.e., absent, mild, moderate, and severe) are not necessarily equal in terms of clinical significance, although they are treated as equal in the "change from baseline" analyses referred to above.

7.3.7.4.1 Change From Baseline in Total Symptom Severity Score

In the guidance from FDA for the clinical development of drugs to treat allergic rhinitis (Draft Guidance, April 2000), assessment of changes from baseline in total nasal symptom scores in the early days of a study can be used to evaluate a drug's onset of action. The onset of action is described in the guidance as the point at which patients might reasonably expect to see a meaningful decrease in their allergic rhinitis symptoms. Statistically, it is the first time point after initiation of treatment when the drug demonstrates a change from baseline greater than the placebo treatment for the relevant symptom severity measure, which is usually the primary endpoint of total nasal symptom score.

This approach to analyzing onset of action is applicable to the assessment of patients with colds, an illness in which patients on either active treatment or placebo will both experience an improvement of symptoms as the disease resolves. Therefore, the mean total symptom severity score (i.e., the composite score for rhinorrhea, nasal congestion, sore throat, cough, malaise, and myalgia; scale: 0-18) was evaluated at each reporting interval (half-day) throughout the treatment period. As shown in Table 22, these analyses showed that pleconaril patients had lower total symptom severity scores relative to placebo within one day after initiating treatment. Mean total symptom severity scores over the treatment period are depicted in Figure 12.

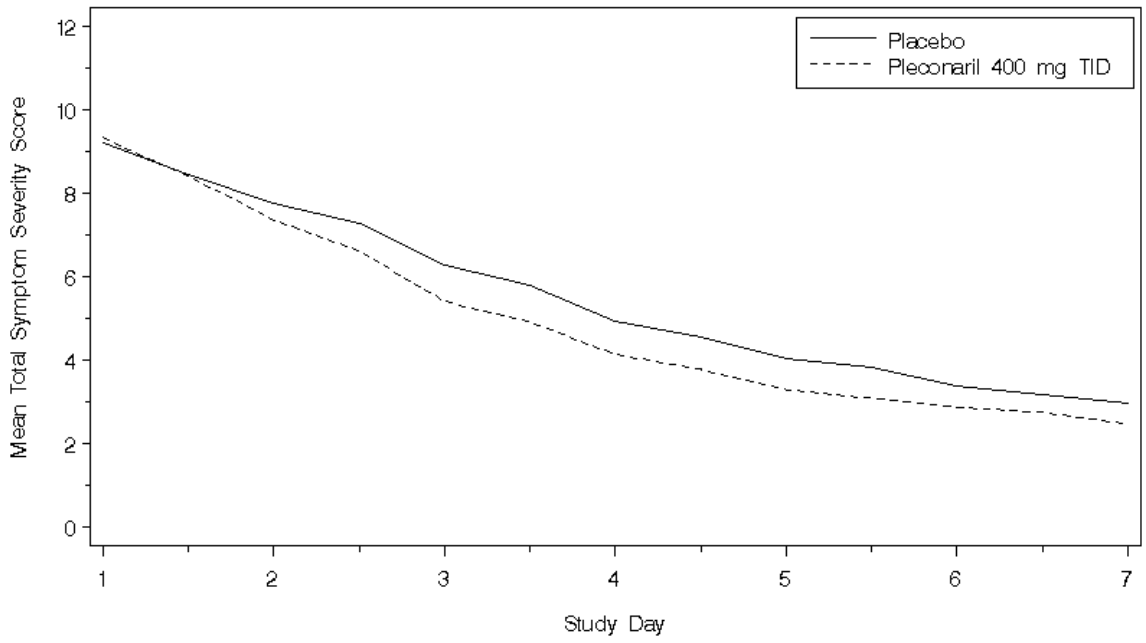
Table 22. Change From Baseline in Total Symptom Severity Score by Day During the Treatment Period (Days 1-6), ITT-I

	843-043		843-044		Pooled Data	
	Placebo	Pleconaril	Placebo	Pleconaril	Placebo	Pleconaril
	326	337	356	344	682	681
Prior to Dosing Mean (SD) Score	9.49 (2.58)	9.47 (2.47)	8.99 (2.46)	9.22 (2.52)	9.23 (2.53)	9.34 (2.50)
Day 1 PM Mean (SD) Score Mean % Change p-value[a]	8.65 (3.02) -6.5	8.37 (2.91) -10.3 0.162	8.29 (3.04) -6.4	8.48 (3.18) -7.3 0.923	8.46 (3.03) -6.5	8.43 (3.05) -8.8 0.383
Day 2 AM Mean (SD) Score Mean % Change p-value[a]	7.80 (3.28) -15.2	7.38 (3.12) -20.2 0.052	7.76 (3.22) -10.8	7.36 (3.20) -17.9 0.019	7.78 (3.25) -12.9	7.37 (3.16) -19.0 0.002
Day 2 PM Mean (SD) Score Mean % Change p-value[a]	7.27 (3.46) -20.5	6.61 (3.42) -28.8 0.007	7.28 (3.38) -16.2	6.65 (3.57) -25.7 0.003	7.28 (3.42) -18.3	6.63 (3.49) -27.2 <0.001
Day 3 AM Mean (SD) Score Mean % Change p-value[a]	6.20 (3.61) -31.7	5.39 (3.20) -41.9 0.001	6.35 (3.52) -26.7	5.45 (3.45) -39.8 <0.001	6.28 (3.56) -29.1	5.42 (3.32) -40.9 <0.001
Day 3 PM Mean (SD) Score Mean % Change p-value[a]	5.75 (3.79) -37.1	4.87 (3.31) -47.4 <0.001	5.82 (3.55) -33.2	4.98 (3.54) -45.3 <0.001	5.79 (3.66) -35.1	4.93 (3.42) -46.3 <0.001
Day 4 AM Mean (SD) Score Mean % Change p-value[a]	5.06 (3.78) -45.1	4.19 (3.17) -55.0 <0.001	4.82 (3.23) -44.6	4.10 (3.22) -54.9 <0.001	4.94 (3.50) -44.9	4.14 (3.19) -54.9 <0.001
Day 4 PM Mean (SD) Score Mean % Change p-value[a]	4.66 (3.70) -49.5	3.78 (3.11) -59.5 <0.001	4.48 (3.27) -48.9	3.78 (3.35) -58.8 <0.001	4.57 (3.48) -49.2	3.78 (3.23) -59.2 <0.001
Day 5 AM Mean (SD) Score Mean % Change p-value[a]	4.19 (3.63) -54.4	3.24 (2.87) -65.3 <0.001	3.92 (3.21) -55.6	3.35 (3.16) -63.8 0.004	4.05 (3.42) -55.1	3.30 (3.02) -64.5 <0.001
Day 5 PM Mean (SD) Score Mean % Change p-value[a]	4.03 (3.72) -55.9	3.04 (2.89) -67.7 <0.001	3.63 (3.19) -59.3	3.14 (3.19) -66.5 0.009	3.82 (3.46) -57.7	3.09 (3.04) -67.1 <0.001
Day 6 AM Mean (SD) Score Mean % Change p-value[a]	3.55 (3.49) -61.7	2.80 (2.81) -69.9 0.001	3.26 (3.04) -63.5	2.95 (3.09) -68.6 0.064	3.40 (3.26) -62.7	2.88 (2.96) -69.3 <0.001
Day 6 PM Mean (SD) Score Mean % Change p-value[a]	3.36 (3.55) -64.0	2.67 (2.86) -71.4 0.003	3.02 (3.11) -66.5	2.83 (3.18) -70.1 0.205	3.18 (3.33) -65.3	2.75 (3.03) -70.7 0.003

[a] p-values were calculated from an ANOVA of total symptom severity score with effects for study, baseline total symptom severity score (covariate), treatment, smoking status, and pre-enrollment use of cold symptom relief medication.

NOTE: The last-observation-carried-forward approach was used to impute missing values.

Figure 12. Mean Total Symptom Severity Scores Over the Treatment Period, Studies 843-043 and 843-044 Pooled – ITT-I



Day 1 data are pretreatment patient qualifying scores.
The last observation carried forward approach is used to impute missing values.
The maximum possible symptom score for the six symptoms evaluated is 18.

7.3.7.4.2 Change From Baseline in Individual Symptom Severity Scores

The mean scores for individual symptoms (rhinorrhea, nasal congestion, cough, pharyngeal symptoms, malaise, and myalgia) were evaluated at each reporting interval (half-day) throughout the treatment period (See Appendix B; Tables 1-6) in the ITT-I patients. The range of each individual symptom severity score (0-3) was substantially smaller than that of the composite total symptom severity score (range 0-18), reducing the likelihood that significant differences could be demonstrated.

Despite this limitation, the analyses showed lower mean individual symptom scores for rhinorrhea, nasal congestion, cough, and myalgia for ITT-I patients in the pleconaril group compared to the placebo group. These differences became apparent within a day of initiation of treatment. The mean symptom score for each of these four symptoms was lower than that of the placebo group at virtually all reporting periods. For sore throat and malaise, symptom

scores for pleconaril compared to placebo patients approached, but did not reach, statistical significance.

7.3.7.4.3 Time to ≥50% Reduction from Baseline in Total Symptom Severity Score

Among ITT-I patients, pleconaril patients achieved reductions from baseline of ≥50% in total symptom severity scores earlier than did placebo patients, as shown in Table 23. The pleconaril patients reached this endpoint a day or more sooner than the placebo patients in both studies. These analyses support the prospective analyses in showing a >25% shorter time to reach a ≥50% reduction from baseline in total symptom severity score in both studies.

Table 23. Time to ≥50% Reduction from Baseline in Total Symptom Severity Score, ITT-I

	Study 843-043		Study 843-044		Pooled Data	
	Placebo	**Pleconaril**	**Placebo**	**Pleconaril**	**Placebo**	**Pleconaril**
ITT-I	**326**	**337**	**356**	**344**	**682**	**681**
Patients reaching endpoint	298 (91%)	309 (92%)	333 (94%)	323 (94%)	631 (93%)	632 (93%)
Median days to event	4.0	2.8	3.9	2.9	3.9	2.9
p-value[a]		<0.001		<0.001		<0.001

[a] p-values were calculated from a Wilcoxon test (strata: smoking status and pre-enrollment use of cold symptom relief medication).

7.3.7.4.4 Patients With Moderate or Severe Symptoms

The proportion of ITT-I patients at each reporting interval who described any of the six cold symptoms as moderate or severe was compared between treatment groups (Table 24). The percentage of pleconaril patients who reported any moderate or severe symptom was significantly reduced within 24 hours of the first dose of study drug, compared to placebo patients.

Table 24. Proportion of Patients With Any Moderate or Severe Cold Symptom at Each Reporting Interval, ITT-I

	843-043		843-044		Pooled Data	
	Placebo N=326	**Pleconaril N=337**	**Placebo N=356**	**Pleconaril N=344**	**Placebo N=682**	**Pleconaril N=681**
Proportion of Patients with Any Moderate/ Severe Cold Symptom(s)						
Prior to Dosing	326 (100%)	337 (100%)	356 (100%)	344 (100%)	682 (100%)	681 (100%)
Day 1 PM p-value[a]	301 (92%)	311 (92%) 0.914	338 (95%)	309 (90%) 0.010	639 (94%)	620 (91%) 0.054
Day 2 AM p-value[a]	274 (84%)	272 (81%) 0.216	311 (87%)	282 (82%) 0.044	585 (86%)	554 (81%) 0.022
Day 2 PM p-value[a]	249 (76%)	234 (69%) 0.035	285 (80%)	244 (71%) 0.005	534 (78%)	478 (70%) <0.001
Day 3 AM p-value[a]	210 (64%)	188 (56%) 0.016	249 (70%)	189 (55%) <0.001	459 (67%)	377 (55%) <0.001
Day 3 PM p-value[a]	182 (56%)	169 (50%) 0.106	205 (58%)	173 (50%) 0.047	387 (57%)	342 (50%) 0.011
Day 4 AM p-value[a]	165 (51%)	152 (45%) 0.109	177 (50%)	150 (44%) 0.087	342 (50%)	302 (44%) 0.019
Day 4 PM p-value[a]	149 (46%)	134 (40%) 0.083	170 (48%)	127 (37%) 0.003	319 (47%)	261 (38%) <0.001
Day 5 AM p-value[a]	137 (42%)	113 (34%) 0.015	145 (41%)	118 (34%) 0.063	282 (41%)	231 (34%) 0.002
Day 5 PM p-value[a]	125 (38%)	109 (32%) 0.066	122 (34%)	111 (32%) 0.522	247 (36%)	220 (32%) 0.081
Day 6 AM p-value[a]	106 (33%)	88 (26%) 0.042	115 (32%)	100 (29%) 0.296	221 (32%)	188 (28%) 0.031
Day 6 PM p-value[a]	94 (29%)	95 (28%) 0.711	103 (29%)	94 (27%) 0.569	197 (29%)	189 (28%) 0.506
Day 7 AM p-value[a]	103 (32%)	79 (23%) 0.010	89 (25%)	90 (26%) 0.776	192 (28%)	169 (25%) 0.106
Day 7 PM p-value[a]	99 (30%)	72 (21%) 0.004	94 (26%)	76 (22%) 0.148	193 (28%)	148 (22%) 0.002

[a] p-values were calculated from a CMH chi-square test controlled by study, smoking status, and pre-enrollment use of cold symptom relief medication.

NOTE: The last-observation-carried-forward approach was used to impute missing values.

In summary, these *post hoc* analyses indicate an early difference in symptom severity in favor of pleconaril. The *post hoc* analyses support the prospectively designated primary and secondary endpoint analyses showing the effect of pleconaril in reducing the duration and severity of the common cold.

7.3.7.5 Demographic Subgroup Analyses

Results of analyses of the primary efficacy endpoint in the primary efficacy population (ITT-I), subset by gender, race and age, are shown in Table 25. Although many of the subgroups were relatively small, the time to alleviation of cold symptoms was shorter in all pleconaril subgroups compared to placebo except for non-whites. *Post hoc* creation of subgroups (i.e., nonstratified) together with small numbers in many of the subgroups is the most logical explanation for the apparent absence of benefit in the non-white subgroup. Further division of this group into black, Hispanic, and other was not revealing.

Table 25. Subgroup Analyses of the Primary Endpoint Subset by Demographic Factors – ITT-I Patients, Pooled Data

Factor	Statistic	Placebo	Pleconaril	p-value[a]
Gender				
Male	Patients reaching endpoint/patients analyzed Median days	185/220 (84%) 6.1	186/220 (85%) 5.7	 0.210
Female	Patients reaching endpoint/patients analyzed Median days	359/462 (78%) 8.1	386/461 (84%) 6.9	 <0.001
Race				
White	Patients reaching endpoint/patients analyzed Median days	470/591 (80%) 7.8	482/580 (83%) 6.5	 <0.001
Non-white	Patients reaching endpoint/patients analyzed Median days	74/91 (81%) 5.7	90/101 (89%) 6.1	 0.568
Age Group				
18-44 years	Patients reaching endpoint/patients analyzed Median days	414/505 (82%) 7.0	443/516 (86%) 6.3	 0.003
45-64 years	Patients reaching endpoint/patients analyzed Median days	117/155 (75%) 9.0	114/148 (77%) 6.9	 0.019
>64 years	Patients reaching endpoint/patients analyzed Median days	13/22 (59%) 9.7	15/17 (88%) 7.8	 0.129

[a] p-values were calculated from a Wilcoxon test (strata: study, smoking status, and pre-enrollment use of cold symptom relief medication).

The relationship between treatment and gender was examined by analyzing the primary endpoint with a Cox regression model. The model included smoking history and use of symptom relief medication before study entry as strata, and effects of treatment, gender and treatment-by-gender interaction. The interaction term was not significant ($p>0.9$), indicating that the observed difference between genders was no different than would be expected by chance.

7.3.7.6 Stratified Analyses by Smoking Status and Pre-enrollment Use of Cold Symptom Relief Medication

The results of earlier cold studies indicated that smoking status and use of cold symptom relief medication might obscure the ability to observe a treatment benefit of pleconaril in patients with colds. To ensure balance between the two treatment groups for these variables, the randomization of Phase III studies was stratified by smoking history and pre-enrollment use of cold symptom relief medication.

Efficacy analyses specified in the protocol included stratification by smoking status and prior cold symptom relief medication use, using the Wilcoxon-Gehan test. Analyses of the primary endpoint and many of the secondary endpoints demonstrated a treatment effect in the ITT-I patients in both studies. *Post hoc* analyses using Cox regression were also performed, with similar outcomes.

The Phase III studies were not designed or powered to examine the effects of the strata variables on the duration/severity of the cold symptoms or on the interaction between strata and treatment. Therefore, the pooled data, providing a larger sample size, are the most appropriate dataset to investigate the relationships among strata, treatment and duration/severity of colds.

7.3.7.6.1 Distribution of Patients by Smoking Status and Pre-enrollment Use of Cold Symptom Relief Medication

As shown in Table 26, most (51%) patients neither smoked nor used cold medications before entry into the study. Only 8% of subjects both smoked and used cold medications before entry into the study. Approximately 20% smoked, but did not use cold medications before entry into the study; and another 21% did not smoke but did use cold medications before entry into the study. There was no relationship between smoking and use of cold medications before entry into the study ($p=0.969$ for a Cochran-Mantel-Haenzel test).

The distribution of patients in these strata was similar between the two studies and between the two treatment groups. The distribution in the ITT-I patients was similar to the distribution among ITT patients.

Table 26. Number (%) of Patients by Strata – ITT, Pooled

	Used cold symptom relief medication prior to study	
Smoker	**No**	**Yes**
No	1063 (51%)	445 (21%)
Yes	415 (20%)	173 (8%)

7.3.7.6.2 Examination of the Relationships Between Smoking, Use of Cold Symptom Relief Medication Prior to Enrollment, and Treatment Effects

As previously reported in the NDA, the primary analysis specified in the statistical analysis plan was a Wilcoxon-Gehan test, stratified by smoking status and use of cold symptom relief medication prior to enrollment. However, the effect of pleconaril on the duration of the cold in the two strata is of interest. These relationships were examined in the pooled data, using a Cox regression model that included treatment, study, smoking status, and use of cold symptom relief medications prior to study entry. None of the three-way interactions (among treatment, study and smoking status; among treatment, study and pre-enrollment cold medication use; and among treatment, smoking status and pre-enrollment cold medication use) was statistically significant (all $p>0.1$). The two-way interaction between study and treatment was not significant ($p>0.6$) nor was the interaction between treatment and prior cold symptom relief medication use ($p>0.1$).

However, the two-way interaction between treatment and smoking status was statistically significant ($p=0.013$). Analyses of the primary study endpoint (time to resolution of rhinorrhea and alleviation of five other cold symptoms to absent or mild without use of concomitant cold medications, sustained for four consecutive reporting periods [≥48 hours]), as well as analysis of time to ≥50% reduction in total symptom severity score, are presented in Table 27 for ITT-I patients by smoking status. ITT-I patients who were non-smokers and who received pleconaril experienced a significant reduction in duration of illness. Of note, the difference between the pleconaril and placebo groups in the length of time required to reach the primary endpoint was substantially larger (1.3 days) in the non-smokers stratum than in the unstratified analyses of all ITT-I patients (1.0 days), indicating a median treatment benefit based on the primary endpoint of greater than one day in non-smokers (70% of population) who have a picornavirus cold.

Table 27. Clinical Efficacy Endpoints, Subset by Smoking Status – ITT-I Patients

	Placebo	Pleconaril	Placebo	Pleconaril
	Non-Smokers		Smokers	
Time to Resolution of Rhinorrhea with Other Cold Symptoms to Mild or Absent				
Number of patients reaching endpoint/analyzed	406/498 (82%)	417/477 (87%)	138/184 (75%)	155/204 (76%)
Median number of days	7.3	6.0	7.4	8.3
p-value[a]		<0.001		0.692
Time to ≥50% Reduction in Total Symptom Severity Score				
Number of patients reaching endpoint/analyzed	471/498 (95%)	455/477 (95%)	160/184 (87%)	177/204 (87%)
Median number of days	3.7	2.7	4.8	3.6
p-value[a]		<0.001		0.046

[a] p-values were calculated from a Wilcoxon test (strata: study, smoking status, and pre-enrollment use of cold symptom relief medication)

Patients who smoked showed no evidence of a treatment benefit based on the primary study endpoint. However, in *post hoc* analyses smokers did experience a shorter time to ≥50% reduction from baseline in symptom severity that was of similar magnitude to that seen in non-smokers.

Smoking is known to impair mucociliary clearance of the upper respiratory epithelium, lead to altered vascular and epithelial permeability due to chronic inflammation, and adversely affect immune function (Patel and Homnick, 2000; Marcy and Merrill, 1987). In addition, smoking is a risk factor for colds of longer duration, and smokers are more likely to report chronic nasal symptoms compared to nonsmokers (Montnemery et al., 2002; Turkeltaub and Gergen, 1991; Bensenor et al., 2001). Thus, resolving cold symptoms may be difficult to discern from these chronic symptoms in smokers, obscuring clinical treatment benefit in analyses that require symptoms to resolve to mild or absent.

7.4 Overall Conclusions Regarding Efficacy

- Pleconaril is a specific inhibitor of rhinoviruses, the most prevalent cause of the common cold, and of enteroviruses, which cause a smaller proportion of colds. As such, the potential efficacy of pleconaril can be shown only in patients infected with one of these viruses.

- The appropriate primary efficacy population is the 65% of patients who were identified as picornavirus infected (ITT-I). The efficacy of pleconaril was demonstrated in two Phase III studies using the primary endpoint and most of the secondary endpoints, including direct measures of antiviral activity. No efficacy on any endpoint was evident in the RT-PCR negative population of patients.

- *Post hoc* analyses of reduction in symptom severity were performed to determine onset of clinical action of pleconaril, which was significantly more rapid than placebo, beginning the first day following initiation of treatment.

- The magnitude of the treatment benefit across the entire population studied (ITT) provides a measure of the "average" effect under the conditions of the study, but underestimates the treatment benefit in picornavirus-infected individuals. Nevertheless, the treatment benefit of pleconaril was evident in most analyses of the primary and secondary endpoints in the ITT population in both studies, although the magnitude of the benefits was not as great as in the ITT-I patients.

8. CLINICAL VIROLOGY

8.1 Summary of Key Points

- In the Phase III studies, 87% of picornaviruses isolated at baseline from patients with colds were susceptible to pleconaril at concentrations ≤3.8 μg/mL, the highest pleconaril level testable in *in vitro* cell culture assay.

- Post-baseline viruses with reduced susceptibility to pleconaril in cell culture (>10-fold change relative to baseline isolates) were found in 10.7% of pleconaril-treated patients.

- Evaluation of the primary and secondary endpoints in patients with post-baseline viruses having reduced drug susceptibility indicated no decrease in benefit from pleconaril.

8.2 Identification of Picornavirus Infected Patients

Two experimental RT-PCR assays, a real-time TaqMan® assay and a colorimetric ELOSA, were used to identify picornavirus-infected patients enrolled in the Phase III studies. The performance characteristics of the TaqMan® assay and ELOSA were established with respect to their spectrum of picornavirus serotype detection, selectivity for picornaviruses detection, test sensitivity and specificity, and other attributes.

The selectivity for picornavirus detection by both assays was assured by use of picornavirus-specific amplification primers (the TaqMan® assay and ELOSA used distinct primer pairs) and picornavirus-specific hybridization probes. The two RT-PCR assays differed in the range of picornavirus serotype detection, as shown in Table 28. The TaqMan® assay detected 90 of the 101 prototypic HRV serotypes and 3 of 53 culturable prototypic enteroviruses. The ELOSA detected all HRV and enteroviruses tested. Neither assay detected unrelated viruses including coronavirus, parainfluenza virus 3, influenza viruses A and B, adenovirus, mumps virus, measles virus, and respiratory syncytial virus.

Table 28. Spectrum of Picornavirus Detection by the TaqMan® Assay and ELOSA

	TaqMan®	ELOSA
HRV serotypes detected	90/101	101/101
Enteroviruses serotypes detected	3/53	53/53

Since RT-PCR assays are typically more sensitive than traditional culture methods, the sensitivity and specificity of the TaqMan® assay and ELOSA were established using an expanded gold standard analysis. In this analysis, the results of both RT-PCR tests had to agree for a sample to be considered positive, minimizing the potential for false-positive results by the more sensitive RT-PCR assays, while the traditional gold standard virus culture was considered 100% specific. Thus, for the expanded gold standard, "true positives" were considered to be either: (1) virus culture positives regardless of RT-PCR results or (2) TaqMan® assay *and* ELOSA positives regardless of virus culture results. Using these criteria, the sensitivity and specificity of the RT-PCR assays were assessed by testing 855 baseline blown nasal mucus samples from patients who had enrolled in Study 843-032 (a cold study conducted in the U.S. in the fall of 1999) in the TaqMan® assay, ELOSA and virus culture (performed at 33°C to favor rhinovirus isolation).

The results of these tests indicated that both RT-PCR assays exhibited high sensitivity and specificity for detection of picornavirus material in nasal mucus samples from patients with colds, as shown in Table 29.

Table 29. Sensitivity and Specificity of TaqMan® Assay and ELOSA

	TaqMan®	ELOSA
Sensitivity	96%	97%
Specificity	97%	87%

Practical differences between the two RT-PCR assays determined how they were used in Studies 843-043 and 843-044 to establish the picornavirus infection status of patients. The TaqMan® assay is partially automated and capable of a much higher sample throughput than the manually performed ELOSA. Approximately 6000 nasal mucus samples from the Phase III clinical studies were processed using the TaqMan® assay (three samples from each patient). Additionally, the TaqMan® assay provides information regarding the relative levels of picornavirus material in nasal mucus, making it possible to estimate changes in relative

virus levels within individual patients. These two attributes dictated that the TaqMan® assay be the primary RT-PCR test of all patient samples.

However, since the TaqMan® assay has a narrower spectrum of picornavirus detection than does the ELOSA, all TaqMan® negative baseline samples were assayed by ELOSA in the pivotal studies. After aliquots of all nasal mucus samples were evaluated in the TaqMan® assay, independent aliquots of baseline samples from those patients negative in the TaqMan® assay were tested in the ELOSA in an effort to identify patients infected with picornavirus serotypes outside the detection spectrum of the TaqMan® assay. Approximately 14% of samples that were TaqMan® negative at baseline were positive by the ELOSA.

Patients who tested both TaqMan® negative and ELOSA negative at baseline were considered to be infected with a picornavirus if either of their Days 3 or 6 nasal mucus samples tested positive in either assay. Only 4.7% of patients were in this category, and the clinical efficacy conclusions and magnitude of benefit were unchanged by excluding these patients. Thus, the ITT-I population of patients, which formed the primary efficacy population for analysis of the Phase III studies, was comprised of patients who tested positive by either assay on any day, as shown in Table 30.

Table 30. Number of RT-PCR Positive Patients by Assay and Study Day

	Study 843-043			Study 843-044		
	Placebo	**Pleconaril**	**Total**	**Placebo**	**Pleconaril**	**Total**
ITT	**526**	**526**	**1052**	**524**	**520**	**1044**
Missing baseline RT-PCR	3	1	4	7	5	12
TaqMan®-positive at baseline	262	276	538	301	290	591
TaqMan®-negative at baseline	261	249	510	216	225	441
ELOSA-positive at baseline	35	39	74	32	30	62
RT-PCR positive at baseline	297	315	612	333	320	653
RT-PCR negative at baseline	226	210	436	184	195	379
RT-PCR positive on Days 3 or 6	29	22	51	23	24	47
RT-PCR positive on any day (ITT-I)	326	337	663	356	344	700
RT-PCR negative on all days	200	189	389	168	176	344

8.3 Virus Culture and Baseline Susceptibility of Virus Isolates to Pleconaril

All RT-PCR positive baseline samples from Studies 843-043 and 843-044 were subjected to picornavirus culture by independent clinical diagnostic laboratories. Virus culture conditions

were optimized for rhinovirus propagation. HeLa-I cells, a cell line that overexpresses the receptor (ICAM-1) for the majority of HRV serotypes, were grown at 33°C and monitored microscopically for the appearance of characteristic picornavirus cytopathic effect. If a baseline sample was positive for picornavirus by virus culture, the Days 3 and 6 nasal mucus samples from the same patient were then cultured. All virus culture positive sample outgrowths were sent to VIROPHARMA for testing for *in vitro* susceptibility to pleconaril.

It was deemed unnecessary to conduct virus culture analysis on RT-PCR negative baseline samples since studies conducted prior to the pivotal trials showed that the RT-PCR assays were considerably more sensitive than virus culture for detection of picornavirus in nasal mucus samples. In these performance studies, 0.6% of RT-PCR negative samples were virus culture positive.

In Studies 843-043 and 843-044, picornavirus-infected patients who were both RT-PCR and virus culture positive at baseline represented approximately 40% of patients in both studies (Table 31).

Table 31. Number of Patients with Picornavirus Infection as Identified by RT-PCR Assays and Baseline Virus Culture

	Study 843-043		Study 843-044		Pooled	
	Placebo	**Pleconaril 400 mg TID**	**Placebo**	**Pleconaril 400 mg TID**	**Placebo**	**Pleconaril 400 mg TID**
ITT	**526**	**526**	**524**	**520**	**1050**	**1046**
ITT-I	326 (62%)	337 (64%)	356 (68%)	344 (66%)	682 (65%)	681 (65%)
RT-PCR and virus culture positive at baseline	196 (37%)	201 (38%)	224 (43%)	206 (40%)	420 (40%)	407 (39%)

Virus isolates from patients were tested for inhibition by pleconaril in an *in vitro* viral cytopathic effect assay. Among the 90% of baseline picornavirus isolates for which IC_{50} values could be determined, approximately 87% (649/744) were inhibited by pleconaril at concentrations ≤3.8 µg/mL, the highest non-cytotoxic concentration that can be tested in the *in vitro* culture assay (Table 32). This proportion of susceptible picornaviruses is similar to that reported in a study by Kaiser and coworkers, in which pleconaril inhibited 89% (41 of 46) of rhinovirus clinical isolates from adults and children with colds between 1988 and 1998 (Kaiser et al., 2000).

Table 32. Inhibition by Pleconaril of Virus Isolates from Baseline Virus Culture Positive Samples – Patients With a Drug Susceptibility Result at Baseline[a]

	Study 843-043		Study 843-044		Pooled	
	Placebo	**Pleconaril**	**Placebo**	**Pleconaril**	**Placebo**	**Pleconaril**
Baseline virus isolates inhibited by pleconaril	154/173 (89%)	147/173 (85%)	181/207 (87%)	167/191 (87%)	335/380 (88%)	314/364 (86%)

[a] The denominator includes all baseline virus culture positive samples for which valid IC_{50} values were obtained. Reasons for cases without valid IC_{50} values include samples that were not available for testing, grew too poorly in culture, or failed to provide reproducible IC_{50} values.

8.4 Emergence of Virus Isolates with Reduced Susceptibility to Pleconaril

In the Phase III studies, virus isolates from Day 3 and Day 6 nasal mucus samples (from patients with baseline virus isolates) were assessed for their susceptibility to pleconaril in the *in vitro* culture assay. To identify post-baseline viruses with reduced pleconaril susceptibility from pleconaril-treated patients, a minimum level of change in IC_{50} values between baseline and post-baseline samples was established by assessing the range of variation in IC_{50} values between baseline and post-baseline virus pairs in the placebo group. The proportion of virus sample pairs from placebo-treated patients in which the IC_{50} values between baseline and post-baseline virus differed by 4-fold or greater was 3.1% (9 of 294) and by 10-fold or greater was 0.7% (2 of 294) (Table 33). Since the proportion of patients in the pleconaril group with 4-fold and 10-fold or greater changes in drug susceptibility was 10%-15%, a change in susceptibility occurring in 3% of placebo patients was considered unacceptably high. Therefore, a post-baseline virus isolate was considered to have "reduced drug susceptibility" when its IC_{50} value increased relative to that of its corresponding baseline isolate value by 10-fold or more. The incidence of patients with a post-baseline virus isolate having reduced drug susceptibility in the pleconaril-treated group was 10.7% (28 of 263).

Table 33. Patients With Post-Baseline Virus Isolates With Reduced Drug Susceptibility

Reduced susceptibility (Fold change from baseline in IC_{50}):	Number of Patients	
	Placebo	**Pleconaril**
≥4-<10	7 (2.4%)	11 (4.2%)
≥10-100	1 (0.3%)	12 (4.6%)
>100-1000	1 (0.3%)	11 (4.2%)
>1000	0 (0%)	5 (1.9%)
All ≥4	9/294 (3.1%)	39/263 (14.8%)
All ≥10	2/294 (0.7%)	28/263 (10.7%)

NOTE: Denominator represents all patients with baseline virus isolates with IC_{50} ≤3.8 µg/mL and any post-baseline day isolates with any IC_{50} plus all patients with baseline virus isolates with IC_{50} ≤3.8 µg/mL and confirmed post-baseline negative samples (post-baseline samples negative in both virus culture and TaqMan® assay).

As shown in Table 34, patients with a post-baseline virus with reduced drug susceptibility appeared to experience a slightly greater clinical benefit than the overall picornavirus-infected group, indicated by a shorter median duration of illness and reduced mean total symptom severity score over the 18-day study, compared to pleconaril-treated patients from whom viruses with reduced drug susceptibility were not derived. Since the patient numbers for the reduced drug susceptibility group were quite low, the significance of this observation cannot be ascertained. However, these assessments indicated that there were no adverse clinical consequences in recovery from the common cold in pleconaril-treated patients with a post-baseline virus that had reduced drug susceptibility compared to baseline.

Table 34. Clinical Outcome in Culture Positive Patients With a Baseline Susceptible Virus Isolate, Pooled Data

	All Placebo[a]	All Pleconaril[a]	Reduced Susceptibility[b]
Number of Patients	**333**	**286**	**28**
Duration of Illness[c] (primary endpoint)	8.6	6.5	4.9
Duration of Illness (time to no cold)[d]	7.7	6.8	4.2
Total symptom severity score[e]	38.3	28.1	22.2

[a] All culture-positive patients with an $IC_{50} \leq 3.8$ µg/mL minus the 28 pleconaril-treated patients from whom a virus with reduced drug susceptibility was isolated in the respective treatment group.

[b] All pleconaril-treated patients with post-baseline virus isolates with IC_{50} values increased >10-fold relative to baseline.

[c] Median duration of illness (days) as measured by the primary endpoint (resolution of rhinorrhea and other cold symptoms to mild or absent without use of cold symptom relief medication).

[d] Median duration of illness (days) as measured by patient's assessment of overall recovery from the cold.

[e] Geometric mean of total symptom severity scores during the study.

9. CLINICAL SAFETY

9.1 Summary of Key Points

- Pleconaril was safe and well tolerated in clinical studies in which over 3200 adults received pleconaril and 2275 received placebo.

- In studies of 5-7 days of treatment, the most commonly reported adverse events were headache and gastrointestinal symptoms (nausea, diarrhea, vomiting) in both pleconaril and placebo recipients, with a slight excess of these adverse events associated with pleconaril. Approximately 3% of patients in the pleconaril and placebo groups discontinued treatment as a result of an adverse event.

- In studies of 5-7 days of treatment, pleconaril was shown to have no effect on routine laboratory safety evaluations, with the exception of transient, small elevations in median platelet count and total cholesterol level, neither of which was clinically significant.

- Six-week exposure to pleconaril at 400 mg QD or BID in a prophylaxis study had a similar safety profile to that of the proposed treatment regimen of 400 mg TID for 5 days, with the exception of an increased incidence of menstrual disorders (e.g., breakthrough bleeding/spotting) in women taking oral contraceptives.

- The 6-week study confirmed the transient small median increase in platelet counts and cholesterol levels observed in the larger treatment database. Fasting lipid profiles in the 6-week study revealed that HDL and LDL cholesterol increased proportionally, and both decreased when treatment was discontinued. The total cholesterol/HDL ratio remained unchanged during treatment, indicating no evidence of associated cardiovascular risk.

- The adverse events of early menses and breakthrough bleeding/spotting observed in the 6-week prophylaxis study were mild or moderate in intensity and resulted in very few discontinuations of treatment.

- In studies of 5-7 days of treatment, the incidence of early menses and breakthrough bleeding/spotting was low (3.1%) in women receiving pleconaril who were also taking oral contraceptives.

9.2 Overall Exposure to Pleconaril

The clinical safety database for pleconaril consists of 6570 subjects (2674 placebo, 3896 pleconaril) who participated in 39 completed adult and pediatric clinical studies of presumptive viral infections, including viral meningitis and viral respiratory infection (through June 2001). The number of subjects is summarized in Table 35. Because early

clinical studies were conducted with an oil-based liquid formulation of pleconaril, the number of subjects who received a tablet formulation is also shown.

Table 35. Number of Treated Subjects in the NDA Safety Database

	Placebo	Pleconaril	Total
Total Subjects	**2674**	**3896**	**6570**
All Adults	2275	3218	5493
Phase II/III	*2225*	*2868*	*5093*
Phase I	*50*	*350*	*400*
All Pediatric	399	678	1077
Phase II/III	*399*	*628*	*1027*
Phase I	*0*	*50*	*50*
Adult Phase II/III Cold	1975	2472	4447
Adult Phase II/III Cold Tablet	1484	1480	2964

The 30 adult and 9 pediatric studies are summarized in Table 36 and Table 37, respectively.

Table 36. Overall Exposure in the Pleconaril Clinical Development Program (Completed Adult Studies)

Study Phase	Number of Treated Patients	Dose Levels (Range)	Indication	Number of Studies
I – Single dose	21 placebo 227 pleconaril	- 50-1000 mg	Not applicable	12
I/Ib - Multiple dose	29 placebo 123 pleconaril	- 50-400 mg TID	Not applicable	9
TOTAL Adult Phase I = 400 (50 placebo, 350 pleconaril)				
II/III	250 placebo 396 pleconaril	- 200-400 mg TID	Viral meningitis	3
	1975 placebo 2472 pleconaril	- 200-400 mg TID	Common cold	6
TOTAL Adult Phase II/III = 5093 (2225 placebo, 2868 pleconaril)				

NOTE: In Phase II/III multiple-dose studies, exposures varied from 5-7 days in duration.
The data for 203 patients treated in the ongoing compassionate use program (Study 843-038) are presented separately in Section 9.10.

Table 37. Overall Exposure in the Pleconaril Clinical Development Program (Completed Pediatric Studies)

Study Phase	Number of Treated Patients	Dose Levels (Range)	Indication	Number of Studies
I – Single dose	0 placebo 34 pleconaril	- 5.0-7.5 mg/kg	Acute viral infection Sepsis in neonates	1 1
I – Multiple dose	0 placebo 16 pleconaril	- 2.5 mg/kg TID	Viral meningitis	1
TOTAL Pediatric Phase I = 50 (0 placebo, 50 pleconaril)				
II	5 placebo 12 pleconaril	- 2.5-5.0 mg/kg TID	Hand, foot and mouth disease	2
	247 placebo 378 pleconaril	- 2.5-5.0 mg/kg TID	Viral meningitis	2
	147 placebo 238 pleconaril	- 2.5-10.0 mg/kg TID	Common cold	2
TOTAL Pediatric Phase II = 1027 (399 placebo, 628 pleconaril)				

NOTE: In Phase II multiple-dose studies, exposures varied from 5-7 days in duration.

The safety data for all treated patients who received a tablet formulation (1484 placebo, 1480 pleconaril) are summarized and presented in this document. A prototype tablet was administered at 400 mg TID for 7 days in Study 843-032 (434 placebo, 434 pleconaril), and the proposed commercial tablet formulation was administered at 400 mg TID for 5 days in Studies 843-043 and 843-044 (1050 placebo, 1046 pleconaril). The formulation and dosing regimens used in these three adult cold studies are representative of the proposed dose and indication in the NDA.

The larger adult database of all treated patients consists of 5093 patients (2225 placebo, 2868 pleconaril) who were enrolled in nine placebo-controlled studies (six Phase II/III studies of the common cold and three enteroviral meningitis studies). An oral liquid formulation was used in the enteroviral meningitis studies and in three of the six common cold studies.

The results of the safety analyses of the larger database and the tablet database are similar regarding type and frequency of adverse events. Small numbers of patients in the larger database received different dosing regimens (i.e., 400 mg BID or 200 mg TID for 7 days), in addition to the 2111 patients who received 400 mg TID for 5-7 days. The results of safety analyses in the overall database can be found in Appendix D.

In addition, 1069 adults received 6 weeks of the proposed commercial tablet formulation (357 placebo, 359 pleconaril 400 mg QD, and 353 pleconaril 400 mg BID) in a prophylaxis study for the common cold (Study 843-062). Safety data from Study 843-062, six Phase II pediatric studies (N=1027), and the Compassionate Use program (N=203) are summarized separately in Sections 9.8, 9.9, and 9.10, respectively.

9.3. Adverse Events

9.3.1 Treatment-Emergent Adverse Events

Among all patients treated with a tablet formulation in adult Phase II/III cold studies, headache, diarrhea and nausea were the most commonly reported treatment-emergent adverse events (reporting period was defined as during treatment or within 5 days of completion of treatment) (see Table 38 below).

Table 38. Treatment-Emergent Adverse Events (>1% in Either Treatment Group) – Adult Phase II/III Cold Studies (Tablet Formulation)

	Placebo	Pleconaril 400 mg TID
Number of treated patients	1484	1480
Number of treated patients with ≥1 AE	799 (54%)	809 (55%)
Headache	323 (22%)	348 (24%)
Diarrhea	97 (7%)	114 (8%)
Nausea	57 (4%)	89 (6%)*
Bronchitis	37 (2.5%)	37 (2.5%)
Sinusitis	30 (2.0%)	36 (2.4%)
Fever	37 (2.5%)	34 (2.3%)
Pain	37 (2.5%)	34 (2.3%)
Vomiting	26 (1.8%)	30 (2.0%)
Abdominal pain	36 (2.4%)	29 (2.0%)
Dizziness	21 (1.4%)	28 (1.9%)
Rhinitis	35 (2.4%)	28 (1.9%)
Cough increased	24 (1.6%)	21 (1.4%)
Dysmenorrhea#	8 (0.8%)	19 (1.9%)*

#Signifies a gender-specific term (refers to women; N=1015 in placebo and N=1016 in pleconaril).
* $p<0.05$; placebo versus pleconaril (Fisher's exact test)

Similar results were observed among all treated patients in the adult Phase II/III database, as shown in Appendix D, Table 1.

9.3.2 Severity of Treatment-Emergent Adverse Events

Among all patients treated with a tablet formulation in adult Phase II/III cold studies, ≤5% of patients in both the placebo and pleconaril groups reported an adverse event of severe intensity (Table 39). The most frequently observed severe treatment-emergent adverse event for patients who received pleconaril 400 mg TID or placebo was headache (≤1.6% in both groups).

Table 39. Severe Treatment-Emergent Adverse Events (≥0.5% in Either Treatment Group) – Adult Phase II/III Cold Studies (Tablet Formulation)

	Placebo	Pleconaril 400 mg TID
Number of treated patients	1484	1480
Number of treated patients with ≥1 severe AE	74 (5%)	60 (4%)
Headache	22 (1.5%)	24 (1.6%)
Diarrhea	3 (0.2%)	9 (0.6%)
Nausea	8 (0.5%)	3 (0.2%)

As shown in Appendix D, Table 2, similar findings were observed among all treated patients in the adult Phase II/III studies.

9.4 Discontinuation of Study Drug Due to Adverse Events

Among adult Phase II/III patients treated with a tablet formulation, 2.7% of placebo-treated patients and 3.4% of pleconaril-treated patients experienced one or more adverse events that resulted in premature discontinuation of the study drug (Table 40). The most common adverse events leading to discontinuation were headache and events associated with the gastrointestinal system (diarrhea, nausea, and vomiting).

Table 40. Adverse Events That Resulted in Discontinuation of Treatment (≥0.2% in Either Treatment Group) – Adult Phase II/III Cold Studies (Tablet Formulation)

	Placebo	Pleconaril 400 mg TID
Number of treated patients	1484	1480
Number of patients discontinued due to an adverse event[a]	40 (2.7%)	51 (3.4%)
Headache	6 (0.4%)	7 (0.5%)
Diarrhea	3 (0.2%)	9 (0.6%)
Nausea	5 (0.3%)	6 (0.4%)
Vomiting	4 (0.3%)	6 (0.4%)
Bronchitis	5 (0.3%)	4 (0.3%)
Sinusitis	2 (0.1%)	4 (0.3%)
Dizziness	3 (0.2%)	2 (0.1%)
Bacterial infection	3 (0.2%)	1 (0.1%)

[a] A patient may have attributed discontinuation to more than one adverse event.

As shown in Appendix D, Table 3, among all treated patients in the adult Phase II/III studies, the most common adverse events leading to discontinuation were associated with the gastrointestinal system (nausea, vomiting, diarrhea, and abdominal pain; ≤1% for any specific event in the placebo and pleconaril 400 mg TID groups).

9.5 Serious Adverse Events

A list of patients with a serious adverse event is presented in Table 41. Among all treated patients who received a tablet formulation, six (0.4%) patients in the placebo group and seven (0.5%) patients in the pleconaril 400 mg TID group had a serious adverse event reported. All except two events were considered not related to study drug.

There was one death reported in the Study 843-044. This patient, a 60-year-old white female in the pleconaril 400 mg TID group, was involved in an automobile accident 30 days posttreatment, and died due to the injuries she sustained. This event was reported as not related to study drug.

Table 41. Serious Adverse Events – Adult Phase II/III Cold Studies (Tablet Formulation)

Patient Number	Event	Intensity	Relationship to study drug	Outcome
Placebo (N=1484)				
50915	Pulmonary edema	Severe	Not related	Recovered
50339	Lung disorder (COPD exacerbation)	Moderate	Not related	Improved
50514	Cellulitis	Severe	Not related	Recovered
50311	Abnormal vision Aphasia	Mild Severe	Not related Not related	Improved Improved
40413	Diarrhea	Severe	Not related	Recovered
40084	Cholelithiasis	Severe	Not related	Recovered
Pleconaril 400 mg TID (N=1480)				
50342	Tachycardia	Severe	Related	Recovered
50813	Pneumonia	Moderate	Not related	Recovered
51308	Hepatitis C virus	Mild	Not related	Ongoing[a]
40521	Arthritis Pneumonia	Moderate Moderate	Not related Not related	Improved Recovered
40701	Overdose[b]	Mild	Related	Recovered
40792	Chest pain	Severe	Not related	Recovered
40287	Accidental injury	Severe	Not related	Death

[a] Ongoing at end of study.
[b] The patient's 2-year-old child chewed and swallowed one pleconaril 200 mg tablet (16.3 mg/kg). No adverse effects were reported for the child.

Appendix D, Table 4 provides serious adverse event data for all treated patients in the adult Phase II/III studies.

9.6 Adverse Events in Patients with Underlying Pulmonary Conditions

Among all treated patients in the adult Phase II/III cold study database with a history of asthma, 220 were treated with pleconaril 400 mg TID for 5 or 7 days and 213 were treated with placebo. The adverse event profile in these patients was similar to that of the overall study population, with a slight excess of headache and gastrointestinal symptoms in pleconaril-treated patients compared to placebo. The most commonly reported adverse events in asthma patients were headache (19% vs. 16%), diarrhea (16% vs. 13%), nausea (14% vs. 9%), and abdominal pain (9% vs. 6%) in these pleconaril- and placebo-treated patients, respectively. Acute respiratory complications including bronchitis (6% vs. 6%) and sinusitis (5% vs. 5%) were reported more frequently than in the overall database, but at similar rates in pleconaril and placebo groups. In a subset of patients with moderate asthma (measured one-minute forced expiratory volume [FEV_1] of 50%-85% of the predicted value), pleconaril 400 mg TID for 7 days (N=84) had no adverse impact on pulmonary function as determined by serial measurements of FEV_1 over a 6-week period.

Among all treated patients in the adult Phase II/III cold study database, 23 patients with a history of chronic obstructive pulmonary disease (COPD) were treated with pleconaril 400 mg TID for 5 or 7 days. Compared to 20 placebo-treated patients with a history of COPD, the most commonly reported adverse events were headache (4[17%] vs. 3[15%]), abdominal pain (3[13%] vs. 2[10%]), and flatulence (2[9%] vs. 0%) in these pleconaril- and placebo-treated patients, respectively. Two (9%) pleconaril-treated patients and one (5%) placebo-treated patient reported an exacerbation of COPD following the onset of their colds in these studies.

9.7 Laboratory Safety Evaluations

9.7.1 Change From Baseline Clinical Laboratory Evaluations

Table 42 presents the median change from baseline in pleconaril-treated patients in the adult Phase II/III studies using a tablet formulation. In the placebo and pleconaril 400 mg TID treatment groups, the median baseline values were comparable for all laboratory parameters assessed. Changes in median values from baseline to the end of treatment were similar

between the two groups, with the exception of small increases in the median serum cholesterol values and platelet counts. However, blood samples collected for clinical laboratory evaluation were not in the fasted state. The magnitude of the median cholesterol change (6.0 mg/dL for pleconaril 400 mg TID and –3 mg/dL for placebo) is not clinically significant. The small increase in median platelet counts (17.0 x 10^3/mm^3 for pleconaril 400 mg TID and 11 x 10^3/mm^3 for placebo) is also not clinically significant.

Table 42. Clinical Laboratory Evaluations: Median Change From Baseline to End of Treatment – Adult Phase II/III Cold Studies (Tablet Formulation)

	Placebo		Pleconaril 400 mg TID	
No. of Treated Patients	**1484**		**1480**	
Laboratory parameter (units)	**Baseline median**	**Median change**	**Baseline median**	**Median change**
HEMATOLOGY				
Hematocrit (%)	41.0	-0.4	41.0	0.0
Hemoglobin (g/dL)	13.9	-0.1	14.0	-0.1
Platelets (x10^3/mm^3)	251.0	11.0	257.0	17.0
RBC count (x10^6/mm^3)	4.7	0.0	4.7	0.0
WBC count (x10^3/mm^3)	7.8	-0.6	8.0	-0.6
CLINICAL CHEMISTRIES				
Alk. phosphatase (IU/L)	71.0	0.0	70.0	1.0
AST/SGOT (IU/L)	21.0	0.0	20.0	-1.0
ALT/SGPT (IU/L)	18.0	0.0	18.0	-1.0
Total bilirubin (mg/dL)	0.4	0.0	0.4	-0.1
Protein (g/dL)	7.4	-0.1	7.4	0.0
BUN (mg/dL)	12.0	0.0	12.0	0.0
Creatinine (mg/dL)	0.8	0.0	0.8	0.0
Cholesterol (mg/dL)	185.0	-3.0	184.0	6.0
Triglyceride (mg/dL)	133.0	-1.0	131.5	0.0
Glucose (mg/dL)	90.0	3.0	90.0	3.0
LDH (IU/L)	149.0	-1.0	148.0	-2.0
Calcium (mg/dL)	9.4	0.0	9.4	0.0
Chloride (mEq/L)	105.0	0.0	105.0	0.0
Potassium (mEq/L)	4.2	0.0	4.2	0.0
Sodium (mEq/L)	141.0	0.0	141.0	0.0
Uric Acid (mg/dL)	4.8	0.1	4.7	0.4

No.=number; Seg=segmented; alk=alkaline
NOTE: All patients did not have each laboratory parameter assessed.

As shown in Appendix D, Table 5, similar findings were observed among all treated patients in the adult Phase II/III studies.

9.7.2 Laboratory Values Classified as Potentially Clinically Significant

Among adult Phase II/III patients treated with a tablet formulation who had a serum cholesterol level below 250 mg/dL at baseline, 2% of placebo patients and 3% of pleconaril

400 mg TID had a cholesterol level ≥250 mg/dL at the end of treatment, which was the prespecified value of potential clinical significance. The majority of these patients had a baseline cholesterol value above 200 mg/dL but less than 250 mg/dL. There were no other notable findings in the analysis of shifts in laboratory values from within to outside of prespecified limits of potential clinical significance.

Similar findings were seen among adults in all Phase II/III studies (2% of placebo patients and 3% of pleconaril 400 mg TID patients had a cholesterol level ≥250 mg/dL at the end of treatment).

Among adult Phase II/III patients treated with a tablet formulation who were taking lipid-lowering drugs during study, the median change in serum cholesterol levels from baseline to the end of treatment was minimal in both placebo-treated (N=55, -0.6 mg/dL) and pleconaril-treated (N=58, 0.5 mg/dL) patients.

9.7.3 Change from Baseline in Serum Cholesterol Levels by Baseline Cholesterol Quartile

Among adult Phase II/III patients treated with a tablet formulation, median changes of serum cholesterol values from baseline to end of treatment are shown in Table 43 for patients in each quartile of baseline cholesterol values. For both treatment groups, increases in cholesterol values were observed in the lowest quartile, and decreases were observed in the highest quartile, suggesting regression toward the mean. However, small differences between placebo-treated and pleconaril-treated patients remained evident in each quartile.

Table 43. Median Change from Baseline in Serum Cholesterol Levels by Baseline Cholesterol Quartile – Adult Phase II/III Cold Studies (Tablet Formulation)

Baseline Cholesterol Quartile	Placebo	Pleconaril 400 mg TID
I (≤161 mg/dL)		
Number of Patients	336	349
Baseline median	148	146
Median change	2	10
II (>161 to ≤185 mg/dL)		
Number of Patients	343	334
Baseline median	173	174
Median change	-1	7
III (>185 to ≤212 mg/dL)		
Number of Patients	342	326
Baseline median	198	199
Median change	-4	4
IV (>212 mg/dL)		
Number of Patients	331	344
Baseline median	231	235
Median change	-13	-1

As shown in Appendix D, Table 6, similar findings were observed among all treated patients in the adult Phase II/III studies.

9.8 Safety of 6 Weeks of Exposure to Pleconaril in Adults

In the fall of 2001, after the NDA was submitted, VIROPHARMA conducted a 6-week placebo-controlled Phase II study of pleconaril 400 mg BID or QD for prophylaxis of colds. A total of 1069 healthy adults were randomized (placebo, 357; pleconaril 400 mg QD, 359; pleconaril, 400 mg BID, 353) and dosed at 13 sites (12 U.S., 1 Canada). The safety data were analyzed and the efficacy analyses are pending the completion of the virological testing.

Subjects used hand-held electronic devices to record study data, including adverse events and the occurrence of cold symptoms. Blood samples for laboratory safety evaluations were obtained at baseline and at Weeks 2, 4, 6, 8, and 12 (at Week 12 only platelet count and lipid profile were obtained). A fasting lipid profile was obtained at each visit except Week 2.

Early in the study, two women at one site who were taking an oral contraceptive (OC) reported breakthrough menstrual bleeding. This information raised the possibility that

pleconaril administration might affect the effectiveness of concomitantly administered OCs. All investigators were immediately informed of the unexpected adverse events and instructed to contact women enrolled in the study. The FDA also was notified about the events. A questionnaire regarding OC use and breakthrough bleeding and spotting was administered to women at all sites, and interval menstrual histories were obtained at subsequent visits. Spontaneous reports of menstrual disorders as well as reports obtained from the questionnaires were combined and are presented in the adverse event tables that follow.

9.8.1 Adverse Events

9.8.1.1 Treatment-Emergent Adverse Events – All Treated Subjects

As shown in Table 44 below, 61% to 70% of subjects across treatment groups reported one or more treatment-emergent adverse events. Epimenorrhea (early menses), intermenstrual bleeding (breakthrough bleeding and spotting), hypercholesterolemia, and nausea were reported at higher rates in pleconaril-treated subjects than in placebo-treated subjects.

Table 44. Treatment-Emergent Adverse Events (Occurring in ≥5% of Subjects in Any Group) – All Treated Subjects – Study 843-062

	Placebo	Pleconaril 400 mg QD	Pleconaril 400 mg BID
Number of treated subjects	**357**	**359**	**353**
Number of subjects with a treatment-emergent AE	216 (61%)	235 (65%)	247 (70%)
Headache NOS	63 (18%)	65 (18%)	80 (23%)
Urine crystals present	27 (8%)	29 (8%)	22 (6%)
Intermenstrual bleeding#	13 (5%)	29 (12%)*	31 (13%)*
Nausea	16 (4%)	17 (5%)	33 (9%)*
Diarrhea NOS	20 (6%)	14 (4%)	25 (7%)
Epimenorrhea#	9 (4%)	17 (7%)	22 (9%)*
Hypercholesterolemia	10 (3%)	16 (4%)	21 (6%)*
Pharyngolaryngeal pain	10 (3%)	21 (6%)	13 (4%)
Dysmenorrhea#	8 (3%)	15 (6%)	11 (5%)
Menstrual disorder NOS#	12 (5%)	7 (3%)	5 (2%)

* $p<0.05$; placebo versus pleconaril (Fisher's exact test)
#=Gender-specific (refers to women; N=245 in placebo, N=245 in pleconaril QD, N=232 in pleconaril BID); NOS=not otherwise specified; AE=adverse event
NOTE: AEs in Study 843-062 were coded using the Medical Dictionary for Regulatory Activities Terminology (MedDRA)

9.8.1.2 All Menstrual Disorder Adverse Events

The percentage of women with menstrual disorder adverse events, including epimenorrhea (early menses) and intermenstrual bleeding (breakthrough bleeding and spotting), was higher among pleconaril-treated women in both dosing groups compared to placebo-treated women (Table 45). Most (63%) menstrual disorders, including epimenorrhea and intermenstrual bleeding, in pleconaril-treated women occurred in those subjects who were using an OC. There were no reports of menstrual disorders among the 49 pleconaril-treated women who were using any other estrogen- or progestin-containing compounds (intramuscular medroxyprogesterone [Depo-Provera®] or hormone replacement therapies [e.g., Premarin®, Provera®]).

Table 45. Menstrual Disorder Adverse Events[a] in Women – Study 843-062

	Placebo	Pleconaril 400 QD	Pleconaril 400 mg BID
All treated women	**245**	**245**	**232**
With ≥1 menstrual disorder events	51 (21%)	79 (32%)	66 (28%)
With ≥1 epimenorrhea and/or intermenstrual bleeding events	28 (11%)	56 (23%)	55 (24%)
Women taking any estrogen/progestin compounds	**113**	**117**	**88**
With ≥1 menstrual disorder events	23 (20%)	52 (44%)	40 (45%)
With ≥1 epimenorrhea and/or intermenstrual bleeding events	16 (14%)	41 (35%)	33 (38%)
Women taking oral contraceptives	**81**	**98**	**58**
With ≥1 menstrual disorder events	20 (25%)	52 (53%)	40 (69%)
With ≥1 epimenorrhea and/or intermenstrual bleeding events	14 (17%)	41 (42%)	33 (57%)
Women not taking any estrogen/progestin compounds	**132**	**128**	**144**
With ≥1 menstrual disorder events	28 (21%)	27 (21%)	26 (18%)
With ≥1 epimenorrhea and/or intermenstrual bleeding events	12 (9%)	15 (12%)	22 (15%)

[a] "Menstrual disorders" includes any menstrual bleeding disorders and menstrual disorders not otherwise specified (NOS).

All menstrual disorder adverse events were of mild or moderate intensity in the pleconaril groups. There were two reports of severe menorrhagia (heavy bleeding) in the placebo group. No event was serious. The proportion of all treated women who discontinued study drug due to a menstrual disorder event was low and similar across the three treatment groups (placebo, 0.8%; pleconaril 400 mg QD, 0.8%; pleconaril 400 mg BID, 0.4%).

As shown in Table 46, pleconaril-treated women taking oral contraceptives reported a higher incidence of menstrual disorder adverse events (53% and 69% for the pleconaril QD and BID groups, respectively) than placebo-treated women taking oral contraceptives (25%). Epimenorrhea was approximately three times more frequent in the pleconaril 400 mg QD group (14%) and six times more frequent in the pleconaril 400 mg BID group (29%) than in the placebo group (5%). The incidence of intermenstrual bleeding was more than two times higher in both pleconaril groups (400 mg QD, 33%; 400 mg BID, 34%) compared with the placebo group (14%).

Table 46. All Menstrual Disorder Adverse Events[a] in Women Taking Oral Contraceptives During the Study Period – Study 843-062

	Placebo	Pleconaril 400 mg QD	Pleconaril 400 mg BID
Number of treated women	**245**	**245**	**232**
Women taking OCs	**81**	**98**	**58**
Women taking OCs with ≥1 menstrual disorder event[a]	**20 (25%)**	**52 (53%)**	**40 (69%)**
Amenorrhea NOS	1 (1.2%)	7 (7%)	2 (3%)
Epimenorrhea (early menses)	4 (5%)	14 (14%)	17 (29%)
Intermenstrual bleeding	11 (14%)	32 (33%)	20 (34%)
Menorrhagia	2 (2.5%)	4 (4%)	4 (7%)
Menses delayed	0	1 (1.0%)	3 (5.2%)
Menstrual cycle prolonged	0	1 (1.0%)	2 (3.4%)
Menstrual disorder NOS	5 (6%)	7 (7%)	6 (10%)

[a] "Menstrual disorders" includes any menstrual bleeding disorders and menstrual disorders not otherwise specified (NOS).

A similar analysis of the women in Phase II/III cold studies who received a tablet formulation of pleconaril or placebo for 5 or 7 days showed that, among women taking oral contraceptives, the incidence of epimenorrhea and intermenstrual bleeding adverse events was low; zero in the placebo group (N=223) and 3.1% in the pleconaril group (N=229).

9.8.1.3 All Menstrual Disorder Adverse Events – Women Not Using Any Estrogen/Progestin Compounds

Among women who did not take any estrogen/progestin compounds during the study, the incidences of intermenstrual bleeding and epimenorrhea were higher in the pleconaril 400 mg BID group compared with the placebo and pleconaril 400 mg QD groups (Table 47). The incidences of all other menstrual disorder adverse events were similar among women in the three treatment groups.

Table 47. All Menstrual Disorder Adverse Events[a] in Women Not Taking Estrogen/Progestin Compounds During the Study Period – Study 843-062

	Placebo	Pleconaril 400 mg QD	Pleconaril 400 mg BID
Women not taking any E/P compounds during the study	**132**	**128**	**144**
Women with ≥1 menstrual disorder events	**28 (21%)**	**27 (21%)**	**26 (18%)**
Epimenorrhea	5 (4%)	6 (5%)	10 (7%)
Intermenstrual bleeding	5 (4%)	4 (3%)	11 (8%)
Menorrhagia	4 (3%)	5 (4%)	3 (2%)
Menses delayed	3 (2%)	4 (3%)	1 (1%)
Menstrual cycle prolonged	3 (2%)	2 (2%)	1 (1%)
Menstrual disorder NOS	8 (6%)	2 (2%)	0

[a] "Menstrual disorders" includes menstrual bleeding disorders and menstrual disorders not otherwise specified (NOS).

A similar analysis of the women in Phase II/III cold studies who received a tablet formulation of pleconaril or placebo for 5 or 7 days showed that, among women who did not take any estrogen-progestin compounds during the study period, the incidence of epimenorrhea and intermenstrual bleeding adverse events was 0.2% in the placebo group (N=646) and zero in the pleconaril group (N=637).

9.8.2 Pregnancies

Seven pregnancies were reported in women enrolled in Study 843-062 during the study period of 12 weeks. Five occurred in subjects in the pleconaril 400 mg BID group, one in the pleconaril 400 mg QD group, and one in the placebo group. Two of the five pregnancies in the pleconaril 400 mg BID group occurred in women taking an oral contraceptive. These data are summarized in Table 48 below.

Table 48. Pregnancies Reported in Study 843-062

	Placebo	Pleconaril 400 mg QD	Pleconaril 400 mg BID
Number of women	**245**	**245**	**232**
Number of women taking OCs	**81**	**98**	**58**
Number of reported pregnancies	**1**	**1**	**5**
Method of birth control	Abstinence	Barrier method	Abstinence - 2 OC – 2 Barrier method - 1
Duration of study drug	40 days	10 days	36-44 days
Timing of pregnancy diagnosis	End of study (Week 10)	Day 11	Weeks 5-8
Outcome of pregnancy	Spontaneous abortion	Missed abortion followed by a D & C	Elective abortion – 2 Pregnancy progressing - 3

The overall reported pregnancy rate was higher than the rate reported in the 5- to 7-day treatment studies, as expected for a 12-week period of time. In the 5- to 7-day treatment studies, one pregnancy was reported in a woman taking an OC who received placebo. The total number of events was small, and no conclusions can be drawn regarding the possible impact of pleconaril on the efficacy of oral contraceptives.

9.8.3 Clinical Laboratory Evaluations

With the exception of platelet count and serum lipid parameters, median changes from baseline to Week 6 (end of treatment) and Week 8 (2 weeks posttreatment) in clinical laboratory parameters were similar among the treatment groups, with no evidence of a drug-related effect.

9.8.3.1 Platelet Counts

Small transient increases from baseline in median platelet counts were detected at Week 2 in both pleconaril groups (6.0 x $10^3/mm^3$ and 10 x $10^3/mm^3$ in the QD and BID groups, respectively) and in the placebo group (3.0 x $10^3/mm^3$), which were not clinically significant. There were no drug-related changes from baseline in median platelet counts at any subsequent time points (Weeks 4, 6, 8, and 12).

9.8.3.2 Serum Lipid Profiles

Median increases in cholesterol were observed in the pleconaril groups at Weeks 6, 8, and 12, with greater increases in the pleconaril BID group than the QD group. The median change in cholesterol was greatest at the end of treatment (Week 6), with small increases of 7 and 14 mg/dL in the pleconaril QD and BID groups, respectively. Serum cholesterol values decreased at each successive evaluation (i.e., Weeks 8 and 12) during the posttreatment follow-up period.

At Week 12, serum lipid parameters had returned to baseline in the pleconaril QD group. In the pleconaril BID group, lipid parameters at Week 12 were above baseline, but declining (serum total cholesterol +10 mg/dL at Week 12 compared with baseline). The increases in serum cholesterol values in subjects taking pleconaril were comprised of proportionate increases in both HDL and LDL cholesterol. The cholesterol/HDL ratio (a better indicator of cardiovascular risk than the components considered individually) remained unchanged or decreased compared to baseline in subjects taking pleconaril (Table 49). As a result, the small median increases in cholesterol values are not clinically significant.

Table 49. Serum Lipid Values: Median Changes From Baseline to Week 6 (End of Treatment), Week 8 (2 Weeks Posttreatment), and Week 12 (End of Study) – All Treated Subjects

	Placebo				Pleconaril 400 mg QD				Pleconaril 400 mg BID			
	N=354				N=358				N=352			
Laboratory parameter (units)	Baseline median	Median change Week 6	Week 8	Week 12	Baseline median	Median change Week 6	Week 8	Week 12	Baseline median	Median change Week 6	Week 8	Week 12
Serum Lipid Parameters												
Cholesterol (mg/dL)	188.0	0.0	-1.0	0.0	185.0	7.0	4.0	1.0	184.5	14.0	11.0	10.0
HDL Cholesterol (mg/dL)	53.0	0.0	0.0	-2.0	52.0	4.0	3.0	1.0	50.0	7.0	6.0	4.0
LDL Cholesterol (mg/dL)	111.0	0.0	-2.0	1.0	107.0	5.0	2.0	1.0	107.0	7.0	5.0	6.0
VLDL Cholesterol	21.0	0.0	0.0	0.0	20.0	-1.0	-1.0	-1.0	20.0	0.0	-1.0	0.0
Non-HDL Cholesterol (mg/dL)	135.0	0.0	-1.0	0.0	129.0	4.0	1.0	1.0	131.0	7.0	5.0	6.0
Cholesterol/HDL Ratio	3.6	0.0	0.0	0.1	3.5	-0.1	-0.1	0.0	3.6	-0.2	-0.2	0.0
Triglyceride (mg/dL)	103.0	2.0	1.0	1.0	101.0	-6.0	-2.0	-5.0	102.0	-2.0	-4.0	-1.0

9.9 Pediatric Patients

A total of 1027 patients were enrolled and treated in Phase II pediatric studies: 385 cold, 625 enteroviral meningitis, and 17 hand, foot and mouth disease patients. In each of these studies, pleconaril was administered as an oral liquid or oral suspension formulation for a period of 5 to 7 days. The age range of study participants was 1 to 16 years; 52% of children were older than 7 years; 57% were male. Adverse events for the 628 children treated with pleconaril (2.5 mg/kg TID, 5.0 mg/kg TID, and 10.0 mg/kg TID) are shown in Table 50.

Table 50. Treatment-Emergent Adverse Events by Frequency (≥5% in Any Treatment Group) – Phase II Pediatric Studies - All Treated Patients

	Placebo	Pleconaril 2.5 mg/kg TID	Pleconaril 5.0 mg/kg TID	Pleconaril 10.0 mg/kg TID
Number of treated patients	399	278	249	101
Headache	22 (6%)	7 (3%)	24 (10%)	8 (8%)
Back pain	19 (5%)	18 (6%)	20 (8%)	0
Diarrhea	18 (5%)	10 (4%)	19 (8%)	5 (5%)
Abdominal pain	15 (4%)	15 (5%)	11 (4%)	6 (6%)
Vomiting	14 (4%)	9 (3%)	16 (6%)	4 (4%)
Otitis media	9 (2%)	0	5 (2%)	9 (9%)

Headache and back pain (possibly associated with the disease under study or with lumbar puncture for viral meningitis) were the most frequently reported treatment-emergent adverse events. The incidence of otitis media was higher in the pleconaril 10.0 mg/kg TID group compared to the other treatment groups; however, all patients in the pleconaril 10.0 mg/kg TID group were treated in Study 843-051. When otitis media events were compared between placebo and pleconaril 10.0 mg/kg TID within Study 843-051 only, the incidence was similar (7% and 9%, respectively).

The overall incidence of serious adverse events (1.2% for placebo-treated children versus 2.2% for all pleconaril-treated children) and discontinuations due to adverse events (0.8% for placebo-treated children versus 1.4% for all pleconaril-treated children) were similar between treatment groups. Few changes in laboratory parameters were observed; as in the adult studies, pediatric patients who received pleconaril had slightly higher median platelet counts and cholesterol levels than did those who received placebo; these changes were not clinically significant.

9.10 Compassionate Use Program

Two hundred three (203) patients with potentially life-threatening infections (e.g., neonatal sepsis, chronic meningoencephalitis in children with immune deficiencies, and acute myocarditis in otherwise healthy adults) were treated with the oral liquid formulation of pleconaril for 5-10 days in the compassionate use program (November 1996 through November 2000 data cut-off; Study 843-038). Patients ranged in age from newborns to 85 years. Review of the compassionate use program indicates that:

- The most commonly reported adverse events were those associated with the gastrointestinal system, including vomiting (9%), diarrhea (7%), and nausea (5%).
- Sixteen patients (8%) discontinued study drug due to an adverse event. Only two of these adverse events were evaluated as possibly or probably treatment-related.
- Serious adverse events were reported by 80 patients (39%); the vast majority (93%) were assessed as not related or unlikely to be related to study drug.
- There were two serious adverse events considered by the investigators to be possibly related to study drug (heart failure in a patient with neonatal sepsis and kidney vasculitis in a patient with enteroviral myocarditis) with the outcome of death. Both patients were <1 year of age.
- Pleconaril was well tolerated in this critically ill patient population.

9.11 Overall Conclusions Regarding Safety

- Safety data from 3896 individuals (3218 adults and 678 children) who received pleconaril in 39 clinical studies demonstrate that pleconaril administered orally at doses up to 400 mg TID for 5 to 7 days is safe and well tolerated.

- The overall safety database supporting the 5-day treatment regimen is comprised of all treated patients in adult Phase II/III studies, during which 2868 patients received pleconaril. The safety profile was very similar in the entire adult database and in the subset of 1480 patients with a cold who received a tablet formulation of pleconaril. Among patients who received the tablet formulation:

  - The most commonly reported adverse events, in both placebo- and pleconaril-treated patients, were headache (22% vs. 24%), diarrhea (7% vs. 8%), and nausea (4% vs. 6%). These adverse events were considered by the investigator to be of severe intensity in ≤1.5% of patients receiving placebo and in ≤1.6% of patients receiving pleconaril.

- The incidence of discontinuation from treatment due to adverse events was low in both placebo-treated (2.7%) and pleconaril-treated (3.4%) patients. The most common adverse events leading to discontinuation in both treatment groups were headache, diarrhea, nausea, and vomiting.

- No clinically significant changes were noted in any laboratory parameter. Examination of clinical laboratory evaluations revealed small increases in median serum cholesterol levels and platelet counts in patients who received pleconaril compared with placebo.

- Safety was evaluated in a prophylaxis study (843-062) in which 1069 healthy adult subjects received 6 weeks of placebo or pleconaril (357 placebo, 359 pleconaril 400 mg QD, 353 pleconaril 400 mg BID). Safety in this study was comparable to that observed in other adult Phase II/III studies in which pleconaril was administered for 5 or 7 days, with the exception of certain menstrual disorders in women taking an oral contraceptive.

  – The proportion of all treated women who discontinued the study drug due to any menstrual disorder event was low and similar across the three treatment groups (placebo, 0.8%; pleconaril 400 mg QD, 0.8%; pleconaril 400 mg BID, 0.4%).

  – The incidence of epimenorrhea (early menses) and intermenstrual bleeding (breakthrough bleeding/spotting) among women taking an oral contraceptive was 17% (14/81) in the placebo group, 42% (41/98) in the pleconaril 400 mg QD group, and 57% (33/58) in the pleconaril 400 mg BID group.

  – There was no evidence of a drug-related effect on any of the clinical laboratory parameters, with the exception of small increases in platelet counts and serum cholesterol. These changes are not clinically significant.

  – The cholesterol/HDL ratio from subjects who received pleconaril remained unchanged or decreased compared to baseline. These results indicate that the small changes in cholesterol levels following pleconaril treatment pose no long-term cardiovascular risk.

- The overall safety and tolerability profile of pleconaril indicates minimal safety risk and is supportive of the proposed 5-day treatment regimen.

10. BENEFIT-RISK SUMMARY

Pleconaril is a specific antiviral drug that has the potential to provide benefit to patients infected with a picornavirus. No benefit is to be expected for those patients who are not infected with a picornavirus. Since treatment of the cold with pleconaril will be empiric, assessment of risks associated with its use must consider all potential patients that might receive the drug irrespective of their picornavirus-infection status. With these considerations in mind, the benefits of pleconaril in reducing the morbidity associated with picornavirus colds are greater than the risks of its anticipated use. This conclusion is based on the following evidence, which is detailed in previous sections of this document.

The Common Cold Causes Considerable Morbidity

- There are approximately 1 billion colds per year in the U.S. The magnitude of this illness and its societal and economic consequences are substantial.
- Approximately 75% of adults seek treatment for the cold.
- Current management of the cold is inadequate and involves widespread use of symptom relief medications that may provide transient benefits often with side effects, and frequent inappropriate antibiotic use.
- A more effective means of managing the cold would provide benefit by lessening of the burden of the cold and by reducing risks associated with current disease management practices.

Pleconaril Specifically Inhibits Picornaviruses, The Leading Cause Of Colds

- Picornaviruses are the leading cause of the common cold on an annual basis, causing 60% to 80% of all episodes of colds in the peak fall months.
- Pleconaril is an anti-picornavirus agent that specifically inhibits virus attachment and uncoating through a direct interaction with the virus capsid, preventing viral replication and rendering intact virions non-infectious. Pleconaril is active against approximately 87% of clinical picornavirus isolates obtained from patients with the cold.
- By acting directly and specifically on the leading etiologic agent of the common cold, pleconaril has the potential to alter the course of the illness.

Pleconaril Has Been Shown To Provide Meaningful Clinical Benefit Over Placebo For The Treatment Of Picornavirus Colds

- The Phase III studies in this NDA established the direct benefits of pleconaril in reducing the duration and severity of illness in patients with a cold caused by a picornavirus.

- Compared to placebo, pleconaril causes more rapid reductions in the severity of multiple cold symptoms, beginning within one day of initiation of treatment.

- The magnitude of pleconaril's effect in reducing the duration of illness is what would be expected in the case of an acute, self-limited illness, and is similar to that achieved by other antiviral drugs used to treat such diseases, for example, those used for influenza virus infections.

- Stratified analyses of the primary endpoint in the Phase III studies of pleconaril indicate that non-smokers experienced treatment benefits that are substantially larger than the overall population median values.

Pleconaril Is Safe And Well-Tolerated

- The overall safety profile of pleconaril at the proposed dose of 400 mg three times daily for 5 days supports its empiric use in treating the common cold.

- Compared to placebo, treatment with pleconaril for 5 days is associated with a slightly increased incidence of headache, diarrhea, and nausea and a small increase in median serum cholesterol values that is not clinically significant.

- Treatment with pleconaril for 5 days is associated with a low incidence of breakthrough bleeding/spotting in women taking an oral contraceptive.

Current Data Indicate No Adverse Consequences Of Treatment-Emergent Viruses With Reduced Drug Susceptibility

- Viruses with reduced susceptibility to pleconaril were recovered from approximately 10.7% of patients with a picornavirus cold who were treated with pleconaril at the proposed dose and duration (400 mg TID x 5 days). These patients experienced no decrease in clinical benefit.

- Currently available information indicates that viruses with reduced susceptibility isolated from patients who have been treated with pleconaril possess specific amino acid changes in the virus VP1 protein that negatively affect the stability of the virion. Based on viruses isolated in cell culture with analogous amino acid changes, these variants are likely to have attenuated virulence compared to drug-susceptible wild-type viruses. No data are available at this time to address directly the transmissibility of treatment-emergent picornaviruses with reduced susceptibility to pleconaril.

- Picornaviruses typically cause acute self-limited illnesses. The virus is cleared from the body by the immune system within a few weeks and immunologic memory is established. Individuals do not normally become persistently infected with these viruses, nor do these viruses establish a latent state.

Pleconaril Represents an Appropriate New Treatment Option for the Common Cold

- Pleconaril is the first antiviral agent that has been shown to be safe and effective in reducing the duration and severity of picornavirus colds. If approved for marketing, pleconaril will provide a new treatment option for physicians and patients who desire a medicine that reduces the duration and severity of their cold symptoms by inhibiting the etiologic agent responsible for the illness.

- Physicians and patients will be educated regarding the symptom profile that is characteristic of picornavirus colds (including rhinorrhea and absence of fever), and the need for follow-up contact if fever or lower respiratory symptoms develop, or if there are signs or symptoms suggestive of a bacterial infection.

- Patients will be advised to initiate pleconaril as soon as possible within a day after onset of symptoms and to take pleconaril after a meal or snack to improve drug absorption.

In summary, available evidence supports a favorable benefit-risk ratio of pleconaril as the first safe and effective antiviral agent for the treatment of the common cold.

11. FUTURE CLINICAL DEVELOPMENT PLANS

VIROPHARMA is committed to conducting post-marketing studies to expand the safety and efficacy database in adults and to continuing its development programs for treatment of colds in children. VIROPHARMA is committed to conducting Phase IV studies to investigate the potential clinical significance of virus variants with reduced susceptibility to pleconaril, including the potential for transmission.

11.1 Ongoing Drug Interaction Studies

Three Phase I studies (843-063, 843-064, and 843-065) and a series of *in vitro* studies are being conducted to investigate the possible mechanism for the unexpected breakthrough bleeding/spotting adverse events reported by women taking an oral contraceptive in the 6-week prophylaxis study. Possible mechanisms include CYP3A4 induction, interference with enterohepatic circulation of ethinyl estradiol, protein binding displacement of ethinyl estradiol and progestin, changes in sex hormone binding globulin (SHBG), changes in steroid receptor binding, and partial antagonism of estrogen receptors.

Two Phase I studies are designed to explore potential drug interactions on a 5-day 400 mg TID regimen of pleconaril. In the first study (843-064), the possibility of hepatic induction of CYP 3A4 by pleconaril is being investigated in a midazolam (CYP 3A4 substrate) interaction study. The second study (843-065) will investigate the effect of pleconaril on the pharmacokinetics of ethinyl estradiol and norethindrone.

The third study (843-063) will investigate the effect of pleconaril on the pharmacokinetics of ethinyl estradiol and norgestimate (and 17-deacetyl norgestimate) following 3 weeks of pleconaril administration (400 mg BID). This study will also examine the effect of pleconaril on pharmacodynamic markers of oral contraceptive efficacy through the measurement of serum concentrations of progesterone, luteinizing hormone, and follicle stimulating hormone at selected points in the menstrual cycle.

A series of *in vitro* studies are currently ongoing to investigate plasma protein binding displacement of ethinyl estradiol and norethindrone by pleconaril, CYP450 induction in

human hepatocytes by pleconaril, and the estrogen and progestin receptor binding affinity of pleconaril.

11.2 Colds in Patients With Underlying Pulmonary Conditions

Patients with chronic asthma or chronic obstructive pulmonary disease (COPD) are at higher risk for more severe or prolonged colds (Gern and Busse, 1999) than otherwise healthy patients, and they are also at risk for exacerbations of their underlying respiratory conditions (Seemungal et al., 2001). Children with asthma are at particularly high risk for asthmatic episodes when they develop colds, although the exact relationship of bronchospasm and the cold symptoms is not known.

VIROPHARMA plans to initiate studies of the safety and efficacy of pleconaril in treatment of colds in adults with underlying pulmonary and cardiac conditions. In addition, pending the outcome of the recently completed proof-of-concept adult prophylaxis Study 843-062, VIROPHARMA plans to pursue prophylaxis studies in patients with underlying respiratory conditions to investigate whether preventing picornavirus colds will reduce the number or severity of exacerbations of the underlying pulmonary conditions in these high-risk patients. Appropriate measures of lower respiratory morbidity must be developed to evaluate objectively the medical and functional impact of these exacerbations.

11.3 Colds in Pediatric Patients

VIROPHARMA began Phase II clinical trials of a suspension formulation of pleconaril for the treatment of colds in children in 2000, studying two doses (10 mg/kg and 5 mg/kg TID for 5 days) for safety and pharmacokinetics. In 2001, two pediatric studies of similar design were undertaken, one in older children and one in younger children, to obtain more safety data and to investigate the utility of a modified Canadian Acute Respiratory and Influenza Flu Scale (CARIFS) in assessing the treatment effect of pleconaril in younger and older children with colds (Jacobs et al., 2000). Pending the outcome of these studies, a confirmatory Phase III licensing study will be performed in 2002.

11.4 Transmission of Colds and Development of Resistance

One of the potential benefits of an antiviral drug is reduction in transmission of picornaviruses that cause colds from infected to susceptible individuals. As shown in the Phase III studies in this NDA, patients treated with pleconaril have a more rapid reduction in the levels of virus in nasal mucus than do patients who received placebo. VIROPHARMA is planning to investigate virus transmission and the potential clinical significance of treatment-emergent viruses with reduced drug susceptibility. A design under consideration is a family transmission study in which index cases with colds would be randomized to receive either pleconaril or placebo, and susceptible family contacts would be monitored clinically and virologically for development of colds. Such a study would investigate the frequency of transmission of picornaviruses from pleconaril-treated patients to close contacts. It would also provide an opportunity to investigate the emergence and transmissibility of viruses with reduced susceptibility to pleconaril during treatment, as well as the ability of these viruses to cause symptomatic illness.

If pleconaril is approved for marketing, VIROPHARMA will discuss with FDA strategies for monitoring the emergence and potential impact of virus variants with reduced susceptibility to pleconaril. A strategy for monitoring emergent influenza viruses with reduced susceptibility to anti-influenza drugs exemplifies such a postmarketing drug susceptibility surveillance program. In the case of human picornavirus infection, this approach may be deemed unproductive because of the broad range of susceptibility to pleconaril that exists among the different virus serotypes (inter-serotypic variation), as well as among virus isolates of a single serotype (intra-serotypic variation). This broad range of drug susceptibility and the fact that many distinct serotypes cocirculate each year make it unlikely that a typical drug susceptibility surveillance program will provide useful information.

An experimental virus-challenge model may be a more viable approach to monitoring transmissibility of picornaviruses during antiviral drug therapy and the potential impact of virus variants with reduced susceptibility to pleconaril.

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13. APPENDICES

Appendix A Currently Available Cough/Cold Products

Appendix B Change From Baseline in Symptom Severity Scores by Day During the Treatment Period – ITT-I Patients

Appendix C Secondary Clinical Efficacy Endpoint Analyses and Post Hoc Symptom Severity Analyses - ITT Patients

Appendix D Additional Safety Data

Appendix A Currently Available Cough/Cold Remedies

There are three broad categories of cough and cold remedies currently available to patients in the U.S.:

Homeopathic Remedies, such as zinc or echinacea, which are largely unregulated. Available efficacy data are limited and generally do not support their use in the treatment of the common cold.

Over-the-Counter Products covered by the FDA monographs on cough, cold, allergy, bronchodilator, and antihistaminic drug products for human uses. These products include five major classes of agents:

- Topical or systemic decongestants used to reduce nasal congestion and/or cough due to post-nasal drip;
- First-generation antihistamines to diminish rhinorrhea and sneezing;
- Antitussives to suppress coughing;
- Expectorants to stimulate the flow of respiratory secretions; and
- Systemic analgesics and/or topical anesthetics to relieve sore throat or pharyngitis.

These products are available as single agents or, more commonly, as combination products.

Prescription Products labeled for the relief of one or more symptoms of the cold. This category includes combination products containing many of the same chemical entities as the OTC drugs, as well as older drugs considered for OTC status, but retained for prescription use due to safety concerns, such as promethazine, phenylephrine, or hydrocodone. Ipratroprium bromide nasal spray, which was approved via the NDA process for the treatment of one cold symptom (rhinorrhea), is included in this category.

There has been a proliferation of products containing one or more of the approved generic drugs, resulting in more than 1400 current OTC cold preparations, with approximately 50 new products released annually (Agrawal, 1999; Hulisz and Kaiser, 1995; Colchamiro, 1997).

The most significant effects for the major classes of OTC cold symptom relief medications are summarized briefly below.

Nasal Decongestants. A review of the published trials on the use of nasal decongestants for the common cold concluded that a single dose of nasal decongestant in the common cold is moderately effective (13% decrease in subjective symptoms) for the short-term relief of congestion, but there was no evidence available to show benefit after repeated use over several days (Taverner et al., 2001). The adverse effects of the nasal decongestants include CNS stimulatory effects ranging from mild (nervousness, excitability, restlessness, dizziness, insomnia) to serious (convulsions, cerebrovascular accident, acute delirium, hallucination). Decongestants interact with other commonly used drugs, including monoamine oxidase inhibitors (MAOI), which can result in severe hypertensive crisis (Drug Facts, 2001).

Antihistamines. Evidence to support the use of first-generation antihistamines in the treatment of the common cold is mixed (West et al., 1975; Smith and Feldman, 1993; Luks and Anderson, 1996; English and Bauman, 1997). The anticholinergic effects of first-generation antihistamines result in transient reduction of nasal secretions. The most significant adverse effect is sedation. Other adverse effects of first-generation antihistamines are predominantly associated with their anticholinergic properties (e.g., blurred vision, dry mouth, urinary retention, impotence, tachycardia, nausea, constipation) (Simons, 1999). Second-generation (nonsedating) antihistamines have not been demonstrated to be efficacious in the treatment of the common cold, due to their lack of anticholinergic activity.

Antitussive Agents. Dextromethorphan and the narcotic analgesics, codeine and hydrocodone, are the most frequently used antitussive agents. Codeine and other morphine-like narcotic agonists have strong antitussive effects, which are conferred by increasing the cough threshold. The most common adverse events associated with narcotics are nausea, vomiting, dry mouth, sedation, dizziness, respiratory depression, and constipation.

Expectorants. Guaifenesin is used to decrease the viscosity of respiratory tract secretions, making minimally productive coughs more productive. These claims are based on results of early animal studies, in which guaifenesin increased the volume of respiratory tract

secretions (Perry and Boyd, 1941). Clinical studies of efficacy have not been definitive (Thompson et al., 1973; Kuhn et al., 1982; Cohen, 1983). Guaifenesin is generally well tolerated with reported side effects including nausea and vomiting, especially with excessive dosage, as well as dizziness, headache, rash (including urticaria), diarrhea, drowsiness, and abdominal pain.

Analgesics. The most common analgesics used in combination cough/cold products are acetaminophen and ibuprofen. The efficacy of acetaminophen for pain relief and fever reduction is well established (Prestcott, 1983; Cranswick and Coghlan, 2000), although it has not been specifically studied as a component of cough and cold products in patients with a cold. Acetaminophen has few side effects and is generally well tolerated at recommended dosages. Adverse events associated with acetaminophen usage fall into three broad categories: hematological (hemolytic anemia, neutropenia, leukopenia, pancytopenia, thrombocytopenia), hypersensitivity reactions, and miscellaneous (hypoglycemic coma, jaundice). Acetaminophen hepatotoxicity, which has been fatal, can occur following overdosage or when the maximum daily dose is exceeded for several days (Smilkstein et al., 1988; Makin et al., 1995; Schiodt et al., 1997).

The efficacy of ibuprofen as an OTC analgesic and antipyretic is well established (Hersh et al., 2000), but it has not been specifically studied as a component of cough and cold products in patients with a cold. The most common adverse events associated with ibuprofen usage involve the gastrointestinal tract (e.g., gastric or duodenal ulcer with or without bleeding/perforation, heartburn, as well as the more common symptoms of nausea, vomiting, diarrhea, abdominal cramping, and dyspepsia) (Physicians' Desk Reference, 2000).

Examples of cautions and warnings included on the label for a typical product containing a nasal decongestant, an antihistamine and an antitussive follow:

Flu, Cold and Cough Medicine contains:

- Acetaminophen 650 mg
- Pseudoephedrine hydrochloride 60 mg
- Chlorpheniramine maleate 4 mg
- Dextromethorphan hydrobromide 20 mg

Indications: Provides temporary relief of the symptoms associated with flu, common cold and other upper respiratory allergies including: headache, body aches, fever, minor sore throat pain, nasal and sinus congestion, runny nose, sneezing and cough.

Warnings:

- In case of accidental overdose, seek professional assistance or contact a poison control center immediately. Prompt medical attention is critical for adults as well as children even if you do not notice any signs or symptoms. Do not exceed recommended dosage.
- If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor.
- May cause excitability, especially in children.
- Do not take this product (unless directed by a doctor) if you have:
  - Heart disease
  - High blood pressure
  - Thyroid disease
  - Diabetes
  - Glaucoma
  - A breathing problem such as emphysema or chronic bronchitis
  - Difficulty in urination due to enlargement of the prostate gland
- May cause marked drowsiness; alcohol, sedatives, and tranquilizers may increase the effect.
- Avoid alcoholic beverages while taking this product.
- Do not take this product if you are taking sedatives or tranquilizers, without consulting doctor.
- Use caution when driving a motor vehicle or operating machinery.

Drug Interaction Precaution: Do not take this product if you are now taking a monoamine oxidase inhibitor [MAOI] (certain drugs for depression, psychiatric or emotional conditions or Parkinson's disease), or for 2 weeks after stopping the MAOI.

Alcohol Warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take acetaminophen or other pain relievers/fever reducers.
Acetaminophen may cause liver damage.

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Appendix B Change From Baseline in Symptom Severity Scores by Day During the Treatment Period – ITT-I Patients

Table 1. Change From Baseline in Rhinorrhea Severity Scores by Day During the Treatment Period – ITT-I Patients

	843-043		843-044		Pooled	
	Placebo	Pleconaril	Placebo	Pleconaril	Placebo	Pleconaril
ITT-I	**326**	**337**	**356**	**344**	**682**	**681**
Before First Dose						
Mean (SD)	2.43 (0.51)	2.42 (0.49)	2.40 (0.50)	2.46 (0.50)	2.41 (0.50)	2.44 (0.50)
Day 1 PM						
Mean (SD)	1.92 (0.77)	1.99 (0.76)	2.02 (0.73)	1.97 (0.81)	1.97 (0.75)	1.98 (0.78)
Mean Change	-0.50	-0.44	-0.38	-0.49	-0.44	-0.47
p-value[a]		0.405		0.062		0.443
Day 2 AM						
Mean (SD)	1.71 (0.82)	1.76 (0.83)	1.88 (0.76)	1.71 (0.83)	1.80 (0.80)	1.73 (0.83)
Mean Change	-0.71	-0.67	-0.52	-0.75	-0.61	-0.71
p-value[a]		0.644		<0.001		0.027
Day 2 PM						
Mean (SD)	1.55 (0.85)	1.55 (0.89)	1.67 (0.83)	1.51 (0.89)	1.61 (0.84)	1.53 (0.89)
Mean Change	-0.88	-0.88	-0.73	-0.94	-0.80	-0.91
p-value[a]		0.897		0.002		0.020
Day 3 AM						
Mean (SD)	1.34 (0.88)	1.26 (0.85)	1.49 (0.84)	1.21 (0.82)	1.42 (0.86)	1.23 (0.83)
Mean Change	-1.08	-1.17	-0.92	-1.25	-1.00	-1.21
p-value[a]		0.243		<0.001		<0.001
Day 3 PM						
Mean (SD)	1.19 (0.88)	1.10 (0.92)	1.32 (0.86)	1.05 (0.87)	1.26 (0.87)	1.08 (0.90)
Mean Change	-1.24	-1.32	-1.09	-1.41	-1.16	-1.37
p-value[a]		0.302		<0.001		<0.001
Day 4 AM						
Mean (SD)	1.10 (0.88)	1.01 (0.86)	1.13 (0.80)	0.91 (0.80)	1.12 (0.84)	0.96 (0.83)
Mean Change	-1.33	-1.41	-1.27	-1.55	-1.30	-1.48
p-value[a]		0.272		<0.001		<0.001
Day 4 PM						
Mean (SD)	0.99 (0.87)	0.89 (0.85)	1.00 (0.81)	0.79 (0.79)	1.00 (0.84)	0.84 (0.82)
Mean Change	-1.43	-1.53	-1.41	-1.67	-1.42	-1.60
p-value[a]		0.208		<0.001		<0.001
Day 5 AM						
Mean (SD)	0.94 (0.86)	0.81 (0.83)	0.93 (0.79)	0.76 (0.77)	0.94 (0.82)	0.79 (0.80)
Mean Change	-1.48	-1.61	-1.47	-1.70	-1.48	-1.66
p-value[a]		0.078		<0.001		<0.001
Day 5 PM						
Mean (SD)	0.84 (0.86)	0.74 (0.79)	0.84 (0.76)	0.68 (0.76)	0.84 (0.81)	0.71 (0.77)
Mean Change	-1.59	-1.69	-1.57	-1.78	-1.58	-1.74
p-value[a]		0.178		<0.001		<0.001
Day 6 AM						
Mean (SD)	0.80 (0.82)	0.72 (0.77)	0.83 (0.77)	0.71 (0.78)	0.81 (0.79)	0.72 (0.77)
Mean Change	-1.63	-1.70	-1.57	-1.75	-1.60	-1.72
p-value[a]		0.304		0.009		0.010
Day 6 PM						
Mean (SD)	0.70 (0.81)	0.66 (0.75)	0.73 (0.77)	0.64 (0.75)	0.71 (0.79)	0.65 (0.75)
Mean Change	-1.73	-1.77	-1.67	-1.82	-1.70	-1.79
p-value[a]		0.625		0.029		0.058

[a] p-values were calculated from a Wilcoxon's rank-sum test of changes from baseline.
NOTE: Only patients with that symptom (score ≥1) at baseline were included in the analysis.

Table 2. Change From Baseline in Nasal Congestion Severity Scores by Day During the Treatment Period – ITT-I Patients

	843-043		843-044		Pooled	
	Placebo	**Pleconaril**	**Placebo**	**Pleconaril**	**Placebo**	**Pleconaril**
ITT-I	**326**	**337**	**356**	**344**	**682**	**681**
Before First Dose Mean (SD)	2.03 (0.61)	2.11 (0.61)	1.99 (0.57)	2.06 (0.62)	2.01 (0.59)	2.09 (0.62)
Day 1 PM Mean (SD)	1.80 (0.76)	1.80 (0.76)	1.71 (0.78)	1.85 (0.75)	1.76 (0.77)	1.82 (0.75)
Mean Change	-0.22	-0.31	-0.28	-0.22	-0.25	-0.26
p-value[a]		0.200		0.236		0.924
Day 2 AM Mean (SD)	1.59 (0.79)	1.58 (0.79)	1.61 (0.80)	1.57 (0.80)	1.60 (0.80)	1.57 (0.79)
Mean Change	-0.43	-0.53	-0.38	-0.50	-0.40	-0.51
p-value[a]		0.236		0.102		0.044
Day 2 PM Mean (SD)	1.45 (0.79)	1.43 (0.81)	1.57 (0.84)	1.42 (0.83)	1.51 (0.82)	1.43 (0.82)
Mean Change	-0.57	-0.68	-0.42	-0.65	-0.49	-0.66
p-value[a]		0.186		0.003		0.002
Day 3 AM Mean (SD)	1.27 (0.77)	1.21 (0.77)	1.37 (0.83)	1.18 (0.82)	1.32 (0.81)	1.20 (0.80)
Mean Change	-0.76	-0.90	-0.62	-0.89	-0.69	-0.89
p-value[a]		0.060		<0.001		<0.001
Day 3 PM Mean (SD)	1.23 (0.80)	1.09 (0.76)	1.26 (0.80)	1.12 (0.80)	1.25 (0.80)	1.11 (0.78)
Mean Change	-0.79	-1.02	-0.73	-0.95	-0.76	-0.98
p-value[a]		0.004		0.004		<0.001
Day 4 AM Mean (SD)	1.08 (0.81)	0.99 (0.79)	1.07 (0.74)	0.97 (0.76)	1.08 (0.78)	0.98 (0.78)
Mean Change	-0.94	-1.12	-0.92	-1.10	-0.93	-1.11
p-value[a]		0.036		0.005		<0.001
Day 4 PM Mean (SD)	0.95 (0.79)	0.88 (0.76)	1.01 (0.75)	0.88 (0.79)	0.98 (0.77)	0.88 (0.78)
Mean Change	-1.07	-1.23	-0.98	-1.18	-1.02	-1.21
p-value[a]		0.062		<0.001		<0.001
Day 5 AM Mean (SD)	0.89 (0.80)	0.79 (0.74)	0.88 (0.74)	0.82 (0.76)	0.89 (0.77)	0.80 (0.75)
Mean Change	-1.14	-1.33	-1.10	-1.25	-1.12	-1.29
p-value[a]		0.015		0.014		<0.001
Day 5 PM Mean (SD)	0.85 (0.84)	0.74 (0.75)	0.83 (0.73)	0.76 (0.78)	0.84 (0.78)	0.75 (0.77)
Mean Change	-1.17	-1.38	-1.16	-1.31	-1.17	-1.34
p-value[a]		0.014		0.008		<0.001
Day 6 AM Mean (SD)	0.72 (0.79)	0.64 (0.72)	0.74 (0.77)	0.72 (0.76)	0.73 (0.78)	0.68 (0.74)
Mean Change	-1.30	-1.48	-1.25	-1.34	-1.27	-1.41
p-value[a]		0.033		0.149		0.010
Day 6 PM Mean (SD)	0.70 (0.80)	0.62 (0.71)	0.69 (0.77)	0.66 (0.75)	0.69 (0.78)	0.64 (0.73)
Mean Change	-1.32	-1.49	-1.30	-1.40	-1.31	-1.45
p-value[a]		0.039		0.191		0.015

[a] p-values were calculated from a Wilcoxon's rank-sum test of changes from baseline.
NOTE: Only patients with that symptom (score ≥1) at baseline were included in the analysis.

Table 3. Change From Baseline in Cough Severity Scores by Day During the Treatment Period – ITT-I Patients

	843-043		843-044		Pooled	
	Placebo	**Pleconaril**	**Placebo**	**Pleconaril**	**Placebo**	**Pleconaril**
ITT-I	**326**	**337**	**356**	**344**	**682**	**681**
Before First Dose Mean (SD)	1.51 (0.64)	1.56 (0.62)	1.48 (0.62)	1.59 (0.66)	1.49 (0.63)	1.57 (0.64)
Day 1 PM Mean (SD)	1.35 (0.77)	1.26 (0.79)	1.25 (0.74)	1.39 (0.78)	1.30 (0.76)	1.32 (0.79)
Mean Change	-0.16	-0.30	-0.23	-0.20	-0.19	-0.25
p-value[a]		0.060		0.622		0.322
Day 2 AM Mean (SD)	1.34 (0.79)	1.27 (0.78)	1.26 (0.80)	1.32 (0.81)	1.30 (0.80)	1.29 (0.80)
Mean Change	-0.17	-0.29	-0.22	-0.28	-0.19	-0.28
p-value[a]		0.086		0.445		0.080
Day 2 PM Mean (SD)	1.30 (0.83)	1.16 (0.82)	1.26 (0.84)	1.26 (0.84)	1.28 (0.84)	1.21 (0.83)
Mean Change	-0.21	-0.39	-0.22	-0.34	-0.22	-0.37
p-value[a]		0.011		0.153		0.005
Day 3 AM Mean (SD)	1.21 (0.83)	1.06 (0.76)	1.24 (0.86)	1.15 (0.88)	1.23 (0.85)	1.10 (0.82)
Mean Change	-0.30	-0.50	-0.24	-0.44	-0.27	-0.47
p-value[a]		0.015		0.009		<0.001
Day 3 PM Mean (SD)	1.16 (0.87)	1.00 (0.79)	1.19 (0.86)	1.13 (0.91)	1.18 (0.87)	1.06 (0.85)
Mean Change	-0.34	-0.55	-0.29	-0.47	-0.32	-0.51
p-value[a]		0.010		0.018		<0.001
Day 4 AM Mean (SD)	1.09 (0.92)	0.91 (0.82)	1.16 (0.86)	0.99 (0.86)	1.13 (0.89)	0.95 (0.84)
Mean Change	-0.41	-0.64	-0.32	-0.60	-0.36	-0.62
p-value[a]		0.012		0.001		<0.001
Day 4 PM Mean (SD)	1.02 (0.92)	0.89 (0.80)	1.09 (0.90)	0.96 (0.90)	1.06 (0.91)	0.92 (0.85)
Mean Change	-0.48	-0.67	-0.39	-0.63	-0.43	-0.65
p-value[a]		0.060		0.006		<0.001
Day 5 AM Mean (SD)	0.95 (0.95)	0.81 (0.77)	1.02 (0.90)	0.86 (0.92)	0.98 (0.92)	0.83 (0.84)
Mean Change	-0.56	-0.75	-0.46	-0.74	-0.51	-0.74
p-value[a]		0.083		0.003		<0.001
Day 5 PM Mean (SD)	0.97 (0.95)	0.79 (0.82)	0.95 (0.84)	0.81 (0.87)	0.96 (0.90)	0.80 (0.84)
Mean Change	-0.54	-0.76	-0.52	-0.78	-0.53	-0.77
p-value[a]		0.024		0.002		<0.001
Day 6 AM Mean (SD)	0.84 (0.88)	0.73 (0.78)	0.86 (0.83)	0.77 (0.86)	0.85 (0.85)	0.75 (0.82)
Mean Change	-0.66	-0.82	-0.61	-0.83	-0.64	-0.83
p-value[a]		0.132		0.010		0.004
Day 6 PM Mean (SD)	0.77 (0.86)	0.73 (0.81)	0.82 (0.82)	0.74 (0.90)	0.80 (0.84)	0.73 (0.86)
Mean Change	-0.73	-0.83	-0.66	-0.85	-0.70	-0.84
p-value[a]		0.424		0.013		0.021

[a] p-values were calculated from a Wilcoxon's rank-sum test of changes from baseline.
NOTE: Only patients with that symptom (score ≥1) at baseline were included in the analysis.

Table 4. Change From Baseline in Pharyngeal Severity Scores by Day During the Treatment Period – ITT-I Patients

	843-043		843-044		Pooled	
	Placebo	Pleconaril	Placebo	Pleconaril	Placebo	Pleconaril
ITT-I	**326**	**337**	**356**	**344**	**682**	**681**
Before First Dose Mean (SD)	1.83 (0.66)	1.73 (0.64)	1.75 (0.61)	1.74 (0.64)	1.79 (0.64)	1.73 (0.64)
Day 1 PM Mean (SD) Mean Change p-value[a]	1.38 (0.79) -0.45	1.24 (0.78) -0.49 0.563	1.32 (0.78) -0.43	1.31 (0.78) -0.43 1.000	1.35 (0.78) -0.44	1.27 (0.78) -0.46 0.675
Day 2 AM Mean (SD) Mean Change p-value[a]	1.17 (0.86) -0.65	0.96 (0.81) -0.77 0.179	1.06 (0.83) -0.69	0.99 (0.81) -0.74 0.468	1.11 (0.84) -0.67	0.98 (0.81) -0.76 0.146
Day 2 PM Mean (SD) Mean Change p-value[a]	1.02 (0.85) -0.81	0.83 (0.81) -0.89 0.415	0.94 (0.81) -0.81	0.83 (0.83) -0.90 0.146	0.98 (0.83) -0.81	0.83 (0.82) -0.90 0.110
Day 3 AM Mean (SD) Mean Change p-value[a]	0.84 (0.84) -0.99	0.64 (0.77) -1.09 0.257	0.77 (0.84) -0.97	0.64 (0.76) -1.09 0.148	0.81 (0.84) -0.98	0.64 (0.76) -1.09 0.068
Day 3 PM Mean (SD) Mean Change p-value[a]	0.76 (0.85) -1.06	0.59 (0.77) -1.14 0.382	0.65 (0.78) -1.10	0.56 (0.75) -1.18 0.302	0.71 (0.82) -1.08	0.57 (0.76) -1.16 0.180
Day 4 AM Mean (SD) Mean Change p-value[a]	0.59 (0.80) -1.24	0.48 (0.73) -1.25 0.867	0.51 (0.73) -1.24	0.44 (0.64) -1.29 0.661	0.55 (0.76) -1.24	0.46 (0.69) -1.27 0.667
Day 4 PM Mean (SD) Mean Change p-value[a]	0.57 (0.76) -1.26	0.39 (0.65) -1.33 0.432	0.47 (0.70) -1.27	0.42 (0.66) -1.32 0.697	0.52 (0.73) -1.27	0.41 (0.65) -1.33 0.403
Day 5 AM Mean (SD) Mean Change p-value[a]	0.51 (0.80) -1.32	0.33 (0.60) -1.40 0.685	0.39 (0.67) -1.36	0.32 (0.62) -1.41 0.660	0.45 (0.74) -1.34	0.32 (0.61) -1.41 0.560
Day 5 PM Mean (SD) Mean Change p-value[a]	0.50 (0.80) -1.33	0.30 (0.58) -1.43 0.466	0.36 (0.66) -1.38	0.31 (0.60) -1.43 0.918	0.43 (0.73) -1.36	0.30 (0.59) -1.43 0.563
Day 6 AM Mean (SD) Mean Change p-value[a]	0.41 (0.69) -1.41	0.27 (0.56) -1.45 0.934	0.30 (0.60) -1.45	0.28 (0.56) -1.46 0.889	0.35 (0.65) -1.43	0.27 (0.56) -1.46 0.958
Day 6 PM Mean (SD) Mean Change p-value[a]	0.44 (0.73) -1.39	0.24 (0.53) -1.49 0.317	0.27 (0.59) -1.48	0.26 (0.57) -1.48 0.754	0.35 (0.67) -1.43	0.25 (0.55) -1.49 0.632

[a] p-values were calculated from a Wilcoxon's rank-sum test of changes from baseline.
NOTE: Only patients with that symptom (score ≥1) at baseline were included in the analysis.

Table 5. Change From Baseline in Malaise Severity Scores by Day During the Treatment Period – ITT-I Patients

	843-043		843-044		Pooled	
	Placebo	Pleconaril	Placebo	Pleconaril	Placebo	Pleconaril
ITT-I	**326**	**337**	**356**	**344**	**682**	**681**
Before First Dose						
Mean (SD)	1.92 (0.74)	1.81 (0.74)	1.77 (0.71)	1.78 (0.73)	1.84 (0.73)	1.80 (0.74)
Day 1 PM						
Mean (SD)	1.75 (0.83)	1.75 (0.84)	1.70 (0.83)	1.73 (0.84)	1.72 (0.83)	1.74 (0.84)
Mean Change	-0.17	-0.06	-0.07	-0.05	-0.12	-0.06
p-value[a]		0.062		0.723		0.135
Day 2 AM						
Mean (SD)	1.47 (0.88)	1.48 (0.84)	1.56 (0.87)	1.43 (0.81)	1.52 (0.88)	1.45 (0.83)
Mean Change	-0.45	-0.33	-0.21	-0.35	-0.32	-0.34
p-value[a]		0.173		0.067		0.691
Day 2 PM						
Mean (SD)	1.43 (0.89)	1.32 (0.84)	1.42 (0.86)	1.31 (0.90)	1.42 (0.88)	1.32 (0.87)
Mean Change	-0.49	-0.49	-0.35	-0.47	-0.42	-0.48
p-value[a]		0.916		0.086		0.237
Day 3 AM						
Mean (SD)	1.11 (0.86)	1.07 (0.83)	1.15 (0.92)	1.03 (0.88)	1.13 (0.89)	1.05 (0.85)
Mean Change	-0.81	-0.74	-0.61	-0.75	-0.71	-0.75
p-value[a]		0.408		0.144		0.616
Day 3 PM						
Mean (SD)	1.06 (0.92)	0.92 (0.78)	1.07 (0.86)	0.95 (0.87)	1.06 (0.89)	0.94 (0.83)
Mean Change	-0.86	-0.88	-0.70	-0.83	-0.78	-0.86
p-value[a]		0.911		0.110		0.202
Day 4 AM						
Mean (SD)	0.89 (0.93)	0.71 (0.75)	0.75 (0.77)	0.67 (0.79)	0.82 (0.85)	0.69 (0.77)
Mean Change	-1.03	-1.10	-1.01	-1.11	-1.02	-1.10
p-value[a]		0.612		0.137		0.171
Day 4 PM						
Mean (SD)	0.87 (0.93)	0.68 (0.76)	0.70 (0.78)	0.63 (0.79)	0.78 (0.86)	0.66 (0.78)
Mean Change	-1.05	-1.13	-1.07	-1.15	-1.06	-1.14
p-value[a]		0.430		0.217		0.170
Day 5 AM						
Mean (SD)	0.72 (0.89)	0.49 (0.68)	0.55 (0.75)	0.54 (0.75)	0.63 (0.82)	0.51 (0.71)
Mean Change	-1.20	-1.32	-1.22	-1.25	-1.21	-1.28
p-value[a]		0.258		0.600		0.236
Day 5 PM						
Mean (SD)	0.71 (0.92)	0.46 (0.69)	0.52 (0.74)	0.55 (0.78)	0.61 (0.84)	0.50 (0.74)
Mean Change	-1.20	-1.35	-1.24	-1.23	-1.23	-1.29
p-value[a]		0.208		0.957		0.333
Day 6 AM						
Mean (SD)	0.60 (0.82)	0.44 (0.68)	0.46 (0.71)	0.44 (0.73)	0.53 (0.77)	0.44 (0.70)
Mean Change	-1.32	-1.37	-1.31	-1.34	-1.31	-1.36
p-value[a]		0.645		0.663		0.518
Day 6 PM						
Mean (SD)	0.59 (0.85)	0.41 (0.69)	0.45 (0.72)	0.46 (0.75)	0.52 (0.79)	0.44 (0.72)
Mean Change	-1.33	-1.40	-1.32	-1.32	-1.32	-1.36
p-value[a]		0.519		0.883		0.559

[a] p-values were calculated from a Wilcoxon's rank-sum test of changes from baseline.
NOTE: Only patients with that symptom (score ≥1) at baseline were included in the analysis.

Table 6. Change From Baseline in Myalgia Severity Scores by Day During the Treatment Period – ITT-I Patients

	843-043		843-044		Pooled	
	Placebo	Pleconaril	Placebo	Pleconaril	Placebo	Pleconaril
ITT-I	**326**	**337**	**356**	**344**	**682**	**681**
Before First Dose Mean (SD)	1.52 (0.63)	1.47 (0.61)	1.51 (0.61)	1.48 (0.64)	1.51 (0.62)	1.47 (0.63)
Day 1 PM Mean (SD)	1.50 (0.79)	1.29 (0.78)	1.48 (0.80)	1.50 (0.84)	1.49 (0.79)	1.39 (0.81)
Mean Change	-0.02	-0.18	-0.03	0.02	-0.02	-0.08
p-value[a]		0.126		0.689		0.403
Day 2 AM Mean (SD)	1.37 (0.83)	1.01 (0.83)	1.28 (0.86)	1.18 (0.77)	1.32 (0.84)	1.09 (0.81)
Mean Change	-0.15	-0.46	-0.24	-0.30	-0.19	-0.38
p-value[a]		<0.001		0.523		0.005
Day 2 PM Mean (SD)	1.24 (0.87)	0.90 (0.86)	1.15 (0.83)	1.0 (0.84)	1.20 (0.85)	0.95 (0.85)
Mean Change	-0.28	-0.57	-0.36	-0.48	-0.32	-0.53
p-value[a]		0.002		0.210		0.002
Day 3 AM Mean (SD)	0.95 (0.84)	0.63 (0.74)	0.93 (0.81)	0.81 (0.86)	0.94 (0.82)	0.72 (0.80)
Mean Change	-0.57	-0.84	-0.58	-0.67	-0.58	-0.76
p-value[a]		0.007		0.427		0.013
Day 3 PM Mean (SD)	0.82 (0.88)	0.52 (0.68)	0.86 (0.79)	0.68 (0.83)	0.84 (0.84)	0.59 (0.76)
Mean Change	-0.70	-0.95	-0.65	-0.80	-0.68	-0.88
p-value[a]		0.018		0.147		0.006
Day 4 AM Mean (SD)	0.74 (0.89)	0.43 (0.66)	0.64 (0.68)	0.48 (0.71)	0.69 (0.79)	0.45 (0.68)
Mean Change	-0.78	-1.03	-0.87	-1.00	-0.82	-1.02
p-value[a]		0.019		0.130		0.006
Day 4 PM Mean (SD)	0.65 (0.84)	0.38 (0.60)	0.62 (0.68)	0.45 (0.72)	0.63 (0.76)	0.41 (0.66)
Mean Change	-0.87	-1.09	-0.89	-1.03	-0.88	-1.06
p-value[a]		0.033		0.138		0.010
Day 5 AM Mean (SD)	0.53 (0.84)	0.31 (0.56)	0.48 (0.68)	0.37 (0.67)	0.51 (0.76)	0.34 (0.62)
Mean Change	-0.98	-1.16	-1.03	-1.11	-1.01	-1.14
p-value[a]		0.136		0.392		0.094
Day 5 PM Mean (SD)	0.48 (0.82)	0.30 (0.61)	0.45 (0.67)	0.35 (0.68)	0.46 (0.75)	0.32 (0.64)
Mean Change	-1.03	-1.16	-1.06	-1.13	-1.05	-1.15
p-value[a]		0.237		0.560		0.207
Day 6 AM Mean (SD)	0.44 (0.76)	0.26 (0.54)	0.35 (0.63)	0.32 (0.62)	0.39 (0.70)	0.28 (0.58)
Mean Change	-1.08	-1.21	-1.16	-1.16	-1.12	-1.19
p-value[a]		0.203		0.695		0.511
Day 6 PM Mean (SD)	0.43 (0.77)	0.27 (0.58)	0.36 (0.64)	0.35 (0.67)	0.39 (0.71)	0.31 (0.62)
Mean Change	-1.09	-1.19	-1.15	-1.12	-1.12	-1.16
p-value[a]		0.415		0.629		0.789

[a] p-values were calculated from a Wilcoxon's rank-sum test of changes from baseline.
NOTE: Only patients with that symptom (score ≥1) at baseline were included in the analysis.

Appendix C Secondary Clinical Efficacy Endpoint Analyses and Post Hoc Symptom Severity Analyses - ITT Patients

Table 1. Time to Patient Assessment of "No Cold," ITT Patients

	Study 843-043		Study 843-044		Pooled	
	Placebo	Pleconaril	Placebo	Pleconaril	Placebo	Pleconaril
ITT	**526**	**526**	**524**	**520**	**1050**	**1046**
Patient Assessment						
Patients reaching endpoint	445 (85%)	446 (85%)	443 (85%)	455 (88%)	888 (85%)	901 (86%)
Median (days)	6.3	5.8	6.7	5.9	6.4	5.9
p-value[a]		0.079		0.030		0.005

[a] p-values were calculated using a Wilcoxon test (strata: study, smoking status and pre-enrollment use of cold symptom relief medication).

Table 2. Proportion of Patients With a Cold by Investigator Assessment, ITT Patients

	Study 843-043		Study 843-044		Pooled	
	Placebo	Pleconaril	Placebo	Pleconaril	Placebo	Pleconaril
ITT	**526**	**526**	**524**	**520**	**1050**	**1046**
Number of Patients with a Cold/Number of Patients Assessed						
Day 3	460/490 (94%)	425/485 (88%)	439/485 (91%)	443/488 (91%)	899/975 (92%)	868/973 (89%)
p-value[a]		<0.001		0.913		0.024
Day 6	267/489 (55%)	223/479 (47%)	275/490 (56%)	263/489 (54%)	542/979 (55%)	486/968 (50%)
p-value[a]		0.015		0.480		0.023

[a] p-values were calculated from a Fisher's exact test.
NOTE: The analysis windows were Days 2-4 for visit Day 3 and Days 5-9 for visit Day 6.

Table 3. Time to Resolution of Individual Cold Symptoms, ITT Patients

	843-043		843-044		Pooled	
	Placebo	**Pleconaril**	**Placebo**	**Pleconaril**	**Placebo**	**Pleconaril**
ITT	**526**	**526**	**524**	**520**	**1050**	**1046**
Rhinorrhea						
Number of patients analyzed	526	525	524	520	1050	1045
Median (days)	6.3	6.0	6.6	5.8	6.4	5.9
p-value[a]		0.243		0.008		0.007
Nasal Congestion						
Number of patients analyzed	519	520	520	515	1039	1035
Median (days)	6.0	5.8	6.1	5.9	6.0	5.9
p-value[a]		0.164		0.346		0.099
Sore Throat						
Number of patients analyzed	479	468	468	463	947	931
Median (days)	4.0	3.0	3.9	3.1	3.9	3.0
p-value[a]		0.004		0.009		<0.001
Cough						
Number of patients analyzed	478	465	477	459	955	924
Median (days)	5.8	5.1	6.1	5.3	5.9	5.2
p-value[a]		0.366		0.031		0.030
Malaise						
Number of patients analyzed	508	501	501	502	1009	1003
Median (days)	4.3	3.9	4.1	3.9	4.2	3.9
p-value[a]		0.101		0.390		0.077
Myalgia						
Number of patients analyzed	422	404	403	405	825	809
Median (days)	4.0	3.0	3.9	3.1	3.9	3.0
p-value[a]		<0.001		0.040		<0.001

[a] p-values are from a Wilcoxon test (strata: study, smoking status and pre-enrollment use of cold symptom relief medication).

Table 4. Sum of the Twice-Daily Cold Symptom Severity Score Over the 18-Day Study Period, ITT Patients

	Study 843-043		Study 843-044		Pooled	
	Placebo	**Pleconaril**	**Placebo**	**Pleconaril**	**Placebo**	**Pleconaril**
ITT	**526**	**526**	**524**	**520**	**1050**	**1046**
Geometric mean (CV%)	32.7 (27.1)	29.4 (27.7)	32.0 (26.8)	29.2 (26.6)	32.3 (27.0)	29.3 (27.1)
Median	34.9	29.5	34.0	29.3	34.1	29.3
p-value[a]		0.081		0.037		0.008

[a] p-values were calculated using an ANCOVA of log-transformed data (model includes treatment, smoking status, and pre-enrollment use of cold symptom relief medication and covariate of baseline total cold symptom severity score).

NOTE: The last-observation-carried-forward approach was used to impute missing values.

Table 5. Other Secondary Clinical Efficacy Endpoints, ITT Patients

	843-043		843-044		Pooled	
	Placebo	**Pleconaril**	**Placebo**	**Pleconaril**	**Placebo**	**Pleconaril**
ITT	**526**	**526**	**524**	**520**	**1050**	**1046**
Total Tissue Use During the Treatment Period (Days 1-6)						
Geometric mean (CV%)	64.9 (22.6)	62.5 (20.9)	71.5 (19.7)	60.9 (21.4)	68.1 (21.2)	61.7 (21.1)
Median	70.0	64.0	78.0	67.0	72.5	65.0
p-value[a]		0.524		0.003		0.013
Total Tissue Use During the Study Period (Days 1-18)						
Geometric mean (CV%)	93.8 (23.6)	86.5 (22.1)	102.5 (19.9)	84.7 (22.6)	98.1 (21.8)	85.6 (22.3)
Median	107.0	92.5	118.0	88.0	111.0	90.0
p-value[a]		0.213		0.002		0.002
Number of Nights With Sleep Disturbance During the Study Period (Days 1-18)						
Mean (SD)	4.2 (4.37)	3.4 (3.66)	3.9 (4.16)	3.6 (4.09)	4.0 (4.27)	3.5 (3.88)
Median	3.0	2.0	3.0	2.0	3.0	2.0
p-value[b]		<0.001		0.260		0.002
Number of Days With Cold Symptom Relief Medication Use During the Treatment Period (Days 1-6)						
Geometric mean (CV%)	0.83 (112.9)	0.72 (119.5)	1.00 (101.4)	0.81 (113.6)	0.92 (106.9)	0.76 (116.5)
Median	0.0	0.0	1.0	0.0	1.0	0.0
p-value[a]		0.123		0.015		0.005
Number of Days With Cold Symptom Relief Medication Use During the Study Period (Days 1-18)						
Geometric mean (CV%)	1.10 (110.6)	0.91 (118.1)	1.29 (101.6)	1.05 (114.1)	1.19 (106.0)	0.98 (116.2)
Median	1.0	0.4	1.0	1.0	1.0	1.0
p-value[a]		0.060		0.025		0.003
Number of Days With Impairment of Normal Activity Due to Cold Symptoms During the Study Period (Days 1-18)						
Mean (SD)	4.4 (4.45)	4.1 (4.09)	4.3 (4.37)	4.2 (4.23)	---	---
Median	3.0	3.0	3.0	3.0		
p-value[b]		0.284		0.587		

[a] p-values were calculated using an ANOVA of log transformed data (model included treatment, study, smoking status, and pre-enrollment use of cold symptom relief medication).

[b] p-values are calculated from an ANOVA of arcsine of square root transformed proportion of days (model includes treatment, study, smoking status, and pre-enrollment use of cold symptom relief medication).

Table 6. Newly Diagnosed Acute Respiratory Complications, ITT Patients

	843-043		843-044		Pooled	
	Placebo	**Pleconaril**	**Placebo**	**Pleconaril**	**Placebo**	**Pleconaril**
ITT	**526**	**526**	**524**	**520**	**1050**	**1046**
Number of patients with:						
Otitis media	3 (0.6%)	7 (1.3%)	4 (0.8%)	8 (1.5%)	7 (0.7%)	15 (1.4%)
Bronchitis	16 (3.0%)	15 (2.9%)	16 (3.1%)	17 (3.3%)	32 (3.0%)	32 (3.1%)
Sinusitis	12 (2.3%)	12 (2.3%)	15 (2.9%)	18 (3.5%)	27 (2.6%)	30 (2.9%)
Pneumonitis	0	2 (0.4%)	1 (0.2%)	0	1 (0.1%)	2 (0.2%)

Table 7. Change From Baseline in Total Symptom Severity Score by Day During the Treatment Period (Days 1-6), ITT Patients (Post Hoc Analysis)

	843-043		843-044		Pooled	
	Placebo	Pleconaril	Placebo	Pleconaril	Placebo	Pleconaril
ITT	**526**	**526**	**524**	**520**	**1050**	**1046**
Prior to Dosing						
Mean (SD)	9.47 (2.53)	9.35 (2.45)	8.93 (2.44)	9.10 (2.47)	9.20 (2.50)	9.23 (2.46)
Day 1 PM						
Mean (SD)	8.24 (3.03)	8.20 (3.07)	8.04 (3.11)	8.11 (3.13)	8.14 (3.07)	8.15 (3.10)
Mean % Change	-11.3	-11.6	-8.9	-10.0	-10.1	-10.8
p-value[a]		0.812		0.663		0.940
Day 2 AM						
Mean (SD)	7.43 (3.25)	7.30 (3.25)	7.46 (3.29)	7.17 (3.11)	7.45 (3.27)	7.24 (3.18)
Mean % Change	-19.5	-20.8	-14.5	-19.1	-17.0	-19.9
p-value[a]		0.742		0.029		0.074
Day 2 PM						
Mean (SD)	6.98 (3.45)	6.62 (3.47)	6.88 (3.45)	6.49 (3.40)	6.93 (3.45)	6.56 (3.43)
Mean % Change	-24.0	-28.5	-21.1	-26.6	-22.6	-27.6
p-value[a]		0.128		0.017		0.005
Day 3 AM						
Mean (SD)	5.98 (3.62)	5.56 (3.47)	5.98 (3.61)	5.44 (3.40)	5.98 (3.61)	5.50 (3.44)
Mean % Change	-34.3	-40.0	-31.3	-39.0	-32.8	-39.5
p-value[a]		0.075		0.003		<0.001
Day 3 PM						
Mean (SD)	5.48 (3.73)	5.01 (3.50)	5.56 (3.57)	5.00 (3.47)	5.52 (3.65)	5.01 (3.49)
Mean % Change	-40.1	-45.8	-36.2	-44.1	-38.2	-45.0
p-value[a]		0.049		0.002		<0.001
Day 4 AM						
Mean (SD)	4.89 (3.76)	4.34 (3.48)	4.68 (3.33)	4.16 (3.30)	4.78 (3.55)	4.25 (3.39)
Mean % Change	-46.7	-53.0	-46.6	-53.6	-46.7	-53.3
p-value[a]		0.019		0.002		<0.001
Day 4 PM						
Mean (SD)	4.48 (3.65)	3.98 (3.46)	4.40 (3.40)	3.91 (3.36)	4.44 (3.53)	3.95 (3.41)
Mean % Change	-51.0	-57.1	-49.9	-56.5	-50.4	-56.8
p-value[a]		0.031		0.005		<0.001
Day 5 AM						
Mean (SD)	3.99 (3.62)	3.49 (3.26)	3.90 (3.30)	3.44 (3.25)	3.94 (3.46)	3.47 (3.25)
Mean % Change	-56.2	-62.2	-56.1	-62.0	-56.1	-62.1
p-value[a]		0.023		0.007		<0.001
Day 5 PM						
Mean (SD)	3.84 (3.66)	3.29 (3.33)	3.65 (3.33)	3.23 (3.31)	3.75 (3.50)	3.26 (3.32)
Mean % Change	-57.5	-64.6	-59.0	-64.7	-58.3	-64.7
p-value[a]		0.014		0.012		<0.001
Day 6 AM						
Mean (SD)	3.39 (3.45)	2.98 (3.14)	3.27 (3.14)	3.02 (3.23)	3.33 (3.30)	3.00 (3.19)
Mean % Change	-63.1	-67.5	-63.5	-67.1	-63.3	-67.3
p-value[a]		0.052		0.089		0.013
Day 6 PM						
Mean (SD)	3.18 (3.46)	2.82 (3.18)	3.04 (3.21)	2.90 (3.21)	3.11 (3.34)	2.86 (3.19)
Mean % Change	-65.6	-69.4	-66.4	-68.3	-66.0	-68.8
p-value[a]		0.095		0.258		0.058

[a] p-values were calculated from an ANOVA of total cold symptom severity score with effects for study, baseline total symptom severity score (covariate), treatment, smoking status, and pre-enrollment use of cold symptom relief medication.

NOTE: The last-observation-carried-forward approach was used to impute missing values.

Table 8. Change From Baseline in Rhinorrhea Severity Scores by Day During the Treatment Period – ITT Patients

	843-043		843-044		Pooled	
	Placebo	Pleconaril	Placebo	Pleconaril	Placebo	Pleconaril
ITT	**526**	**526**	**524**	**520**	**1050**	**1046**
Before First Dose						
Mean (SD)	2.41 (0.50)	2.39 (0.49)	2.38 (0.50)	2.39 (0.50)	2.39 (0.50)	2.39 (0.49)
Day 1 PM						
Mean (SD)	1.82 (0.77)	1.86 (0.78)	1.89 (0.75)	1.83 (0.83)	1.86 (0.76)	1.84 (0.80)
Mean Change	-0.59	-0.54	-0.48	-0.57	-0.54	-0.55
p-value[a]		0.480		0.100		0.498
Day 2 AM						
Mean (SD)	1.63 (0.83)	1.65 (0.83)	1.76 (0.80)	1.61 (0.83)	1.70 (0.82)	1.63 (0.83)
Mean Change	-0.77	-0.74	-0.62	-0.78	-0.70	-0.76
p-value[a]		0.600		0.003		0.080
Day 2 PM						
Mean (SD)	1.48 (0.84)	1.49 (0.86)	1.53 (0.86)	1.43 (0.86)	1.51 (0.85)	1.46 (0.86)
Mean Change	-0.93	-0.90	-0.85	-0.97	-0.89	-0.93
p-value[a]		0.718		0.022		0.176
Day 3 AM						
Mean (SD)	1.31 (0.87)	1.25 (0.85)	1.36 (0.85)	1.20 (0.81)	1.34 (0.86)	1.22 (0.83)
Mean Change	-1.10	-1.15	-1.02	-1.19	-1.06	-1.17
p-value[a]		0.390		0.001		0.004
Day 3 PM						
Mean (SD)	1.14 (0.88)	1.08 (0.90)	1.20 (0.86)	1.04 (0.85)	1.17 (0.87)	1.06 (0.87)
Mean Change	-1.27	-1.32	-1.18	-1.35	-1.22	-1.33
p-value[a]		0.492		0.002		0.008
Day 4 AM						
Mean (SD)	1.06 (0.87)	1.02 (0.85)	1.06 (0.80)	0.92 (0.81)	1.06 (0.83)	0.97 (0.83)
Mean Change	-1.34	-1.38	-1.32	-1.48	-1.33	-1.43
p-value[a]		0.654		0.005		0.024
Day 4 PM						
Mean (SD)	0.95 (0.87)	0.88 (0.83)	0.95 (0.83)	0.83 (0.80)	0.95 (0.85)	0.86 (0.82)
Mean Change	-1.46	-1.51	-1.43	-1.57	-1.44	-1.54
p-value[a]		0.473		0.019		0.032
Day 5 AM						
Mean (SD)	0.86 (0.86)	0.82 (0.84)	0.89 (0.80)	0.77 (0.79)	0.88 (0.83)	0.79 (0.82)
Mean Change	-1.54	-1.58	-1.48	-1.62	-1.51	-1.60
p-value[a]		0.603		0.007		0.026
Day 5 PM						
Mean (SD)	0.78 (0.85)	0.73 (0.80)	0.81 (0.80)	0.69 (0.79)	0.80 (0.82)	0.71 (0.80)
Mean Change	-1.62	-1.67	-1.57	-1.71	-1.60	-1.69
p-value[a]		0.486		0.010		0.022
Day 6 AM						
Mean (SD)	0.74 (0.83)	0.72 (0.78)	0.79 (0.79)	0.69 (0.79)	0.77 (0.81)	0.70 (0.78)
Mean Change	-1.66	-1.67	-1.59	-1.71	-1.63	-1.69
p-value[a]		0.871		0.044		0.128
Day 6 PM						
Mean (SD)	0.66 (0.81)	0.64 (0.76)	0.69 (0.78)	0.63 (0.77)	0.68 (0.80)	0.64 (0.76)
Mean Change	-1.74	-1.75	-1.69	-1.77	-1.71	-1.76
p-value[a]		0.940		0.193		0.332

[a] p-values were calculated from a Wilcoxon's rank-sum test of changes from baseline.
NOTE: Only patients with that symptom (score ≥1) at baseline were included in the analysis.

Table 9. Change From Baseline in Nasal Congestion Severity Scores by Day During the Treatment Period – ITT Patients

	843-043		843-044		Pooled	
	Placebo	**Pleconaril**	**Placebo**	**Pleconaril**	**Placebo**	**Pleconaril**
ITT	**526**	**526**	**524**	**520**	**1050**	**1046**
Before First Dose Mean (SD)	2.00 (0.61)	2.07 (0.57)	1.96 (0.57)	2.00 (0.62)	1.98 (0.59)	2.03 (0.60)
Day 1 PM Mean (SD) Mean Change p-value[a]	1.66 (0.81) -0.34	1.73 (0.76) -0.34 0.909	1.63 (0.78) -0.33	1.72 (0.77) -0.28 0.178	1.64 (0.80) -0.33	1.72 (0.77) -0.31 0.428
Day 2 AM Mean (SD) Mean Change p-value[a]	1.48 (0.81) -0.52	1.54 (0.78) -0.52 0.938	1.54 (0.80) -0.42	1.51 (0.81) -0.49 0.262	1.51 (0.80) -0.47	1.52 (0.79) -0.51 0.452
Day 2 PM Mean (SD) Mean Change p-value[a]	1.35 (0.80) -0.64	1.41 (0.81) -0.66 0.808	1.45 (0.85) -0.50	1.37 (0.82) -0.62 0.059	1.40 (0.82) -0.57	1.39 (0.81) -0.64 0.130
Day 3 AM Mean (SD) Mean Change p-value[a]	1.20 (0.80) -0.79	1.23 (0.82) -0.84 0.379	1.28 (0.84) -0.68	1.15 (0.80) -0.85 0.006	1.24 (0.82) -0.74	1.19 (0.81) -0.84 0.010
Day 3 PM Mean (SD) Mean Change p-value[a]	1.15 (0.80) -0.85	1.10 (0.79) -0.97 0.055	1.19 (0.79) -0.77	1.09 (0.79) -0.90 0.032	1.17 (0.80) -0.81	1.10 (0.79) -0.94 0.004
Day 4 AM Mean (SD) Mean Change p-value[a]	1.02 (0.80) -0.98	0.99 (0.81) -1.08 0.118	1.01 (0.76) -0.94	0.95 (0.78) -1.05 0.032	1.02 (0.78) -0.96	0.97 (0.80) -1.06 0.008
Day 4 PM Mean (SD) Mean Change p-value[a]	0.91 (0.79) -1.09	0.91 (0.79) -1.16 0.333	0.95 (0.77) -1.00	0.87 (0.78) -1.12 0.021	0.93 (0.78) -1.05	0.89 (0.79) -1.14 0.020
Day 5 AM Mean (SD) Mean Change p-value[a]	0.83 (0.80) -1.16	0.82 (0.79) -1.25 0.188	0.85 (0.77) -1.10	0.81 (0.77) -1.18 0.103	0.84 (0.78) -1.13	0.82 (0.78) -1.21 0.036
Day 5 PM Mean (SD) Mean Change p-value[a]	0.77 (0.82) -1.23	0.75 (0.78) -1.32 0.255	0.80 (0.76) -1.16	0.76 (0.79) -1.23 0.084	0.78 (0.79) -1.19	0.76 (0.78) -1.28 0.041
Day 6 AM Mean (SD) Mean Change p-value[a]	0.68 (0.77) -1.32	0.67 (0.75) -1.40 0.180	0.71 (0.77) -1.25	0.71 (0.76) -1.29 0.386	0.69 (0.77) -1.28	0.69 (0.76) -1.35 0.114
Day 6 PM Mean (SD) Mean Change p-value[a]	0.65 (0.77) -1.34	0.64 (0.74) -1.43 0.158	0.65 (0.76) -1.31	0.66 (0.75) -1.34 0.787	0.65 (0.77) -1.33	0.65 (0.74) -1.38 0.218

[a] p-values were calculated from a Wilcoxon's rank-sum test of changes from baseline.

NOTE: Only patients with that symptom (score ≥1) at baseline were included in the analysis.

Table 10. Change From Baseline in Cough Severity Scores by Day During the Treatment Period – ITT Patients

	843-043		843-044		Pooled	
	Placebo	**Pleconaril**	**Placebo**	**Pleconaril**	**Placebo**	**Pleconaril**
ITT	**526**	**526**	**524**	**520**	**1050**	**1046**
Before First Dose Mean (SD)	1.54 (0.64)	1.55 (0.62)	1.51 (0.62)	1.57 (0.66)	1.53 (0.63)	1.56 (0.64)
Day 1 PM Mean (SD) Mean Change p-value[a]	1.29 (0.74) -0.25	1.30 (0.78) -0.25 0.983	1.29 (0.77) -0.22	1.34 (0.79) -0.24 0.789	1.29 (0.75) -0.23	1.32 (0.78) -0.25 0.862
Day 2 AM Mean (SD) Mean Change p-value[a]	1.25 (0.78) -0.29	1.27 (0.79) -0.29 0.965	1.25 (0.82) -0.26	1.26 (0.82) -0.32 0.369	1.25 (0.80) -0.28	1.26 (0.81) -0.30 0.510
Day 2 PM Mean (SD) Mean Change p-value[a]	1.21 (0.82) -0.33	1.17 (0.82) -0.38 0.349	1.19 (0.86) -0.32	1.19 (0.85) -0.38 0.364	1.20 (0.84) -0.33	1.18 (0.84) -0.38 0.193
Day 3 AM Mean (SD) Mean Change p-value[a]	1.14 (0.83) -0.40	1.05 (0.82) -0.50 0.092	1.16 (0.88) -0.35	1.12 (0.89) -0.45 0.093	1.15 (0.85) -0.37	1.09 (0.85) -0.48 0.017
Day 3 PM Mean (SD) Mean Change p-value[a]	1.07 (0.86) -0.47	1.0 (0.83) -0.55 0.198	1.15 (0.87) -0.36	1.10 (0.93) -0.47 0.057	1.11 (0.87) -0.42	1.05 (0.88) -0.51 0.023
Day 4 AM Mean (SD) Mean Change p-value[a]	1.03 (0.92) -0.51	0.90 (0.84) -0.65 0.041	1.07 (0.89) -0.44	0.96 (0.87) -0.61 0.020	1.05 (0.91) -0.47	0.93 (0.86) -0.63 0.002
Day 4 PM Mean (SD) Mean Change p-value[a]	0.95 (0.91) -0.59	0.87 (0.83) -0.69 0.233	1.02 (0.92) -0.49	0.93 (0.91) -0.64 0.030	0.99 (0.92) -0.54	0.90 (0.87) -0.67 0.017
Day 5 AM Mean (SD) Mean Change p-value[a]	0.88 (0.91) -0.66	0.79 (0.80) -0.76 0.215	0.94 (0.90) -0.57	0.85 (0.93) -0.72 0.029	0.91 (0.91) -0.62	0.82 (0.87) -0.74 0.016
Day 5 PM Mean (SD) Mean Change p-value[a]	0.88 (0.91) -0.66	0.78 (0.85) -0.77 0.112	0.91 (0.88) -0.60	0.80 (0.89) -0.77 0.013	0.90 (0.89) -0.63	0.79 (0.87) -0.77 0.004
Day 6 AM Mean (SD) Mean Change p-value[a]	0.79 (0.85) -0.75	0.71 (0.81) -0.85 0.184	0.83 (0.87) -0.68	0.77 (0.90) -0.80 0.059	0.81 (0.85) -0.72	0.74 (0.86) -0.82 0.024
Day 6 PM Mean (SD) Mean Change p-value[a]	0.72 (0.82) -0.82	0.70 (0.83) -0.86 0.680	0.79 (0.86) -0.72	0.74 (0.90) -0.83 0.068	0.75 (0.84) -0.77	0.72 (0.86) -0.84 0.120

[a] p-values were calculated from a Wilcoxon's rank-sum test of changes from baseline.

NOTE: Only patients with that symptom (score ≥1) at baseline were included in the analysis.

Table 11. Change From Baseline in Pharyngeal Severity Scores by Day During the Treatment Period – ITT Patients

	843-043		843-044		Pooled	
	Placebo	Pleconaril	Placebo	Pleconaril	Placebo	Pleconaril
ITT	**526**	**526**	**524**	**520**	**1050**	**1046**
Before First Dose Mean (SD)	1.82 (0.66)	1.71 (0.63)	1.74 (0.62)	1.73 (0.62)	1.78 (0.64)	1.72 (0.63)
Day 1 PM Mean (SD) Mean Change p-value[a]	1.38 (0.78) -0.44	1.29 (0.81) -0.43 0.832	1.37 (0.79) -0.37	1.33 (0.76) -0.41 0.487	1.37 (0.78) -0.41	1.31 (0.79) -0.42 0.759
Day 2 AM Mean (SD) Mean Change p-value[a]	1.14 (0.83) -0.68	1.03 (0.85) -0.68 0.966	1.10 (0.83) -0.64	1.07 (0.79) -0.66 0.612	1.12 (0.83) -0.66	1.04 (0.82) -0.67 0.706
Day 2 PM Mean (SD) Mean Change p-value[a]	1.02 (0.84) -0.80	0.89 (0.82) -0.82 0.798	0.98 (0.82) -0.75	0.89 (0.82) -0.84 0.100	1.00 (0.83) -0.78	0.89 (0.82) -0.83 0.184
Day 3 AM Mean (SD) Mean Change p-value[a]	0.83 (0.84) -0.98	0.72 (0.80) -0.99 0.961	0.81 (0.86) -0.93	0.71 (0.80) -1.02 0.120	0.82 (0.85) -0.96	0.72 (0.80) -1.01 0.265
Day 3 PM Mean (SD) Mean Change p-value[a]	0.77 (0.86) -1.05	0.68 (0.81) -1.04 0.865	0.72 (0.81) -1.02	0.63 (0.78) -1.10 0.189	0.74 (0.84) -1.03	0.65 (0.80) -1.07 0.439
Day 4 AM Mean (SD) Mean Change p-value[a]	0.64 (0.81) -1.18	0.54 (0.78) -1.17 0.881	0.56 (0.77) -1.17	0.50 (0.70) -1.24 0.384	0.60 (0.79) -1.17	0.52 (0.74) -1.20 0.479
Day 4 PM Mean (SD) Mean Change p-value[a]	0.61 (0.76) -1.21	0.47 (0.74) -1.24 0.543	0.53 (0.75) -1.20	0.47 (0.71) -1.26 0.401	0.57 (0.75) -1.21	0.47 (0.72) -1.25 0.308
Day 5 AM Mean (SD) Mean Change p-value[a]	0.54 (0.79) -1.28	0.42 (0.70) -1.30 0.977	0.46 (0.72) -1.28	0.38 (0.68) -1.35 0.250	0.50 (0.76) -1.28	0.40 (0.69) -1.33 0.450
Day 5 PM Mean (SD) Mean Change p-value[a]	0.53 (0.79) -1.29	0.41 (0.72) -1.30 0.891	0.42 (0.71) -1.31	0.37 (0.68) -1.37 0.546	0.47 (0.76) -1.30	0.39 (0.70) -1.33 0.762
Day 6 AM Mean (SD) Mean Change p-value[a]	0.44 (0.71) -1.38	0.35 (0.66) -1.36 0.623	0.36 (0.67) -1.37	0.34 (0.64) -1.39 0.748	0.40 (0.69) -1.38	0.35 (0.65) -1.38 0.887
Day 6 PM Mean (SD) Mean Change p-value[a]	0.44 (0.72) -1.38	0.32 (0.64) -1.39 0.951	0.34 (0.67) -1.40	0.32 (0.65) -1.41 0.749	0.39 (0.69) -1.39	0.32 (0.64) -1.40 0.793

[a] p-values were calculated from a Wilcoxon's rank-sum test of changes from baseline.

NOTE: Only patients with that symptom (score ≥1) at baseline were included in the analysis.

Table 12. Change From Baseline in Malaise Severity Scores by Day During the Treatment Period – ITT Patients

	843-043		843-044		Pooled	
	Placebo	Pleconaril	Placebo	Pleconaril	Placebo	Pleconaril
ITT	**526**	**526**	**524**	**520**	**1050**	**1046**
Before First Dose						
Mean (SD)	1.89 (0.76)	1.81 (0.74)	1.74 (0.71)	1.77 (0.74)	1.82 (0.74)	1.79 (0.74)
Day 1 PM						
Mean (SD)	1.68 (0.85)	1.72 (0.86)	1.63 (0.84)	1.65 (0.84)	1.65 (0.84)	1.68 (0.85)
Mean Change	-0.21	-0.10	-0.12	-0.12	-0.17	-0.11
p-value[a]		0.032		0.802		0.090
Day 2 AM						
Mean (SD)	1.41 (0.87)	1.45 (0.87)	1.48 (0.88)	1.38 (0.81)	1.45 (0.88)	1.42 (0.84)
Mean Change	-0.48	-0.36	-0.26	-0.39	-0.37	-0.38
p-value[a]		0.069		0.052		0.947
Day 2 PM						
Mean (SD)	1.37 (0.89)	1.31 (0.84)	1.36 (0.87)	1.30 (0.86)	1.37 (0.88)	1.30 (0.85)
Mean Change	-0.51	-0.50	-0.38	-0.47	-0.45	-0.49
p-value[a]		0.786		0.147		0.399
Day 3 AM						
Mean (SD)	1.08 (0.86)	1.11 (0.89)	1.10 (0.93)	1.02 (0.85)	1.09 (0.90)	1.07 (0.87)
Mean Change	-0.81	-0.70	-0.64	-0.75	-0.73	-0.73
p-value[a]		0.121		0.206		0.836
Day 3 PM						
Mean (SD)	1.00 (0.90)	0.96 (0.85)	1.03 (0.87)	0.95 (0.85)	1.02 (0.88)	0.95 (0.85)
Mean Change	-0.88	-0.85	-0.71	-0.82	-0.80	-0.84
p-value[a]		0.635		0.126		0.450
Day 4 AM						
Mean (SD)	0.82 (0.91)	0.76 (0.83)	0.76 (0.81)	0.70 (0.80)	0.79 (0.86)	0.73 (0.82)
Mean Change	-1.07	-1.05	-0.98	-1.07	-1.02	-1.06
p-value[a]		0.622		0.121		0.495
Day 4 PM						
Mean (SD)	0.80 (0.90)	0.74 (0.83)	0.73 (0.81)	0.69 (0.81)	0.76 (0.86)	0.71 (0.82)
Mean Change	-1.09	-1.08	-1.02	-1.08	-1.05	-1.08
p-value[a]		0.794		0.297		0.609
Day 5 AM						
Mean (SD)	0.68 (0.86)	0.57 (0.77)	0.58 (0.78)	0.57 (0.77)	0.63 (0.82)	0.57 (0.77)
Mean Change	-1.21	-1.25	-1.16	-1.20	-1.19	-1.22
p-value[a]		0.719		0.422		0.408
Day 5 PM						
Mean (SD)	0.68 (0.89)	0.54 (0.77)	0.56 (0.77)	0.58 (0.79)	0.62 (0.84)	0.56 (0.78)
Mean Change	-1.21	-1.27	-1.18	-1.19	-1.19	-1.23
p-value[a]		0.459		0.592		0.350
Day 6 AM						
Mean (SD)	0.58 (0.82)	0.47 (0.71)	0.47 (0.72)	0.47 (0.75)	0.53 (0.77)	0.47 (0.73)
Mean Change	-1.31	-1.34	-1.27	-1.30	-1.29	-1.32
p-value[a]		0.714		0.529		0.473
Day 6 PM						
Mean (SD)	0.55 (0.83)	0.45 (0.73)	0.47 (0.73)	0.49 (0.77)	0.51 (0.78)	0.47 (0.75)
Mean Change	-1.34	-1.36	-1.27	-1.28	-1.30	-1.32
p-value[a]		0.844		0.647		0.628

[a] p-values were calculated from a Wilcoxon's rank-sum test of changes from baseline.
NOTE: Only patients with that symptom (score ≥1) at baseline were included in the analysis.

Table 13. Change From Baseline in Myalgia Severity Scores by Day During the Treatment Period – ITT Patients

	843-043		843-044		Pooled	
	Placebo	Pleconaril	Placebo	Pleconaril	Placebo	Pleconaril
ITT	**526**	**526**	**524**	**520**	**1050**	**1046**
Before First Dose						
Mean (SD)	1.56 (0.64)	1.54 (0.62)	1.47 (0.61)	1.48 (0.63)	1.52 (0.63)	1.51 (0.62)
Day 1 PM						
Mean (SD)	1.47 (0.77)	1.35 (0.80)	1.44 (0.82)	1.43 (0.82)	1.46 (0.79)	1.39 (0.81)
Mean Change	-0.09	-0.19	-0.04	-0.05	-0.07	-0.12
p-value[a]		0.228		0.738		0.281
Day 2 AM						
Mean (SD)	1.34 (0.82)	1.13 (0.86)	1.23 (0.85)	1.17 (0.77)	1.29 (0.83)	1.15 (0.82)
Mean Change	-0.23	-0.41	-0.24	-0.32	-0.23	-0.36
p-value[a]		0.020		0.465		0.029
Day 2 PM						
Mean (SD)	1.25 (0.84)	1.01 (0.88)	1.13 (0.82)	1.01 (0.82)	1.19 (0.84)	1.01 (0.85)
Mean Change	-0.31	-0.53	-0.34	-0.47	-0.33	-0.50
p-value[a]		0.005		0.149		0.003
Day 3 AM						
Mean (SD)	0.96 (0.85)	0.78 (0.83)	0.90 (0.83)	0.81 (0.81)	0.93 (0.84)	0.79 (0.82)
Mean Change	-0.61	-0.76	-0.58	-0.67	-0.59	-0.72
p-value[a]		0.056		0.348		0.042
Day 3 PM						
Mean (SD)	0.83 (0.85)	0.66 (0.79)	0.83 (0.78)	0.71 (0.79)	0.83 (0.82)	0.69 (0.79)
Mean Change	-0.73	-0.88	-0.64	-0.77	-0.69	-0.83
p-value[a]		0.079		0.149		0.023
Day 4 AM						
Mean (SD)	0.75 (0.85)	0.55 (0.78)	0.68 (0.74)	0.55 (0.77)	0.72 (0.80)	0.55 (0.77)
Mean Change	-0.82	-0.99	-0.79	-0.93	-0.81	-0.96
p-value[a]		0.021		0.053		0.003
Day 4 PM						
Mean (SD)	0.66 (0.81)	0.51 (0.78)	0.65 (0.72)	0.53 (0.73)	0.65 (0.77)	0.52 (0.75)
Mean Change	-0.91	-1.03	-0.83	-0.95	-0.87	-0.99
p-value[a]		0.072		0.100		0.016
Day 5 AM						
Mean (SD)	0.54 (0.81)	0.41 (0.69)	0.52 (0.72)	0.42 (0.71)	0.53 (0.77)	0.41 (0.70)
Mean Change	-1.02	-1.13	-0.95	-1.07	-0.99	-1.10
p-value[a]		0.184		0.106		0.038
Day 5 PM						
Mean (SD)	0.52 (0.82)	0.43 (0.73)	0.48 (0.70)	0.39 (0.72)	0.50 (0.76)	0.41 (0.72)
Mean Change	-1.04	-1.11	-0.99	-1.09	-1.02	-1.10
p-value[a]		0.377		0.150		0.104
Day 6 AM						
Mean (SD)	0.45 (0.74)	0.34 (0.64)	0.41 (0.67)	0.35 (0.64)	0.43 (0.71)	0.35 (0.64)
Mean Change	-1.11	-1.20	-1.06	-1.13	-1.09	-1.16
p-value[a]		0.220		0.533		0.179
Day 6 PM						
Mean (SD)	0.44 (0.74)	0.34 (0.64)	0.43 (0.70)	0.36 (0.64)	0.43 (0.72)	0.35 (0.64)
Mean Change	-1.13	-1.20	-1.05	-1.12	-1.09	-1.16
p-value[a]		0.356		0.451		0.226

[a] p-values were calculated from a Wilcoxon's rank-sum test of changes from baseline.

NOTE: Only patients with that symptom (score ≥1) at baseline were included in the analysis.

Table 14. Subgroup Analyses of the Primary Endpoint Subset by Demographic Factors – ITT Patients, Pooled

Factor	Statistic	Placebo	Pleconaril	p-value[a]
Gender				
Male	Patients reaching endpoint/patients analyzed Median days	264/328 (80%) 6.1	266/327 (81%) 5.7	 0.141
Female	Patients reaching endpoint/patients analyzed Median days	564/722 (78%) 7.3	587/719 (82%) 6.8	 0.030
Race				
White	Patients reaching endpoint/patients analyzed Median days	691/875 (79%) 7.1	706/864 (82%) 6.3	 0.004
Non-white	Patients reaching endpoint/patients analyzed Median days	137/175 (78%) 5.7	147/182 (81%) 6.1	 0.890
Age Group				
18-44 years	Patients reaching endpoint/patients analyzed Median days	615/761 (81%) 6.8	647/772 (84%) 6.2	 0.022
45-64 years	Patients reaching endpoint/patients analyzed Median days	189/248 (76%) 7.2	175/235 (74%) 6.9	 0.545
>64 years	Patients reaching endpoint/patients analyzed Median days	24/41 (59%) 10.0	31/39 (79%) 7.8	 0.077

[a] p-values were calculated from a Wilcoxon test (strata: study, smoking status, and pre-enrollment use of cold symptom relief medication).

Appendix D Additional Safety Data

Table 1. Treatment-Emergent Adverse Events (≥2% in Any Treatment Group) – Adult Phase II/III Studies – All Treated Patients

	Placebo	Pleconaril		
		200 mg TID	400 mg BID	400 mg TID
Number of treated patients	**2225**	**426**	**331**	**2111**
Number of treated patients with ≥1 AE	1193 (54%)	257 (60%)	145 (44%)	1169 (55%)
Headache	388 (17%)	57 (13%)	22 (7%)	403 (19%)
Diarrhea	200 (9%)	38 (9%)	44 (13%)	215 (10%)
Nausea	110 (5%)	52 (12%)	27 (8%)	171 (8%)
Abdominal pain	79 (4%)	19 (4%)	19 (6%)	75 (4%)
Vomiting	61 (3%)	22 (5%)	14 (4%)	72 (3%)
Sinusitis	45 (2%)	7 (2%)	3 (1%)	53 (3%)
Bronchitis	54 (2%)	11 (3%)	4 (1%)	50 (2%)
Dyspepsia	42 (2%)	14 (3%)	7 (2%)	47 (2%)
Rhinitis	55 (2%)	17 (4%)	4 (1%)	45 (2%)
Dizziness	38 (2%)	20 (5%)	3 (1%)	44 (2%)
Pain	52 (2%)	13 (3%)	3 (1%)	43 (2%)
Fever	42 (2%)	5 (1%)	0	42 (2%)
Cough increased	36 (2%)	9 (2%)	2 (1%)	36 (2%)
Pharyngitis	38 (2%)	16 (4%)	5 (2%)	33 (2%)
Back pain	47 (2%)	33 (8%)	3 (1%)	29 (1%)
Myalgia	25 (1%)	12 (3%)	1 (<1%)	24 (1%)
Dysmenorrhea[#]	16 (1%)	3 (1%)	6 (3%)	24 (2%)
Ear pain	22 (1%)	8 (2%)	4 (1%)	22 (1%)
Constipation	15 (1%)	18 (4%)	2 (1%)	21 (1%)
Asthenia	23 (1%)	13 (3%)	2 (1%)	17 (1%)
Urinary tract infection	14 (1%)	2 (<1%)	6 (2%)	17 (1%)
Insomnia	32 (1%)	10 (2%)	2 (1%)	16 (1%)
Anorexia	8 (<1%)	8 (2%)	0	16 (1%)
Rash	18 (1%)	8 (2%)	5 (2%)	15 (1%)
Asthma	15 (1%)	0	5 (2%)	11 (1%)
Tinnitus	6 (<1%)	8 (2%)	0	9 (<1%)
Pruritus	7 (<1%)	10 (2%)	1 (<1%)	5 (<1%)

[#]Signifies a gender-specific term.

Table 2. Severe Treatment-Emergent Adverse Events (≥0.5% in Any Treatment Group) – Adult Phase II/III Studies – All Treated Patients

	Placebo	Pleconaril		
		200 mg TID	400 mg BID	400 mg TID
Number of treated patients	**2225**	**426**	**331**	**2111**
Number of treated patients with ≥1 AE	1193 (54%)	257 (60%)	145 (44%)	1169 (55%)
Number of treated patients with ≥1 severe AE	117 (5%)	36 (8%)	15 (5%)	103 (5%)
Headache	40 (1.8%)	13 (3.1%)	2 (0.6%)	33 (1.6%)
Diarrhea	8 (0.4%)	1 (0.2%)	9 (2.7%)	17 (0.8%)
Nausea	16 (0.7%)	11 (2.6%)	3 (0.9%)	10 (0.4%)
Vomiting	10 (0.4%)	5 (1.2%)	0	10 (0.4%)
Abdominal pain	6 (0.3%)	0	4 (1.2%)	5 (0.2%)
Back pain	5 (0.2%)	3 (0.7%)	0	1 (<0.1%)
Meningitis[a]	0	3 (0.7%)	0	1 (<0.1%)

[a] All meningitis events occurred in patients enrolled in studies of viral meningitis.

Table 3. Adverse Events That Resulted in Discontinuation of Treatment (≥0.5% in Any Treatment Group) – Adult Phase II/III Studies – All Treated Patients

	Placebo	Pleconaril		
		200 mg TID	400 mg BID	400 mg TID
Number of treated patients	**2225**	**426**	**331**	**2111**
Number of patients discontinued due to an adverse event[a]	76 (3%)	23 (5%)	19 (6%)	97 (5%)
Nausea	13 (0.6%)	9 (2.1%)	7 (2.1%)	22 (1.0%)
Vomiting	8 (0.4%)	11 (2.5%)	5 (1.5%)	20 (0.9%)
Diarrhea	10 (0.4%)	2 (0.5%)	6 (1.8%)	24 (1.1%)
Abdominal pain	8 (0.4%)	1 (0.2%)	6 (1.8%)	6 (0.3%)

[a] A patient may have had more than one adverse event that resulted in discontinuation of treatment.

Table 4. Serious Adverse Events – Adult Patients Treated in Phase II/III Studies

	Placebo	Pleconaril		
		200 mg TID	400 mg BID	400 mg TID
Number of treated patients	**2225**	**426**	**331**	**2111**
Total number with serious adverse events	20 (1%)	13 (3%)	1 (<1%)	15 (1%)
Number in meningitis studies	13	13	0	7
Number in VRI studies	7	0	1	8

NOTE: The analysis of serious adverse events showed:

- The majority of the serious adverse events reported were considered not related to study drug.
- Serious adverse events considered related to study drug included:
  - headache (2 meningitis placebo patients)
  - abortion (1 meningitis placebo patient)
  - headache and nausea (1 meningitis pleconaril 200 mg TID patient)
  - vomiting (1 meningitis pleconaril 400 mg TID patient)
  - tachycardia (1 VRI pleconaril 400 mg TID patient)
  - accidental overdose (1 VRI pleconaril 400 mg TID patient)
  - overdose (1 meningitis pleconaril 400 mg TID patient) - however, causality was not assessed.
- The most common serious adverse event reported was headache, which could have been associated with the patients' underlying disease (cold or meningitis) in some cases.

Table 5. Clinical Laboratory Evaluations: Median Change From Baseline to End of Treatment – Adult Phase II/III Studies – All-Treated Patients

	Placebo		Pleconaril					
			200 mg TID		400 mg BID		400 mg TID	
No. of Treated Patients[a]	**2225**		**426**		**331**		**2111**	
Laboratory parameter (units)	**Baseline median**	**Median change**	**Baseline median**	**Median change**	**Baseline median**	**Median change**	**Baseline median**	**Median change**
HEMATOLOGY								
Hematocrit (%)	41.0	-0.5	41.2	0.2	40.8	-0.3	41.0	0.0
Hemoglobin (g/dL)	13.8	-0.1	13.7	0.1			13.9	-0.1
Platelets ($x10^3/mm^3$)	247.0	12.0	229.0	37.0	242.0	18.0	253.0	18.0
RBC count ($x10^6/mm^3$)	4.7	0.0	4.7	0.0			4.7	0.0
WBC count ($x10^3/mm^3$)	7.8	-0.6	7.5	-0.5	7.3	-0.3	7.9	-0.6
CLINICAL CHEMISTRIES								
Alk. phosphatase (IU/L)	72.0	0.0	81.0	0.0			71.0	1.0
AST/SGOT (IU/L)	20.0	0.0	19.0	-1.0			20.0	-1.0
ALT/SGPT (IU/L)	18.0	0.0	18.0	1.0	17.0	-1.0	18.0	-1.0
Total bilirubin (mg/dL)	0.4	0.0	0.5	-0.1			0.4	-0.1
Protein (g/dL)	7.3	-0.1	7.0	0.1	7.2	-0.1	7.3	0.0
BUN (mg/dL)	12.0	1.0	11.0	1.0	11.0	1.0	12.0	0.0
Creatinine (mg/dL)	0.8	0.0	0.8	0.0	0.7	0.0	0.8	0.0
Cholesterol (mg/dL)	185.0	-2.0	175.0	13.0			184.0	6.0
Triglyceride (mg/dL)	133.0	-1.0					131.5	0.0
Glucose (mg/dL)	91.0	2.0	97.0	-2.0	90.0	2.0	91.0	2.0
LDH (IU/L)	149.0	-1.0					148.0	-2.0
Calcium (mg/dL)	9.3	0.0	8.9	0.1	9.3	0.0	9.4	0.0
Chloride (mEq/L)	104.0	0.0	103.0	0.0	102.0	0.0	104.0	0.0
Potassium (mEq/L)	4.2	0.0	4.0	0.1	4.1	0.0	4.2	0.0
Sodium (mEq/L)	140.0	0.0	140.0	1.0	140.0	0.0	141.0	0.0
Uric Acid (mg/dL)	4.7	0.1	4.4	0.4			4.7	0.4

No=number; Seg=segmented; alk=alkaline

[a] All patients did not have each laboratory parameter assessed.

Table 6. Median Change from Baseline in Serum Cholesterol Levels by Baseline Cholesterol Quartile - Adult Phase II/III Studies – All Treated Patients

Baseline Cholesterol Quartile	Placebo	Pleconaril*	
		200 mg TID	400 mg TID
I (≤158 mg/dL)			
Number of Patients	363	77	378
Baseline median	145	141	143
Median change	3	18	11
II (>158 to ≤184 mg/dL)			
Number of Patients	404	50	396
Baseline median	171	172	173
Median Change	1	18	8
III (>184 to ≤211 mg/dL)			
Number of Patients	400	50	378
Baseline median	196	193	197
Median change	-2	8	5
IV (>211 mg/dL)			
Number of Patients	386	44	400
Baseline median	230	229	233
Median change	-12	3	-1

*Serum cholesterol levels were not assessed in the clinical study with the 400 mg BID dosing regimen.

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