CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER for: 021087

MEDICAL REVIEW(S)

Division Director Memorandum

NDA:	**21-087**
Drug and indication:	**Oseltamivir (Tamiflu™) for treatment of uncomplicated acute illness due to influenza infection in adults who have been symptomatic for no more than two days.**
Dose:	**75 mg. b.i.d. for five days**
Applicant:	**Hoffman-La Roche, Inc.**
Submission dated:	**April 30, 1999**
Date of Memorandum:	**October 25, 1999**

In this application, the sponsor has requested approval for oseltamivir for treatment of uncomplicated influenza in adults. In support of this request, the sponsor has submitted reports of two double-blind, randomized, placebo controlled trials conducted in the United States and internationally during the 1997/1998 influenza season. These trials enrolled a total of 1358 individuals with suspected influenza, of whom 849 were diagnosed with confirmed influenza and received study medication. Additional support for the antiviral activity of oseltamivir against influenza viruses A and B is provided by the results of 3 human challenge studies conducted in normal healthy volunteers. Safety in elderly and medically higher risk individuals is further supported by the interim results of ongoing treatment studies WV15819 and WV15812, respectively. Additionally, the safety of longer-term exposure to oseltamivir is supported by data from prophylaxis studies in adults and the elderly.

I am in concurrence with the consensus of the review team that this application is approvable. Together, the two principal studies suggest that treatment with oseltamivir confers a modest benefit in terms of reducing the duration of uncomplicated influenza illness and that this benefit is appropriately balanced by a reasonable safety profile.

The following issues pertaining to this regulatory action merit comment:

1. Estimation of magnitude of treatment effect

Trials WV15671 and WV15670, conducted in 374 and 475 influenza-infected adults, respectively, each demonstrated that treatment with oseltamivir resulted in a 1.3 day reduction in the median time until symptom improvement (defined as the time when 7 major symptoms were reported as either absent or mild). These consistent results, both between studies and between dose groups, suggest that the observed finding is reproducible and that doses higher than 75 mg bid do not confer additional clinical benefit. The treatment effect observed in the primary endpoint analyses was further supported by analyses of secondary endpoints, including assessment of time to alleviation of individual symptoms and fever.

This efficacy database suggests that treatment with oseltamivir confers a modest clinical benefit in otherwise healthy adults with uncomplicated influenza. Populations for whom safety and efficacy have not been demonstrated will be discussed below.

2. Safety profile

The safety database is derived primarily from experience in 452 and 451 otherwise healthy individuals ages 18 - 65 years, treated with oseltamivir 75 mg bid or 150 mg bid, respectively, for five days, in the two principal trials; 77 individuals over the age of 65 years treated with 75 mg bid for five days (ongoing trial WV15819); 151 individuals with chronic cardiac or pulmonary disease treated with 75 mg bid for five days (ongoing trial WV15812); and additional data on normal healthy volunteers enrolled in human challenge studies. There is additional information on the safety of exposure to 75 mg once (n=710) or twice daily (n=520) for up to 42 days, in trials of influenza prophylaxis in adults and the elderly (trials WV15673, WV15679, and WV15708D).

The safety database suggests that the tolerability of oseltamivir is reasonable for the intended indication and population. The most frequent adverse experiences were nausea and vomiting, which were reported more frequently early in the treatment course and by women. Rates of withdrawal due to adverse events, and reports of serious adverse events were both infrequent.

Because of renal elimination, dose reduction to 75 mg once daily is recommended for individuals with a creatinine clearance less than 30 mL/min. Patients with a creatinine clearance less than 10 mL/min. have not been studied, and caution is recommended for use in this population (see discussion of phase IV commitments).

3. Evidence of effectiveness against influenza B virus

Evidence for the effectiveness of oseltamivir against influenza B virus is limited. In the principal trials, the influenza-positive population included only 3% of patients with influenza B. Based on interim analyses, the sponsor's ongoing studies in elderly and medically higher risk populations appear to be enrolling a somewhat higher proportion of patients with influenza B. However, at this time, there have been insufficient numbers of patients recruited into clinical trials with naturally occurring influenza B to allow definitive conclusions about oseltamivir's efficacy against this strain.

However, the division recognizes both the practical limitations of recruiting sufficient numbers of patients with influenza B into trials, and the fact that clinicians are unlikely to be able to distinguish between influenza A and B in clinical practice. Given these factors, it appears reasonable to allow a more general influenza treatment claim based on the totality of the available information, including data supporting influenza A (the aforementioned efficacy trials) and influenza B (the human challenge studies, *in vitro* evidence, and the biologic plausibility of neuraminidase inhibition with influenza types A and B). However, the label will include information about the limited experience with influenza B and the sponsor will provide additional data on clinical effectiveness against influenza B as a phase IV commitment. Further,

the label states that there is no evidence to support use against agents other than influenza A and B (such as influenza C).

4. Outstanding questions

As previously discussed, this application was focused primarily on demonstration of safety and efficacy in the setting of treatment of uncomplicated influenza. Several patient populations and clinical scenarios merit additional investigation, and these issues are either currently under study or will be addressed as phase IV commitments.

Specifically, this application does not contain information on the following important questions: safety and efficacy in individuals under age 18; effectiveness in individuals over age 65 or in medically higher risk individuals; safety and effectiveness in the setting of prophylaxis and interruption of family transmission; effectiveness in preventing complications due to influenza (such as hospitalization, secondary bacterial infections, or mortality); or the potential for development of viral resistance (see below for further discussion). The label will include precautionary information to state the lack of available data in these areas.

5. Resistance

As noted in the microbiology review, virus with reduced susceptibility has been identified in several settings: *in vitro*, human challenge studies, and clinical trials. Available data also identify a potential for development of cross-resistance between oseltamivir and zanamivir. As noted in the labeling, there is currently insufficient data to fully characterize the risk of emergence in clinical use. The sponsor has agreed to Phase IV commitments to provide additional information on issues related to resistance, cross-resistance and antigenic variation related to oseltamivir exposure.

6. Public health role of antiviral treatment

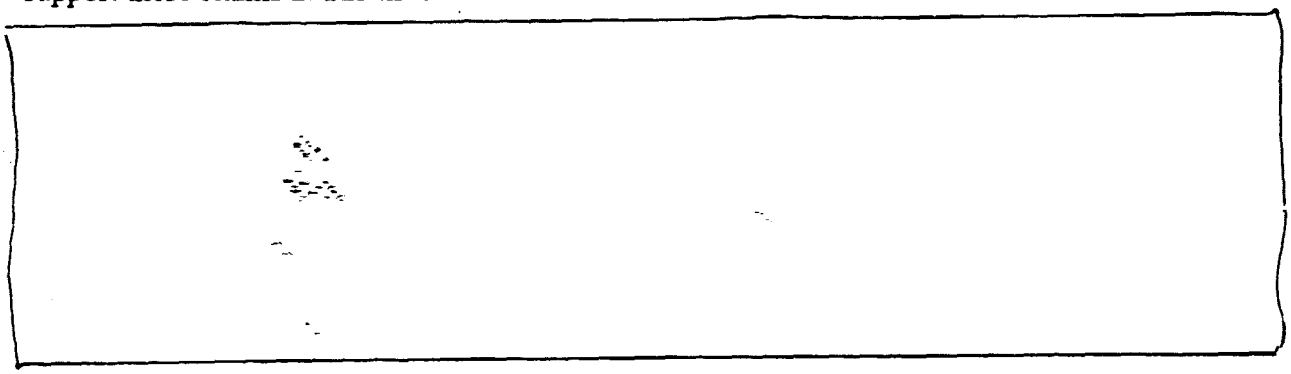
Since the recent approval of zanamivir (July 1999), there has been renewed interest in the role of therapeutic agents for acute influenza. Because this regulatory action coincides with the typical onset of the North American influenza season, it is anticipated that approval of oseltamivir will further stimulate public interest in this topic. Therefore, it is important to comment on the role of influenza treatment in the context of public health and influenza control.

It is extremely important that the public be aware that influenza vaccination remains the primary public health strategy for successful control of influenza, although it is acknowledged that vaccination can not assure absolute protection. Additionally, two other approved antiviral products (amantadine and rimantadine) may play a limited role in prevention strategies. However, once an individual contracts infection and develops influenza symptoms, the role of an antiviral appears to be limited. As demonstrated in the studies submitted in support of the applications for oseltamivir and zanamivir, early antiviral treatment results in only a modest attenuation of the course of clinical illness (approximately one-day shortening in the median duration of major symptoms with both products). Therefore, if promoted to the consumer, balanced promotion should contain information regarding the importance of vaccination, the

reminder that not all viral illness is caused by influenza virus, and the likely modest treatment benefit should a patient and healthcare provider elect to treat influenza with an antiviral medication.

The clinical relevance of the modest treatment benefit is a highly subjective question. It is my opinion that a one-day reduction in the duration of moderate-to-severe symptoms, including fever, is likely to be of clinical importance to many individuals. However, it is ultimately the judgement of the healthcare provider whether use of the product, given the expectation of a modest treatment benefit, is appropriate and indicated for a given patient's circumstance. Because influenza symptoms are self-limited in the majority of individuals, it is anticipated that many persons with influenza will neither require, nor desire treatment with antiviral medication. For those whose illness warrants treatment beyond routine relief medications, approval of oseltamivir allows access to a safe and effective treatment option, when used according to labeled instructions.

More definitive demonstration of clinical or public health relevance with the neuraminidase inhibitors will require additional data, such as studies to demonstrate prevention of influenza transmission or prophylaxis, reduction in influenza-associated complications or mortality, or the pharmacoeconomic gain due to illness shortening. This application does not provide data to support these claims at this time.



The oseltamivir review team should be commended for their excellent collaborative review, which was completed in a priority time frame.

There are no additional outstanding regulatory issues at the time of this action.

/S/

Heidi M. Jolson, M.D., M.P.H.
Director, Division of Antiviral Drug Products

Group Leader's Memorandum
Jeffrey S. Murray M.D., M.P.H.
Medical Officer, Division of Antiviral Drug Products
Oct. 19, 1999

NDA 21-087
Tamiflu™ (oseltamivir) for the treatment of influenza
Hoffmann-La Roche Inc.

I fully concur with Dr. Teresa Wu's detailed clinical review of NDA 21-087 and her recommendation that Tamiflu be approved for the treatment of adults with influenza. The applicant has sufficiently demonstrated that Tamiflu reduces the time to alleviation of influenza symptoms in adults based on two completed clinical studies, one in the U.S. (WV15671) and one outside of the U.S (WV15670). Both studies showed remarkably comparable results with a median reduction in the time to alleviation of symptoms of 1.3 days for Tamiflu compared to placebo. Both studies were robust to sensitivity analyses that evaluated alternate methods for handling censored data. In both studies two doses of Tamiflu, 75 mg and 150 mg ~~bid, were~~ compared to placebo. No difference in treatment effect could be demonstrated between doses; therefore, the 75 mg bid dose will be the recommended dose.

Other clinical study data included in this NDA generally provided additional support for the safety and efficacy of Tamiflu in adults. However, because some of these supportive studies have not been completed or were not fully enrolled, observed treatment differences did not reach statistical significance. Study WV15730, conducted in the Southern Hemisphere, only enrolled 60 patients, but showed a reduction in time to alleviation of symptoms for Tamiflu versus placebo comparable to that of the results of the two pivotal studies. Study WV15819, which evaluated Tamiflu vs placebo in elderly adults aged 65 or greater (n=172) also showed a reduction in the median time to alleviation of symptoms for Tamiflu vs placebo that was comparable to the two pivotal studies. Study WV15812, which evaluated Tamiflu vs. placebo in a group of chronically ill patients, consisting mostly of COPD (chronic obstructive pulmonary disease), did not show a difference between treatment arms for the time to alleviation of symptoms. However, six of the seven protocol symptoms (the composite primary endpoint) were relieved sooner with Tamiflu as compared to placebo. The symptom of fatigue was not relieved sooner; therefore there was no overall difference between treatment groups with respect to the time to alleviation for all symptoms combined. The applicant contends that including fatigue as a symptom for clinically assessing influenza among chronically ill patients may reduce the sensitivity of the symptom score instrument. This explanation is plausible. Overall, the study results do not cast significant doubts regarding the efficacy of Tamiflu.

It should be noted that the vast majority of patients in these studies had influenza, type A. Relatively few patients had type B in the naturally acquired influenza studies. However, challenge studies with type B influenza support the activity of Tamiflu. Given the difficulty of adequately enrolling a sufficient number of patients with type B influenza during most flu seasons, and the fact that in clinical practice influenza type is generally

not known for an individual patient, the division has agreed to allow a more general indication for the treatment of influenza. However, labeling will make it clear that the indication is primarily based on data from patients with naturally acquired influenza A and on challenge studies of subjects infected with attenuated strains of influenza A and B. Further evaluation of the activity of Tamiflu in the treatment of naturally acquired influenza B will be accomplished as part of phase 4 commitments.

Safety was assessed in approximately 1500 patients receiving Tamiflu 75 or 150 mg bid for treatment of influenza and in approximately 1000 subjects receiving 65 mg qd or 75 mg bid in prophylaxis studies (not a pursued indication in this NDA). Aside from gastrointestinal intolerance, primarily nausea and vomiting in up to 12% and 15% of subjects, respectively, Tamiflu appears to be well tolerated. Despite the nausea and vomiting, the frequency of discontinuation of therapy for adverse events was low (< 2%).

Elderly patients and patients with chronic illnesses appeared to tolerate the drug at least as well as healthier subjects. There were no significant differences in any laboratory parameter tested. Serious adverse events were relatively few; no serious adverse event appeared to have a probable relationship with Tamiflu.

In conclusion, Roche's NDA for Tamiflu for the treatment of adult patients with influenza has no deficiencies. The regulatory standards of safety and efficacy have been met.

/S/

Jeffrey S. Murray, M.D., M.P.H.
Medical Team Leader

APPEARS THIS WAY
ON ORIGINAL

Medical Officer Review
Of
NDA 21-087
Tamiflu™ (oseltamivir)
For
Treatment of Influenza

Date Submitted:	04/30/99
Date Completed:	10/12/99
Reviewer:	Teresa C. Wu, M.D., Ph.D.
Applicant:	Hoffmann-La Roche Inc. 340 Kingland Street Nutley, New Jersey 07110-1199
Product Names:	Code: Ro 64-0796 Generic: oseltamivir phosphate Trade: Tamiflu™
Formulation/Dosage:	Capsule (75-mg), 75 mg twice daily for 5 days
Pursued Indication:	Treatment of influenza
NDA Drug Classification:	1P
Related NDA:	NDA 21-036, Relenza (zanamivir for inhalation), Glaxo Wellcome, approved for treatment of influenza on 7/26/99

TABLE OF CONTENTS

1. MATERIALS REVIEWED 5

2. CHEMISTRY AND MANUFACTURING CONTROLS 5

3. ANIMAL PHARMACOLOGY AND TOXICOLOGY 5

4. MICROBIOLOGY 6

5. BIOPHARMACOLOGY 6

6. CLINICAL BACKGROUND 6

6.1 CLINICAL FEATURES 6
6.2 ANTIVIRAL AGENTS 7
6.3 CLINICAL DEVELOPMENT OF RO 64-0796 8

7. CLINICAL TRIALS IN SUPPORT OF THIS APPLICATION 8

7.1 STUDIES IN SUPPORT OF EFFICACY OF RO 64-0796 8
7.2 STUDIES IN SUPPORT OF SAFETY OF RO 64-0796 9

8. TREATMENT TRIALS OF NATURALLY ACQUIRED INFLUENZA 9

8.1 PROTOCOL WV 15671 9
8.1.1 Description of Protocol *10*
8.1.1.1 Objectives 10
8.1.1.2 Patient Eligibility 10
8.1.1.3 Treatment Groups, Drug administration and Compliance 11
8.1.1.4 Diary Card and Schedule of Assessment 11
8.1.1.5 Efficacy Parameters 13
8.1.1.6 Safety Parameters 14
8.1.1.7 Definition of Patient Population 16
8.1.1.8 Missing Primary Efficacy Parameter Data 16
8.1.1.9 Randomization and Planned Sample size 16
8.1.2 Applicant's Presentation of Study Results *17*
8.1.2.1 Patient Disposition and Demographics 17
8.1.2.2 Overview of Analysis Populations 19
8.1.2.3 Subjects Prematurely Withdrawn from the Study 19
8.1.2.4 Time from Symptom Onset to First Study Drug Intake 20
8.1.2.5 Efficacy Results 20
8.1.2.6 Safety Results 26
8.1.3 Reviewer's Assessment and Conclusions *28*
8.2 PROTOCOL WV 15670 30
8.2.1 Description of Protocol *30*
8.2.2 Applicant's Presentation of Study Results *30*
8.2.2.1 Patient Disposition and Demographics 30
8.2.2.2 Overview of Analysis Population 32
8.2.2.3 Subjects Withdrawn Prematurely from the Study 33
8.2.2.4 Time from Symptom Onset to First Study Drug Intake 33
8.2.2.5 Efficacy results 34
8.2.2.6 Safety results 39
8.2.3 Reviewer's Assessment and Conclusions *41*
8.3 PROTOCOL WV 15730 42
8.3.1 Study Design *42*
8.3.2 Results *42*
8.3.2.1 Patient disposition and demographics 42

8.3.2.2 Efficacy results 43
8.3.2.3 Safety 44
8.3.3 Reviewer's Assessment and Conclusions 44
8.4 PROTOCOL WV 15819 45
8.4.1 Results 46
8.4.1.1 Overview of Analysis Populations 46
8.4.1.2 Demograhic Data and Baseline Characteristics 46
8.4.1.3 Efficacy Results 47
8.4.1.4 Safety Results 48
8.4.2 Reviewer's Assessment and Conclusions 49
8.5 PROTOCOL WV 15812 49
8.5.1 Results 50
8.5.1.1 Overview of Analysis Populations 50
8.5.1.2 Demographic Data and Baseline Characteristics 50
8.5.1.3 Efficacy Results 51
8.5.1.4 Safety Results 53
8.5.2 Reviewer's Assessment and Conclusions 53

9. EXPERIMENTAL CHALLENGE TREATMENT STUDIES 54

9.1 PROTOCOL GS 97-801 55
9.1.1 Efficacy results 56
9.1.2 Pharmacokinetic Results 57
9.1.3 Safety Results 57
9.1.4 Reviewer's Assessment and Conclusions 57
9.2 PROTOCOL NP15717 58
9.2.1 Efficacy Results 58
9.2.2 Safety Results 59
9.2.3 Reviewer's Assessment and Conclusions 59
9.3 PROTOCOL NP15827 60
9.3.1 Efficacy Results 60
9.3.2 Safety Results 61
9.3.3 Reviewer's Assessment and Conclusions 61

10 PROPHYLAXIS STUDIES IN NATURALLY ACQUIRED INFLUENZA 61

10.1PROTOCOLS WV15673 AND WV 15679 62
10.1.1 Overall study design 62
10.1.2 Efficacy Results 63
10.1.2.1 Demographics 63
10.1.2.2. Primary Efficacy Parameter: Laboratory Confirmed Clinical Influenza 64
10.1.2.3Secondary Efficacy Parameters 64
10.1.3 Safety Results 65
10.1.3.1 Extent of Exposure to Study Medication 65
10.1.3.2 Subjects Prematurely Withdrawn from the Study 66
10.1.3.3.On-treatment adverse events 66
10.1.3.4 Off-treatment adverse events 66
10.1.3.5 Serious Adverse Events 67
10.2 PROPHYLAXIS STUDY IN ELDERLY :PROTOCOL WV 15708D 67
10.2.1 Efficacy Results 67
10.1.2 Safety Results 68

11 INTEGRATED EVALUATION OF EFFICACY 69

11.1 BASELINE INFECTION TYPE 70
11.2 PRIMARY EFFICACY PARAMETER: TIME TO ALLEVIATION OF ALL SYMPTOMS IN ITTI POPULATION . 70
11.3 ROBUSTNESS ANALYSES 72
11.4 EXPLORATORY ANALYSES 73
11.5 DURATION OF ILLNESS IN THE ITT POPULATION 75
11.6 REDUCTION OF TOTAL SYMPTOM SCORE OVER TIME 76
11.7 VIROLOGY 76

11.8 SEROLOGY 77
11.9 SYMPTOM RELIEF MEDICATION USAGE 77
11.10 SECONDARY ILLNESSES AND ASSOCIATED ANTIBIOTIC USE 78
11.11 EFFICACY AND SUBJECT CHARACTERISTICS (AGE, GENDER, RACE) 78

12 INTEGRATED SUMMARY OF SAFETY 79

12.1 DEMOGRAPHICS 79
12.2 CORE SAFETY STUDIES 80
12.2.1 Adverse Events 80
12.2.2 Events According to Dose and Influenza Status 80
12.2.3 Intensity of Adverse Events, Relationship to Study Treatment 81
12.2.4 Incidence of Adverse Event by Sex, Age, Race, Region and Smoking Status 81
12.2.5 Recrudescence of Influenza-Like Illness 81
12.2.6 Adverse Events in Treatment Studies in the Elderly 83
12.3 SUPPORTING SAFETY DATA 83
12.3.1 Pooled Prophylaxis Studies 83
12.3.2 Adverse Events in Prophylaxis Study in the Elderly 85
12.4 TIME TO EVENT ANALYSIS FOR SELECTED ADVERSE EVENTS 85
12.5 CLINICAL LABORATORY DATA 86
12.6 SERIOUS ADVERSE EVENTS INCLUDING PREGNANCIES 86
12.7 ADVERSE EVENTS LEADING TO PREMATURE WITHDRAWAL 87
12.8 ELECTROCARDIOGRAM CHANGES 88
12.9 PHARMACOKINETIC STUDY IN RENALLY IMPAIRED SUBJECTS (WP15648) 88
12.10 DRUG INTERACTION STUDIES 89
12.10.1 Acetaminophen (WP15676) 89
12.10.2 Cimetidine, Probenicid (NP15728) 89

13 REVIEWER'S OVERALL ASSESSMENT: 91

14. PACKAGE INSERT AND PATIENT PACKAGE INFORMATION 93

15. PHASE 4 COMMITMENTS 93

16. REGULATORY RECOMMENDATION 94

APPEARS THIS WAY
ON ORIGINAL

1. Materials Reviewed

This submission consisted of an archival copy of 363 volumes. The archival copy of sections 11 and 12, which contained patient tabulations and case report summaries, was submitted in electronic form only. In addition to the hard copy, textual and graphical images of this NDA were also provided in CD-ROMS, as were the SAS datasets and clinical pharmacology datasets.

This MOR summarizes a clinical review of the following documents:

Table 1: Original Documents

Description	Volume Identification
Labeling	2
Integrated summary of efficacy	171
Integrated summary of safety	172
Resistance summary	174
Challenge studies	212-237
Treatment studies	237-297
Prophylaxis studies	297-331
Elderly studies	333-344
Virological and serological methods	349

Table 2: Supplementary Documents

Description	Submission Date
WV15819: Treatment study in the elderly patients	7/20/99
WV15812: Treatment study in high risk group	7/20/99
NP15827: Human experimental influenza B	7/30/99
A 4-month safety update	9/1/99

2. Chemistry and Manufacturing Controls

Please refer to Dr. Dan Boring's chemistry review. There were no chemistry concerns precluding approval of this application.

Ro 64-0796 (GS4104) is an ethyl ester prodrug of Ro 64-0802 (GS4071), a rationally designed inhibitor of the neuraminidase enzyme of influenza virus. In this review, the code name Ro 64-0796 will be used throughout.

3. Animal Pharmacology and Toxicology

Please refer to Dr. Ita Yuen's pharmacology review. There were no pharmacology concerns precluding approval of this application.

4. Microbiology

Please refer to Dr. Narayana Battula's microbiology review. There were no microbiology concerns precluding approval of this application.

5. Biopharmacology

Please refer to Dr. Prabhu Rajagopalan's biopharmacology review. There were no biopharmacology concerns precluding approval of this application.

6. Clinical Background

6.1 Clinical Features

Epidemics of influenza occur during the winter months nearly every year and are responsible for an average of approximately 20,000 deaths per year in the U.S. Influenza viruses also can cause global epidemics of disease, known as pandemics, during which rates of morbidity and mortality from influenza-related complications can increase dramatically. Influenza viruses cause disease in all age groups. Rates of infection are highest among children, but rates of serious morbidity and mortality are highest among persons aged $\geq$ 65 years and persons of any age who have medical conditions that place them at high risk for complications from influenza.

Influenza A and B are the two types of influenza viruses that cause epidemic human disease. Influenza A viruses are further classified into subtypes on the basis of two surface antigens: hemagglutinin (H) and neuraminidase (N). Although both influenza A and B viruses undergo continual antigenic drift, influenza B viruses undergo antigenic drift less rapidly and are not divided into subtypes. Since 1977, influenza A (H1N1) viruses, influenza A (H3N2) viruses, and influenza B viruses have been in global circulation.

Typically, clinical manifestations of influenza A and B start after an incubation period of 2-3 days with an abrupt onset of systemic symptoms such as fever, headache, chills, malaise and myalgia accompanied by respiratory symptoms of non productive cough, rhinorrhea or nasal obstruction and sneezing. The pyrexia and systemic illness appear to peak simultaneously after 3 days following onset of symptoms, and patients then enter a recovery period that typically lasts up to 7 days. Cough, fatigue and malaise may persist for 1-2 weeks following recovery from the acute illness. Illness tends to be more severe in cigarette smokers. In some persons, influenza can exacerbate underlying medical conditions (e.g. pulmonary or cardiac disease) or lead to secondary bacterial pneumonia or primary influenza viral pneumonia.

6.2 Antiviral Agents

Currently available anti-influenza medications include two classes of drugs: amantadinamines (amantadine and rimantadine) and a neuraminidase inhibitor (zanamivir).

The amantadinamines primarily exert an antiviral effect by inhibiting the activity of the matrix (M2) ion channel protein of influenza A virus. Amantadine (Symmetrel™ , Endo Labs) and rimantadine (Flumadine™ , Forest) were approved in 1966 and 1993, respectively. Amantadine has been approved for use in prophylaxis of influenza A virus illness, and is also indicated in the treatment of uncomplicated influenza A virus infection in adults and children. Rimantadine has been approved for prophylaxis and treatment of illness in adults caused by strains of influenza A; and in children for prophylaxis against influenza A virus.

The amantadinamines lack activity against influenza B virus and have had limited success due to the rapid development of viral resistance to the drugs and adverse events. Approximately 10-27% of healthy adults shed amantadinamine resistant virus following clinical use of either of these agents. The proportion is higher in immunocompromised adults and children. The side effect profile of these agents is well described. Amantadine is associated with the appearance of CNS side effects including agitation, memory impairment, inability to concentrate and sleep disturbance. Rimantadine appeared to be better tolerated than amantadine when given in comparative trials. Nausea and vomiting were the side effects most frequently reported in trials of rimantadine.

Neuraminidase, or sialidase, is a surface glycoprotein that possesses enzymatic activity essential for viral replication found in both influenza A and B viruses. Based on information gained from crystallographic studies of influenza neuraminidases complexed with sialic acid, several potent and selective inhibitors, in particular sialic acid analogues, of the enzyme have been synthesized. On July 27, 1999 zanamivir became the first sialic acid analogue approved for marketing for treatment of influenza. The approval was based on three placebo-controlled clinical trials in which a five-day treatment course of inhaled dry powder zanamivir, 10 mg b.i.d., was compared with a placebo consisting of the lactose powder vehicle. The primary endpoint for these studies was time to alleviation of major influenza-like symptoms including cough, headache, myalgia, sore throat and feverishness.

One of the limitations seen thus far with zanamivir is its lack of oral bioavailability (estimated as <5% in humans). Attempts have been made to produce newer neuraminidase inhibitors that are more readily absorbed by the gastrointestinal tract. Of these agents under investigation as potential oral agents of neuraminidase inhibitors, Ro 64-0796 (former[redacted]4104), developed by Roche, has had the most extensive preclinical and clinical testings that led to the present submission.

6.3 Clinical Development of Ro 64-0796

The initial clinical development of Ro 64-0796 was undertaken in collaboration with [redacted] who owns the patent for the drug substance. [redacted] completed the initial pre-clinical studies and filed the IND in April 1997. In September 1997, prior to the start of pivotal trials, this IND was transferred to Hoffmann La-Roche.

Two pre-NDA meetings were held on 7/6/98 and 10/2/98, the early one was to discuss the chemistry, manufacturing and control issues while the latter was to discuss the content and strategize the timing of the submission. The division expressed interest in both the safety and efficacy of Ro 64-0796 in elderly and high-risk populations. The applicant, in response, proposed a two-step submission plan: the first submission would include most of the studies in adults, to be followed by a supplementary submission of data from elderly and high-risk populations. (Please refer to Record of Industry Meeting, 10/30/98).

7.Clinical Trials in Support of this Application

7.1 Studies in Support of Efficacy of Ro 64-0796

The clinical development program of Ro 64-0796 can be divided into two categories: naturally acquired influenza trials and experimental human influenza treatment trials, which are listed in Tables 3 and 4, respectively.

Table 3:Naturally Acquired Influenza Trials

Study No.	Description	No.subjects (ITT)	Region	Study period	Strain	Age (yr)	Status
WV15671	**Adult treatment**	**374**	**USA**	**12/97-4/98**	**Smoking**	**18-65**	**Completed**
WV15670	**Adult treatment**	**475**	**NH(non-USA)**	**12/97-4/98**	**Smoking**	**18-65**	**Completed**
WV15730	Adult treatment	38	SH	7/98-9/98	Smoking	18-65	Completed
WV15707*	Elderly treatment	12	SH	7/98-11/98	Vaccination COAD	≥65	Completed
WV15819	Elderly treatment	121	NH	12/98-4/99	Vaccination COAD	≥65	To be continued in SH
WV15812	High risk group	211	NH	12/98-4/99	COAD	≥13 and adult	To be continued in SH

ITTI=intent to treat infected, NH=Northern Hemisphere, SH=Southern Hemisphere, COAD=chronic obstructive airways disease

*Study had small number of enrollment, hence it was elected not to be individually reviewed in this MOR.

Table 4:Experimental Human Influenza Treatment Trials

Study No.	Description	Population	Placebo N	Ro-0796 N	Ro-0796 Dosing	Study Site
GS97-801	Influenza A	Adult	13	56	20-200 mg bid and 200 mg qd	U. Virginia, Charlottesville, VA
NP15717	Influenza B	Adult	13	26	75 or 150 mg bid	New Zealand
WV15827	Influenza B	Adult	39	78	75 mg bid	2 centers in the US, 1 center each in the UK and New Zealand

7.2 Studies in Support of Safety of Ro 64-0796

The safety database for Ro 64-0796 derived from 3 sources: treatment trials, prophylaxis trials, pharmacokinetics trials, and other special studies.

Table 5: Studies in Support of Safety of Ro 64-0796[1]

Treatment Trials (core dataset)	Prophylaxis Trials (Supporting dataset)					PK and Special Studies
As outlined in Tables 3 and 4	Study	Description	N	Season	Region	For PK, please refer to Dr. Rajagopalan's biopharmacology review
	WV15673 WV15697	Adult prophylaxis	1562	1/98-4/98	U.S.	
	WV15708D	Geriatric prophylaxis	385	7/98-10/98	SH	
	GS97-802*	Exper. Influenza A prophylaxis	37	N/A	U.S.	
	NP15757*	Exper. Influenza B prophylaxis	58	N/A	U.S.	

* Study had small number of enrollment, hence it was elected not to be individually reviewed for this MOR.

8. Treatment Trials of Naturally Acquired Influenza

This application contains reports of 6 treatment trials of naturally acquired influenza. Since the study designs for all 6 trials were basically similar, in this MOR the design used in the WV 15671 is chosen for review. Variations noted in other individual study designs will be mentioned when appropriate.

8.1 Protocol WV 15671[2]

Title: **A double-blind, randomized, placebo controlled study of oral Ro-64-0796( )4104) in the treatment of influenza infection**

[1] In addition to the original NDA safety database, more safety data were submitted in the 4-month safety update including both unblinded (n=2591) and blinded (n=1846) data.

[2] Some of the reviewer's comments under this section are pertinent to other similar treatment trials as well.

8.1.1 Description of Protocol

This was a randomized, double-blind, placebo-controlled parallel group study. Subjects were stratified by current smoking status (smoker/non smoker). The study design consisted of a twice daily, oral administration of Ro 64-0796 or placebo for 5 days in patients with the onset of influenza symptoms within 36 hours.

8.1.1.1 Objectives

- To investigate the clinical efficacy of Ro 64-0796 in patients with influenza
- To investigate the antiviral efficacy of Ro 64-0796 in patients with influenza
- To investigate the safety and tolerability of Ro 64-0796 in patients with influenza

> Comment: These objectives were somewhat inconsistent with the proposed safety data analysis as described under section 9.3.5 of the protocol (vol.240, page 32) in which all randomized subjects, infected and non-infected, were to be analyzed for safety.

- To determine the kinetics of Ro 64-0802 (4071, active metabolite) following oral administration of R0 64-0796 (4104) in patients with influenza
- To investigate the impact of treatment on the use of medical and non-medical resources associated with influenza

8.1.1.2 Patient Eligibility

- Patient was febrile defined as $\geq$ 100° F; plus at least one respiratory symptom (cough, sore throat, nasal symptoms); plus at least one constitutional symptom (headache, myalgia, sweats/chills, prostration).
- No more than 36 hours post-onset of feeling unwell

> Comment: These two criteria were later relaxed to accept a baseline temperature of 99° F and an entry into the studies up to 40 hours post onset of illness. The later modification was designed to account for differences between criteria evaluated at time of entry and criteria at the time of first dose.

- Age 18 to 65 years old.
- Patients would be ineligible if any of the following conditions was documented: active renal, cardiac, pulmonary, vascular, neurological, metabolic or immunological disorders; cancer, hepatitis or cirrhosis; transplant recipients, pregnancy or nursing females, HIV-infected, or asthmatics in receipt of chronic therapy.
- Prior to study entry, no episode of acute upper respiratory tract infection, otitis, bronchitis or sinusitis within 2 weeks; no administration of investigational drugs within 4 weeks; no administration of influenza vaccine within 12 months.

8.1.1.3 Treatment Groups, Drug administration and Compliance

Subjects were randomized equally to one of three treatment regimens:

- Ro 64-0796 75 mg b.i.d. for 5 days
- Ro 64-0796 150 mg b.i.d. for 5 days
- Placebo b.i.d. for 5 days

Both doses, 75 mg and 150 mg b.i.d, would give levels of the active moiety in excess of the *in vitro* IC_{50} against strains of both influenza A and B. A dose of 150 mg b.i.d., the maximum dose studied, was expected to give an AUC of 9 mg .h/L which was equivalent to <1:30 of the exposure associated with minimal toxicity in the 14-day rat study.

In order to keep the study double blinded, subjects in the 75 mg b.i.d. group received, in addition to the 75 mg active drug capsule, a matching placebo capsule at the morning and evening dose.

A drug dispensing log for study drug was used to monitor patient compliance.

Patients were provided with a pack of paracetamol/acetaminophen (500mg) for symptomatic relief. The amount of medication taken from this rescue pack was to be recorded. Patients were instructed not to use any other medications for the relief of symptoms during the study treatment period.

8.1.1.4 Diary Card and Schedule of Assessment

Study day 1 was defined as the date of the first dose of study drug. Study Day 2 began at 12 midnight on the same calendar day. Depending on the timing of the first dose, the last dose could fall on either day 5 or day 6. If the first dose of study drug was after 5pm on day 1, the next dose was to be taken on the morning of day 2. In such cases, the last dose of study drug taken was on the morning of study day 6. If the first dose of study drug was taken prior to 5 pm on study day 1, the next dose of study drug was taken in the night of the day (prior to midnight). In these cases, the last dose of study drug was taken on the evening of study day 5.

On the day 1 visit, each patient was issued a first dairy card for days 1-8 entry. The second (for days 8-10) was to be issued at the day 8 visit only if subject's symptoms were persisting. The time when a diary entry was made was recorded as hours and minutes. The symptom scores were documented based on each subject's recollection of symptoms during the preceding 12-hour period. The baseline record (pre-dose) in the diary card was completed by the patient with the help of the investigator or nurse. From study days 2 to 8, subjects were to self record, twice per day, symptom scores, oral temperature, and symptom relief medication. In addition, subjects were to complete the 'quality of life' assessment once per day at the time of the evening dose.

These items were recorded until day 8 or until all symptoms were recorded as 'mild' or 'none' for 24 hours (≤ 1 score).

From study day 9 to 20, a new diary card was issued to subjects with any symptoms not resolved by day 8. The format of diary card and the timing of recording were identical to that for the earlier period.

> Comment: The majority of subjects participating in the treatment trials had only used the first diary card. The second diary card was issued in 15% to 20% of participants.
>
> In response to FDA's request, the applicant provided a summary of diary card dispensing in the 8/6/99 submission. It became apparent that instructions on when to start a second diary card were not uniformly followed in WV15670, WV15671, and WV15730 trials. There were examples of patients who had alleviated symptoms yet also received a second diary card. Conversely, there were also examples of patients who did not alleviate all symptoms but did not receive a second diary card. Thus the second diary card was used inconsistently which is viewed as a flaw of these trials. The lack of consistency in collecting symptom information after alleviation precluded a complete documentation of symptom fluctuation. Also missing second diary cards in subjects who had not alleviated symptoms were responsible for the majority of censored data which may have potentially influenced the results of efficacy analysis. In order to address the impact of censoring, the applicant performed several sensitivity analyses which will be summarized in the Integrated Summary of Efficacy.

On day 1 and day 6, viral swabs/washings were sampled for all patients, but at selected sites, additional viral samplings were taken on day 2, 4, and 8. Like the diary entries, the times when specimens were collected were recorded as hours and minutes. Unlike the diary entries, viral cultures were collected at the time of clinic visit, i.e., could be anytime of the day.

> Comment: The applicant clarified at the 7/22/99 telecon that both nasal and throat swabs were uniformly collected from each subject during the treatment trials. Both swabs were then placed in the same transport vial and treated as one specimen despite differing sources. At selective sites, additional nasal washings were collected. Aliquots of specimens, regardless of the source, were routinely kept frozen for further analyses. The applicant stated that data derived from swab specimens (rather than washings) were consistently used for statistical analyses owing to the fact that swab specimens were generally without any dilution effect as seen with washing specimens.

A follow-up visit was scheduled to occur in a time window from study days 17-25. During the visit, subjects were to have a physical, vital sign measurements, antibody titer, and assessments for secondary illnesses and influenza-like illnesses among household contacts. This follow-up visit could be conducted over the phone for subjects who failed to return to the clinic.

8.1.1.5 Efficacy Parameters

Primary Efficacy Parameter
The primary efficacy parameter was to reflect the duration of illness that was defined as the length of time to alleviation of the symptoms. This was calculated from 'time 0' (study drug initiation) to the time at which all 7 symptoms (i.e. nasal congestion, sore throat, cough, aches, fatigue, headaches and chills/sweats) were alleviated. Alleviation was considered to occur at the start of the 24 hour period in which the symptom was less than or equal to 1 (mild) and remained so for at least 21.5 hours (this allowed a 10% time window around 24 hours for completion of diaries on consecutive days.)

Secondary Efficacy Parameter
The secondary efficacy parameter was to reflect the extent and severity of illness that was defined as the AUC for all symptoms. This was calculated from 'time 0' to the time at which all symptoms were alleviated. Scores were calculated twice daily by totaling the separate symptom scores that form the symptom scale. The AUC of these scores was then calculated for each subject using the trapezoidal rule.

> Comment: The applicant presented the severity of illness by quantifying the AUC of total symptom score over the duration of illness. These symptom scores, assigned as: 0 (absent), 1 (mild), 2 (moderate), and 3(severe), are represented by arbitrarily chosen numbers, irrespective of the differing clinical significance of individual symptoms. These scores merely convey the information that a subject who has a score of 10 is sicker than a subject with a score of 5, not that the former subject is twice as sick as the latter. Accordingly, analyzing changes in mean scores may not be strictly appropriate.

Tertiary Efficacy Parameters

- Duration of viral shedding: defined as the time from treatment initiation to the time of first negative virus culture with no subsequent positive cultures.

> Comments:
>
> - This parameter had been a secondary efficacy parameter in the original protocol until 2/16/98 when an amendment was issued to remove it from being a secondary parameter to a tertiary parameter. The applicant stated that the reason for this change was due to significant variability observed between virological laboratories despite the use of a standardized protocol.

- ♦ Duration of viral shedding was measured from treatment initiation to the time of the first negative virus culture with no subsequent positive cultures. Upon reviewing a list of viral shedding patterns provided by the applicant on 8/16/99, two problems emerged: (1) the pattern of virus shedding was fluctuating in at least 33 subjects (i.e., pos-neg-pos-neg, with or without a subsequent negative result). (2) In at least 100 subjects, the last virus shedding sample was the first negative sample in sequence, meaning there was not a subsequent negative confirmation. Given the fluctuating pattern of virus shedding, to estimate the duration of viral shedding based on the occurrence of a single first negative data poses a high level of uncertainty.

- Distribution of post-baseline antibody titer.
- Time to alleviation of each symptom
- AUC of each of the 7 individual symptoms
  Temperature AUC
  Proportion of subjects with fever determined on a 12 hourly basis
- Total cumulative dose, number of days, and frequency of taking symptoms relief medication from the rescue pack.
- Occurrence of secondary illness, pre-defined as sinusitis, otitis, bronchitis, pneumonia and other chest conditions, plus recurrence of symptoms once alleviation had occurred.

  Comment: Of note, recurrence of symptoms was a clinical judgement made by the investigator since there would be no diary card to record any symptoms once alleviation had been achieved.

- Development of viral resistance
- Virus titer over time calculated as an AUC using the trapezoidal rule
- Quality of life analyses based on the self-assessment of health status.

Additional Exploratory Parameters:

- Virus type
- Temperature AUC
- Time to afebrile state
- Symptom relief medication usage over the dosing period

8.1.1.6 Safety Parameters

As symptoms and common sequelae of influenza were collected as endpoint data, these symptoms, signs and common complications were specifically excluded from reporting as adverse events. The following table lists events associated with influenza syndrome which were excluded from adverse event reporting.

Table 6: Events Excluded from Adverse Event Reporting

Body system	Event
Respiratory	Cough Pneumonia Bronchitis/Tracheitis Sinusitis Dyspnea/Difficulty Breathing
Cardiovascular	Tachycardia
Eyes, Ears, Nose and Throat	Sore throat Nasal obstruction Earache Otitis Coryza Conjunctivitis
CNS	Headache Fatigue
Musculo-skeketal	Myalgia
Other	Fever Rigor Malaise/Asthenia Chills

NOTE: These symptoms may appear as adverse events if they recur, following symptom alleviation, and are isolated events.
Source: Table 2, vol. 237, page 33.

Comment: The safety profile of Ro 64-0796 observed from normal subjects who participated in 6 clinical pharmacology showed that almost none of the above symptoms (except headache and myalygia, on rare occasion) had been reported to be associated with the study drug. Thus the applicant's decision to exclude the above symptoms in adverse event reporting is deemed reasonable.

In addition, following the alleviation of influenza-like symptoms, the recurrence of a single respiratory or constitutional symptom was recorded as an adverse event; however, the reappearance of more than one symptom was recorded as influenza-like syndrome (i.e. secondary illness).

Comment: As the applicant stated in a written response dated 6/11/99, some sites incorrectly reported symptoms occurring prior to the cessation of the primary illness as secondary illness.

Adverse events were reported in two categories:

- Those occurring within a time window of up to 2 days after the last day of study treatment
- Those occurring later than 2 days after end of treatment

8.1.1.7 Definition of Patient Population

The following 'subject populations' were defined prior to unblinding.

A. Safety population: all subjects who were randomized and received at least one dose of study medication and had at least one safety follow-up
B. Intent-to-treat (ITT) population: all subjects who took at least one dose of study medication.
C. Intent-to-treat Infected (ITTI) population: All subjects who received at least one dose of study treatment and had laboratory-confirmed influenza virus infection. Infected subjects with protocol violations or deviations were retained in the ITTI population.
D. Standard population: All subjects who were randomized, had no major protocol violations or deviations (see below), had laboratory-confirmed influenza, and received at least the first 6 scheduled doses of treatment within 72 hours or received the first 5 doses within 72 hours but then went on to take nine out of 10 doses. Subjects were analyzed according to treatment received.

Major protocol violations were: did not fulfill symptom criteria for influenza; more than 40 hours from onset of feeling unwell to start of study drug; and received antiviral therapy for influenza within 2 weeks prior to study day 1.

8.1.1.8 Missing Primary Efficacy Parameter Data

The rules on how to handle missing data were made prior to unblinding.

According to the protocol, subjects ceased recording symptom scores when all of the 7 symptoms were alleviated (or until day 8 if alleviation occurred before day 8). For subjects with missing data or who withdrew or ceased recording data prior to alleviation, data were imputed according to the following rules:

- A missing value was estimated by linear interpolation between 2 available assessments. If the interpolated value was ≤ 1 for the first time (e.g. interpolation between a score of 2 and 0 gives 1) then the interpolated time point was not considered as the beginning of the 24 hour period that determined whether alleviation of that symptom had occurred. Instead, the next observed time point at which symptoms were ≤ 1 was used.

- If there was no subsequent assessment (e.g. subject withdrew before alleviation) then the subject was censored at the time of withdrawal.

8.1.1.9 Randomization and Planned Sample size

Subjects were randomized by center and stratified according to current smoking status. The planned sample size was 750 subjects. This was based on an assumption that an overall two-sided 5% significance level would be distributed

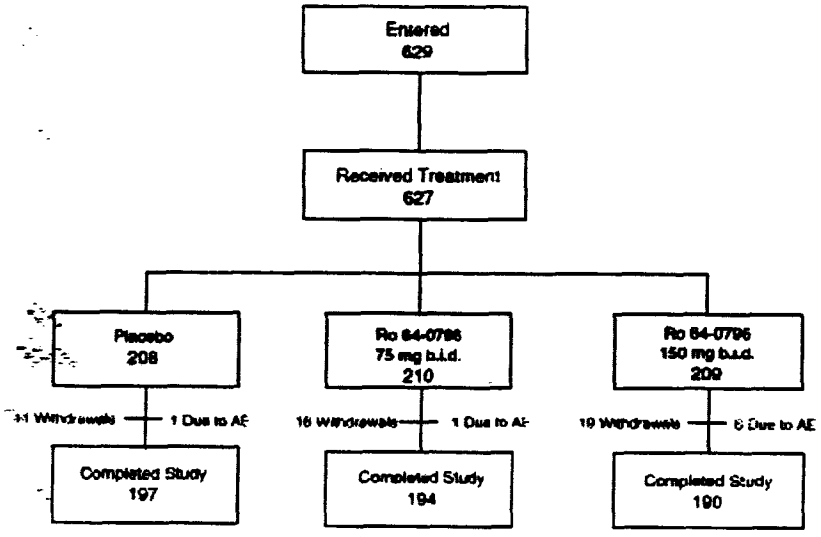
equally amongst the two comparisons (75 mg vs. placebo and 150 mg vs. placebo). It was anticipated that with 120 influenza infected subjects per treatment group, assuming alpha=0.025 and a power of 80% the study could detect a difference of 1.16 days (27.8 hours) as statistically significant.

8.1.2 Applicant's Presentation of Study Results (WV 15671)

8.1.2.1 Patient Disposition and Demographics

A total of 629 subjects were recruited from 57 centers in the U.S. Of the 629 subjects enrolled, 581 completed the entire study. The disposition of these subjects, including the number of premature withdrawals, is shown in the figure below.

Figure 1: Patient Disposition (WV 15671)



Source: Fig 2, vol. 237, page 44

The demographic patterns for the ITT, ITTI, and standard populations were similar. The following table presents the demographics for the ITT population (n=627).

Table 7:Patient Demographics (ITT) (WV 15671)

		Placebo (n=208)	75mg bid (n=210)	150mg bid (n=209)
Sex:	Males	97 (47%)	99(47%)	113(54%)
	Females	111(53%)	111(53%)	96(46%)
Age, yr.:	Mean	32.4	32.3	33.1
	SD	10.2	10.8	9.8
	Median	31.0	30.0	32.0
	Range	18-62	18-64	18-61
Weight, kg:	Mean	80.0	80.9	81.8
	SD	21.2	20.5	19.9
	Median	75.6	77.1	80.7
	Range	42-170	47-152	47-159
Race:	Caucasian	170(82%)	171(81%)	176(84%)
	African American	20(10%)	21(10%)	15(7%)
	Asian American	2(<1%)	4(2%)	1(<1%)
	Hispanic	13(6%)	10(5%)	10(5%)
	Other	3(1%)	4(2%)	7(3%)

Source:Table 4, vol. 237, page 45

Within the ITT population, the groups were comparable with regard to the proportion of subjects with infection.

The infection rate was approximately 60% per treatment group, the majority of whom were infected by the influenza A-H3N2 strain. The following table summarizes the results.

Table 8: Infection in the ITT Population (WV 15671)

Infections	Placebo (n=208)	75mg bid (n=210)	150mg bid (n=209)
Yes:	129(62%)	124(59%)	121(58%)
A (H1N1)	-	-	1(0%)
A (H3N2)	122 (58%)	113(54%)	108(52%)
B	2(1%)	3(1%)	4(2%)
Unknown flu type	5(2%)	8(4%)	8(4%)
No:	80(38%)	86(41%)	87(42%)

Source: Table 11, vol. 237, page 52

Additional demographic data with regard to baseline characteristics for the ITTI population are presented below.

Table 9: Baseline Characteristics (ITTI) (WV 15671)

	Placebo (n=129)	75mg bid (n=124)	150 mg bid(n=121)
Influenza antibody detectable (≥ 1:10)	121/121(100%)	113/113(100%)	113/113(100%)
Smoker	29/129 (22.5%)	30/124 (24%)	35/121(28.9%)

Source: Tables 5, 6 vol. 237, page 45, 46.

In summary, there were no significant differences between treatment groups with respect to infection rate, baseline antibody status and smoking status.

8.1.2.2 Overview of Analysis Populations

There were small numbers of subjects who either were not randomized by the central randomization system (n=4) or received a treatment pack other than that to which they were randomized (n=6). Therefore, the applicant specified treatment groups in two ways: either as 'randomized' which detailed intended treatment using the centralized randomization system or as 'allocated' which detailed the treatment actually received. For their analyses, the applicant made the following decisions regarding these subjects' disposition.

- For the safety and standard populations they were analyzed according to treatment actually received (i.e. allocated).
- For the ITT and ITTI populations they were analyzed according to the treatment to which they were originally randomized.

Comment: A review of the information available on these 10 subjects who were either not randomized or mis-randomized (Appendix 11, vol. 237, page 204) revealed no discernable patterns with particular sites. These mistakes appear to be isolated events.

Among all laboratory confirmed infected subjects, 20 subjects had various types of protocol violations (one subject could have had more than one violation) and they were excluded from the standard population but included in all analyses as the ITTI population. These violations included absence of baseline respiratory symptoms, constitutional symptoms, or fever; non-compliant; baseline symptom duration not met; or received other antiviral agents. (Patient 20662/1125 received rimantidine for influenza-like illness.)

8.1.2.3 Subjects Prematurely Withdrawn from the Study

A summary of the number of subjects withdrawn prematurely and the reasons for withdrawal are given below.

Table 10: Subjects Withdrawn Prematurely (WV 15671)

	Placebo (n=208)	75mg bid (n=211)	150mg bid (n=210)
Premature withdrawal, total	11(5.3%)	16(7.6%)	19(9%)
Fail to return	7(3.4%)	8(3.8%)	6(2.9%)
Refuse to treat	3(1.4%)	4(1.9%)	5(2.4%)
AE/intercurrent ill.	1(0.5%)	1(0.5%)	6(2.9%)
Other violations	-	2(0.9%)	1(0.5%)
Early improvement	-	1(0.5%)	-
Violation Inclusion Criteria	-	-	1(0.5%)

Source: Table 9, vol. 237. Page 51

There were a total of 8 subjects who discontinued from the study due to adverse events/intercurrent illness; of them 6 subjects were from the 150 mg bid group. For a discussion on these patients, please refer to Section 8.1.2.6.2 in this review.

8.1.2.4 Time from Symptom Onset to First Study Drug Intake

For the ITTI population, the groups were comparable with regard to the time from symptom onset to the time of first dosing as shown in the table below.

Table 11: Time from Onset to First Drug Intake (WV 15671)

Time since onset of symptom (hours)	Placebo (n=129)	75 mg bid (n=124)	150 mg bid (n=121)
N	128	121	120
Mean	24.6	23.5	24.6
SD	7.8	8.1	8.3
Median	25.6	24	26.6
Range	2.4 to 39.4	0.3 to 41.2	1.8 to 36.5

Comment: Of note, the 'N's presented for each of the treatment groups are slightly fewer than the figures described for each treatment group in the ITTI population. As the applicant explained (7/22/99 telecon), this was due to a few subjects in each group who had their diaries missing either partially or totally. This slight discrepancy in 'number' was seen in all analyses throughout the entire submission.

8.1.2.5 Efficacy Results

Since the efficacy results from the standard population were similar to that of the ITTI population, in this MOR only the ITTI analyses will be presented.

8.1.2.5.1 Primary Efficacy Parameter

Treatment with Ro 64-0796, 75 mg bid and 150 mg bid, reduced the time (hours) to alleviation of all influenza symptoms by 31% and 32%, respectively, when each group was compared with placebo. These differences were statistically significant. The following table depicts the analyses for the ITTI population.

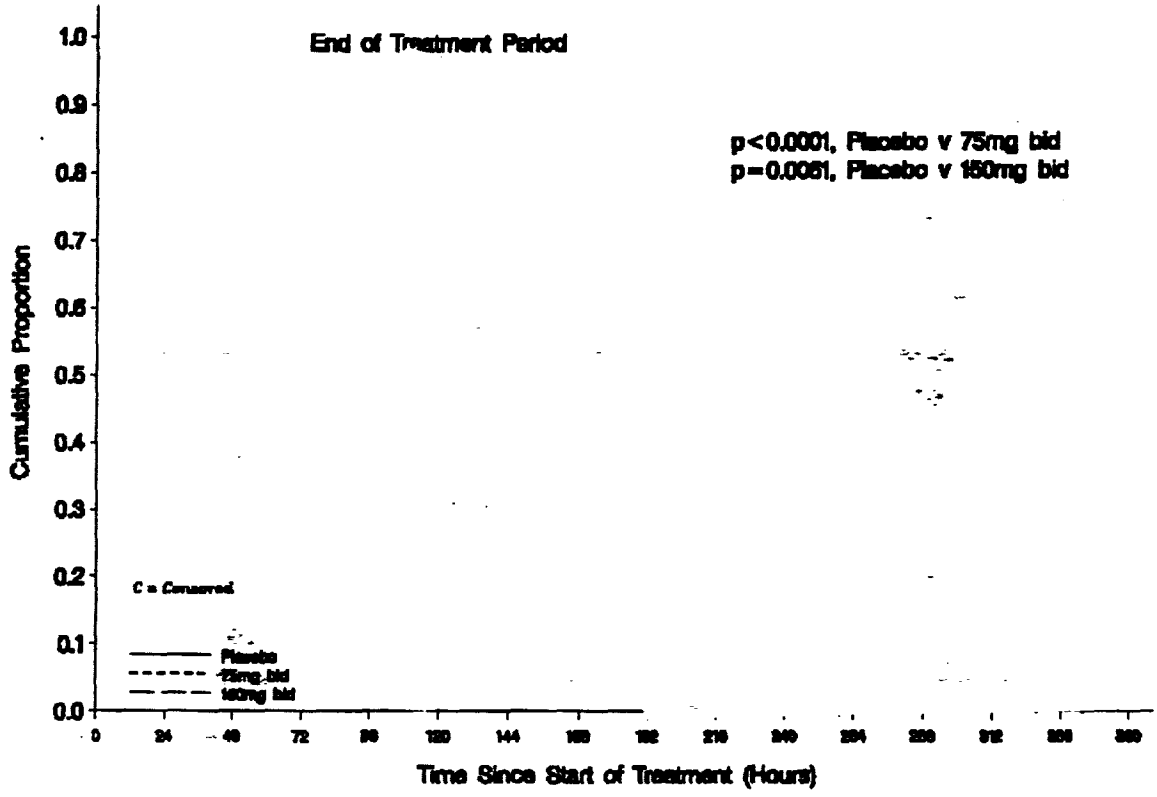
Table 12: Time to Symptoms Alleviation (WV 15671)

	Placebo (n=129)	75mg bid (n=124)	150mg bid (n=121)
N	128	121	119
Mean	124.2	90.9	93.9
SD	7.9	6.8	6.8
Median	103.3	71.5	69.9
Range	0 to 343.3	6.4 to 487.4	0 to 327.6
95% CI for within group median	92.6 to 118.7	60 to 83.2	60 to 87.9
p-value*	NA	<0.0001	0.0061

*Using weighted Mantel-Haenszel test

The Kaplan-Meier curve comparing the time to alleviation of all symptoms for subjects in the placebo group versus those in the 75 mg bid and 150 mg bid doses is presented below.

Figure 2: Time to Symptoms Alleviation (ITTI) (WV 15671)



Source: Appendix 14, vol. 237, page 227

FDA's Analyses:

For more details, please refer to Dr. Hammerstrom's statistical review. Dr. Hammerstrom recalculated the individual time to symptoms alleviation. Unlike the applicant, Dr. Hammerstrom only used the recorded times, no data interpolations. He concluded : "Although there were a number of individual discrepancies in the times, there was no difference in the conclusions that both doses of oseltamivir were statistically significantly superior to placebo and there was no discernible difference between the 75 mg and 150 mg doses." The p-values for the Wilcoxon-Gehan tests, using Dr. Hammerstrom's calculated times, were 0.0004 for comparing the 75 mg dosing regimen to placebo and 0.004 for comparing the 150 mg dosing regimen to placebo.

To investigate the homogeneity of the treatment effect in the ITTI population, two subgroup analyses according to 'region' or 'smoking' status were performed. The study centers were grouped into 4 regions on an approximate geographical basis. The constituents of each region were defined prior to unblinding and were designed to include approximately 40 subjects per treatment group in the ITTI population in an approximate geographic region.

The approximate groups are Region 1=west; Region 2=mid-west; Region 3=south; Region 4=east part of the U.S.

Results of treatment effects by regions and smoking status are shown below.

Table 13: Treatment Effects According to Region/Smoking Status (WV 15671)

Time to alleviation (hours)		Placebo (n=129)	75mg bid (n=124)	150mg bid (n=121)
Region 1:	N	46	38	37
	Mean	126.4	96	103
	SD	12.5	13	16.8
	Median	116.2	82.8	68.8
	Range	0-343.3	6.5 to 273.4	11.1 to 317.2
	95% CI	95.3 to 124.9	46.4 to 102.3	53.1 to 86.7
Region 2:	N	19	16	16
	Mean	120.8	102.7	79.7
	SD	26.8	19.9	14.7
	Median	77.3	96.2	62.1
	Range	0 to 332.1	17.3 to 273.9	19 to 249.3
	95%	46 to 121.4	56.3 to 118.3	47.5 to 88.7
Region 3:	N	42	41	40
	Mean	126	83	94.2
	SD	12.7	10.6	10.5
	Median	104.5	69.1	79.3
	Range	0 to 321.8	6.4 to 487.5	0 to 327.6
	95% CI	46 to 121.4	57.5 to 75.2	68.1 to 122.3
Region 4:	N	21	26	26
	Mean	119.8	82.4	95.2
	SD	18.7	11.9	12.5
	Median	87.2	66.1	67.4
	Range	21.8 to 270	17.8 to 211.5	0 to 202.4
	95% CI	76 to 143.2	50.3 to 86	55.5 to 129.1
Non-smoker:	N	100	92	84
	Mean	131.5	90.9	90.8
	SD	9.3	7.6	7.2
	Median	108.8	72.4	69.9
	Range	0 to 343.3	6.4 to 487.5	0 to 327.6
	95% CI	92.6 to 120.4	60 to 86	56.1 o 87.9
Smokers:	N	28	29	35
	Mean	97.1	84.2	98.5
	SD	11.9	12.5	14.7
	Median	95.7	60.5	78.5
	Range	0 to 208.7	16.2 to 208	5.5 to 317.2
	95%CI	53.1 to 118.7	35.3 to 89.2	55.4 to 117.5

Source: Appendix 16 in vol. 237, page 230

With the exception of region 2, there was no evidence for any differences in the treatment effect of Ro 64-0796 in median treatment effect between the placebo and the 75 mg group.

> Comment: The demographics for subjects from region 2 were similar to other 3 regions except for a slight preponderance of female subjects in the 75 mg group (71% female). The opposite result in the median treatment effect for subjects from Region 2 could have been a result of variability due to the small denominator (n<20) for this group.

With respect to smoking status, although there was no difference in mean treatment effect between the placebo group vs. the 150 mg bid active treatment group for the smokers, the difference in median was consistent with the overall analysis.

8.1.2.5.2 Secondary Parameters

- Total Symptom Score AUC

Baseline median total symptom scores were similar between the three treatment groups (15, 14, and 14 for the placebo, 75mg bid and 150mg bid groups, respectively). A treatment effect was observed with significantly lower median AUC values being reported in the active treatment groups compared with the placebo

The following table shows the total symptom score AUC in the ITTI population.

Table 14: Total Symptom Score AUC (ITTI) (WV 15671)

Symptom AUC (score x hours)	Placebo (n=129)	75mg bid (n=124)	150mg bid (n=121)
N	128	121	119
Mean	1058.4	758.5	740.7
SD	685.5	556.8	512.7
Median	962.6	597.1	626
Range	0 to 4359.7	60.1 to 2821.7	0 to 3079.2
p-value	NA	<0.0001	<0.0001

Source: vol. 237, page 56. Table 15.

- Time to Cessation of Virus Shedding

The proportions of subjects shedding virus at baseline were similar between the three treatment groups (70%, 85% and 87% for the placebo, 75 mg and 150 mg, respectively).

The applicant stated that treatment with Ro 64-0796 reduced the time to cessation of virus shedding when compared with placebo in the ITTI

population, but the effect was significant only for the 75 mg treatment group. The results are shown in the following Table.

Table 15: Duration of Viral Shedding (WV 15671)

Time (hours)	Placebo (n=129)	75mg bid (n=124)	150mg bid (n=121)
N	102	107	106
Mean	73.7	63.8	70.2
SD	3.6	3.7	4.2
Median	70.2	66.8	69.6
Range	0 to 166.7	0 to 192.8	0 to 171.2
95% CI for within group median	68 to 71.4	64.6 to 68.8	67.0 to 72
p-value	NA	0.0332	0.5087

Source: Table 17, vol. 237, page 57

Comment: Although a difference in median time of 3.4 hour (70.2-66.8h) in the duration of viral shedding between the placebo and 75 mg group has achieved statistical significance, this degree of difference is hardly considered a significant clinical benefit.

8.1.2.5.2 Tertiary Efficacy Parameters

- Viral Antibody Titers

At baseline, similar number of subjects in each treatment group in the ITTI population had detectable antibody titers ($\geq$ 1:10): 121, 113, and 113, in the placebo, 75 mg bid and 150 mg bid groups, respectively.

Treatment with Ro 64-0796 does not appear to have reduced the capacity to evoke a type-specific antibody response to influenza virus. As shown in Table 19 of this NDA, increases in antibody levels were similar in all three treatment groups.

- Time to Alleviation of Individual Symptoms and Fever

As shown in Table 20, vol. 237, page 60 of the NDA, the time to alleviation of each individual symptom (nasal congestion, sore throat, cough, aches, fatigue, headache, chills/sweats) was markedly reduced in subjects receiving either dose of Ro 64-076 compared with the placebo group. Of the 7 symptoms, 'cough' was the one symptom which had the most pronounced reduction in median time to alleviation (24.8 h reduction for the 75 mg group compared to placebo.)

The median time to afebrile state ($\leq$ 98.9 F) over the dosing period was longer in subjects in the placebo group compared with Ro 64-0796 treated subjects as shown in the table below.

Table 16: Time to Afebrile State (ITTI)

Time (hours)	Placebo (n=129)	75 mg bid (n=124)	150 mg bid (n=121)
N	129	124	121
Mean	67	52.7	48.8
SD	3.2	3.3	2.9
Median	64.6	41.5	42.7
Range	0 to 120.1	0 to 142	0 to 124.9
95% CI for within group median	59.2 to 76.3	34 to 48	34.6 to 44.8

Source: Table 28, vol.237, page 69.

- Symptom Relief Medication

The pattern of consumption of acetaminophen was summarized for each treatment group in the ITTI population as follows.

Table 17: Acetaminophen Consumption (ITTI) (WV 15671)

	Placebo (n=124)	75mg bid (n=124)	150 mg bid (n=121)
Total consumption dose (gm), median	5.5	4.5	4.0
# of days with consumption, median	2.0	1.5	1.5

Source: Appendix 26

Results in the above Table show that subjects taking Ro 64-0796 took less acetaminophen and fewer days of it compared to those taking placebo.

- Secondary Illness

Secondary illnesses were predefined to include sinusitis, otitis, bronchitis, pneumonia, other chest infections such as the recrudescence of influenza-like symptoms as judged by the investigators.

The most common secondary illnesses reported by all subjects, regardless of treatment, were bronchitis (15/374, 4% of subjects in the ITTI population) and sinusitis (12/374, 3.2%). The overall incidence of secondary illnesses was reduced by approximately 50% in the Ro 64-0796 treated groups when compared with the placebo group. However, this comparison was based on small numbers of patients.

There were 2 cases of recrudescence of influenza like illness (1 in the placebo, 1 in the 150 mg bid group). Review of supplementary information provided by the applicant (6/11/99) revealed that the investigators had not consistently followed the prespecified definition for influenza-like illness. Subject 1125 (placebo) was reported to have a recurrence of influenza-like syndromes on day 13 after initial alleviation of symptoms on day 3. However, subject 1331 (150 mg group) was reported to have a recurrence of influenza-like illness even before alleviation of

all symptoms had been achieved. The latter case illustrates how assessment of the rate of recrudescence of influenza-like illness was problematic in this study.

8.1.2.5.3 Exploratory Analyses

- Influenza B infection

There was an insufficient number of cases of confirmed influenza B infection (1-2% in all 3 treatment groups) to allow the investigation of the primary efficacy parameter in this subset of population.

8.1.2.6 Safety Results

8.1.2.6.1 Adverse Events

The majority of subjects took their study medication twice daily for 5 days as required by the protocol. Only a small number of subjects failed to take all 10 doses of study medication (4, 6, and 10 in the placebo, 75mg bid and 150 mg bid groups, respectively).

The incidence of adverse events was reported with two time windows.

- On treatment: events recorded during treatment and up to 2 days after final dose.
- Off treatment: events occurring within the 3-21 day follow-up period.

During the 'on treatment' period, the number of subjects reporting adverse events was comparable between the 3 treatment groups with 41.7%, 50.5%, and 48.3% of subjects reporting events in the placebo, 75 mg bid and 150 mg bid groups, respectively. The most common adverse events were nausea, vomiting and diarrhea. Over half of the adverse events reported during the 'on treatment' period (56%) were considered unrelated or remotely related to treatment by the investigators. Adverse events considered probably related to treatment were recorded for 2%, 4.9% and 5.9% of the subjects reporting events in the placebo, 75 mg bid and 150 mg bid groups, respectively. These events were nausea, vomiting, diarrhea and abdominal pain. There was one case of dermatitis in a subject in the 150 bid group which was assessed as probably related to the study medication. The majority of these events were classed as mild or moderate, regardless of treatment received. The following table summarizes these results.

Table 18: On Treatment Adverse Event (ITT) (WV 15671)

Body system/AE	Placebo (n=204)	75 mg bid (n=206)	150 mg bid (n=205)
Gastrointestinal:			
Nausea	15 (7.4%)	35(17%)	37(18%)
Vomiting	7(3.4%)	27(13.1%)	29(14.1%)
Diarrhea	24 (11.8%)	18(8.7%)	12(5.9%)
Abdominal pain upper	3(1.5%)	5(2.4%)	3(1.5%)
Dyspepsia	3(1.5%)	1(0.5%)	3(1.5%)
Abdominal pain	3(1.5%)	2(1%)	-
Respiratory:			
Cough	6(2.9%)	6(2.9%)	6(2.9%)
Nasal congestion	8(3.9%)	2(1%)	5(2.4%)
Sore throat	3(1.5%)	4(1.9%)	5(2.4%)
Bronchospasm	1(0.5%)	1(0.5%)	3(1.5%)
Epistaxis	2(1%)	3(1.5%)	-
Neurological:			
Headache	8(3.9%)	9(4.4%)	9(4.4%)
Insomnia	1(0.5%)	5(2.4%)	6(2.9%)
General:			
Dizziness	8(3.9%)	5(2.4%)	4(2%)
Fatigue	5(2.5%)	5(2.4)	5(2.4%)
Pyrexia	3(1.5%)	2(1%)	2(1%)
Pain	-	3(1.5%)	1(0.5%)

Source: Table 30, vol. 237, page 72

Comment: Diarrhea was reported more frequently among subjects receiving placebo than among subjects receiving Ro 64-0796. Diarrhea, although not specified as an inclusion criterion, has been documented to be a clinical manifestation of influenza infection. The reduction in the incidence of diarrhea for the treatment groups compared with the placebo group could be considered as a possible treatment effect of Ro 64-0796.

During the 'off treatment' period, the proportion of subjects reporting adverse events was comparable between the placebo and 75 mg bid groups (21.1% and 17.5% respectively) but lower in the 150 mg bid group (11.7%). Headache was the most commonly reported adverse event and was recorded by 2.3% of subjects. The majority of events were mild or moderate in intensity. The majority of adverse events recorded 'off treatment' were considered unrelated to study medication.

8.1.2.6.2 Premature Discontinuation Due to Adverse Events

Eight subjects reported adverse events which led to their discontinuation from the study (one subject withdrew during the follow-up period). The events and relationship to study drug are detailed in the following table.

Table 19: Adverse Events Leading to Premature Discontinuation (WV 15671)

Events	Relationship to treatment
Suicide attempt	Unrelated
Strep pharyngitis	Unrelated
Pneumonia/dehydration	Unrelated
Rash	Probable
Headache/pneumonia	Unrelated
Pneumonia	Unrelated
Nausea	Possible
Pregnancy	Unrelated

8.1.2.6.3 Deaths

No deaths were reported during the study period or during the 21-day follow-up period.

8.1.2.6.4 Serious Adverse Events

Nine subjects reported a total of 10 serious adverse events, 6 of these serious events were described during the 'on treatment' period. The most common serious adverse events were pregnancy (1 subject in the 150 mg group; 2 in the placebo group) and pneumonia (3 subjects in the 150 mg group). All 3 subjects who had pneumonia received the 150mg bid treatment, none was assessed as being related to study medication.

Of 10 serious adverse events, only 3 were assessed as possibly related to study medication by investigators: 1 case each of pseudomembranous colitis, abdominal pain (75 mg bid group) and pregnancy (150 mg bid).

Comment: Since Ro 64-0796 does not utilize the cytochrome p450 enzymes for metabolism, a drug interaction between Ro 64-796 and oral contraceptives is unlikely. The investigator's assessment on the case of pregnancy is doubtful.

8.1.2.6.5 Clinical Laboratory Data

Because of the low incidence of clinical laboratory abnormalities or changes as presented by the applicant, this section of review will only be discussed under the Integrated Summary of Safety from the pooled database.

8.1.3 Reviewer's Assessment and Conclusions

Study WV15671 was a naturally acquired influenza treatment trial conducted in the US during the 1997-1998 influenza season. A total of 629 subjects were recruited. The predominating influenza type during the trial was type A (H3N2). The infection rate was approximately 60%, which resulted in 374 subjects in the ITTI population.

The primary outcome of this study was a reduced time to alleviation of symptoms defined as the time from start of study drug to the start of the 24-hour period in which all symptoms were reported as mild or absent. A significant reduction in the duration of illness was observed in subjects treated with Ro 64-0796 (75 mg bid and 150 mg bid) when compared with placebo. The clinical benefit can be expressed in 1.3 days (31.8 hours) and 1.4 days (33.4 hours) reduction in illness duration in the 75 mg bid and 150 bid groups, respectively, compared with placebo. A similar trend of reduction in illness duration was observed in both smokers and non-smokers. This conclusion was further supported by the FDA's analyses.

However, there are several weaknesses of the study:

- There were insufficient cases of confirmed influenza B infection to allow the investigation of the primary efficacy parameter in this subset of population.

- Although the protocol provided specific instructions on when to start a second diary card, there were examples of incorrect use. The lack of consistency in collecting symptom information after alleviation precluded a complete documentation of symptom fluctuation (recrudescence of influenza-like syndrome). Also the missing second diary card in subjects who had not alleviated symptoms were responsible for the majority of censored data which could potentially influence the results of the efficacy analysis. To address the latter concern, the applicant performed several sensitivity analyses from pooled database in the Integrated Summary of Efficacy to test the strength of their conclusion.

- The virus shedding status was fluctuating in most patients, possibly a reflection of inadequate sampling, delay in sample transporting, and/or inherent variability and insensitivity of the culture procedure. In addition, a design flaw of this trial was that the sampling schedules were intermittent (days 1,2, 4, 6, 8) rather than a more regular and frequent schedule.

In general Ro 64-0796 was well tolerated at 75 mg bid and 150 mg bid dosing regimens. The most common adverse events in the Ro 64-0796 treated groups were gastrointestinal events, particularly nausea and vomiting. There was no evidence for a dose-related trend in either the occurrence or severity of adverse events reported.

Based on the above, it is concluded that study WV15671 is an adequate pivotal study in support of the indication for treatment of influenza type A infection in otherwise healthy subjects of 18 to 65 years of age. The effectiveness of Ro64-0796 in treatment of influenza type B infection has not been demonstrated by in this study alone due to an insufficient number of cases.

8.2 Protocol WV 15670

Title: A double-blind, randomized, placebo-controlled study of oral Ro64-0796 (also known as [redacted]4104) in the treatment of influenza infection

8.2.1 Description of Protocol

This protocol had an identical design to that of WV15671. Unique to this trial was an amendment issued 01/07/98 in which subjects participating in the study at the Hong Kong center were allowed to be excluded from the study if they were found to be infected with the influenza A/H5N1 virus. In May of 1997 while the study was ongoing, 18 individuals in the Hong Kong community were diagnosed with influenza infection caused by A/H5N1, of whom 6 died as a result of infection. It was considered that in view of the apparent virulence of the A/H5N1 strain type, if any subjects were found to be harboring this strain type they were to be withdrawn from the study without breaking the blind and offered amantidine at the discretion of the investigator. A rapid identification kit was used for the diagnosis of influenza A/H5N1 infection.

Comment: Record (vol. 349, page 39) showed that no subject infected with A/H5N1 virus was enrolled and later withdrawn.

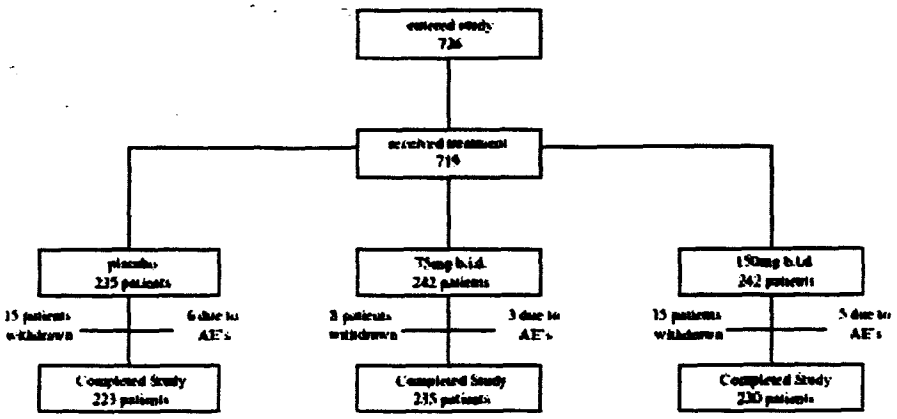
8.2.2 Applicant's Presentation of Study Results

8.2.2.1 Patient Disposition and Demographics

A total of ~~726~~ subjects were recruited from 51 European centers, 11 centers in Canada and 1 center in Hong Kong. The enrollment rate ranged from 1 to 46 per center. Of the 726 subjects enrolled, 719 subjects actually received treatment. The disposition of these subjects, including the number of premature withdrawals is shown in the figure below.

APPEARS THIS WAY
ON ORIGINAL

Figure 3: Patient Disposition (WV 15670)



Source: Fig. 2, vol. 253, page 29

The demographic patterns for the ITT, ITTI, and standard populations were similar. The following table depicts the demographics for the ITT population (n=719).

Table 20: Patient Demographics (ITT)(WV 15670)

	Placebo (n=235)	75mg bid (n=242)	150mg bid (n=242)
Gender: males	118(50%)	120(50%)	129(53%)
Females	117(50%)	122(50%)	113(47%)
Age(yr.):mean	37.4	38.2	36.7
SD	11.9	11.1	11.8
Median	36	37	34
Range	18-68	18-65	18-65
Weight(kg):Mean	72.3	75.8	72.1
SD	14.3	16.2	15.3
Median	71	75	70
Range	40-116	45-140	41-139
Race:Caucasian	219(93%)	229(95%)	230(95%)
Black	2(<1%)	4(2%)	1(<1%)
Asian	13(6%)	8(3%)	9(4%)
Hispanic	0	0	0
Other	1(<1)	1(<1%)	2(<1%)

Source: Table 3, vol. 253, page 43

Comment: The three treatment groups were broadly comparable with respect to age, gender, weight, and race. Compared to WV15671, subjects of Caucasian and Asian ethnic background were recruited at slightly higher rates.

Within the ITT population, the groups were comparable with regard to the proportion of subjects with infection. The infection rate for each treatment group was approximately 65%, which was slightly higher than that reported for

WV15671 (60%). Similar to WV17671, the majority of subjects were infected by the influenza A/H3N2 strain.

Comment: The slightly higher infection rate reported in WV 15670 could be explained in part by a higher proportion of susceptible subjects enrolled in this trial. In WV15670, over 80% of subjects had undetectable influenza antibody at baseline in contrast to 0% reported in WV15671.

In addition, 4% of subjects of the 3 treatment groups were found to have other types of infections including adenovirus, *chlamydia pneumoniae*, mycoplasma pneumonia, parainfluenza, RSV and various combinations of viral infections. Results are summarized in the table below.

Table 21: Infection in the ITT Population (WV 15670)

Infection	Placebo (n=235)	75mg bid (n=241)	150mg bid (n=243)
Yes:	161 (69%)	158(66%)	156(64%)
A/H1N1	5(2%)	8(3%)	11(5%)
A/H3N2	150(64%)	145(60%)	140(58%)
B	6(3%)	5(2%)	5(2%)
No:	74(31%)	83(34%)	87(36%)
Other virus	11 (4%)	11(4%)	14(4%)
Unknown	63(27%)	72(30%)	73(30%)

Source: Table 10, vol. 253, page 51

Baseline characteristics for the ITTI population are presented below.

Table 22: Baseline Characteristics (ITTI) (WV 15670)

	Placebo (n=161)	75mg bid (n=158)	150mg bid (n=156)
Influenza antibody			
N	150	151	142
Detectable (≥ 1:10)	24(16%)	21(14%)	21(15%)
Not detectable (<1:10)	126(84%)	130(86%)	121(85%)
Smoker	59/161 (%)	54/158(%)	54/156(%)

Source:Table 16, vol. 253, page 57

Comment: In summary, there were no significant differences between groups with respect to infection rate, baseline antibody status and smoking status. Compared to WV15671, the majority of infected subjects were reported to have no detectable antibody at baseline and the proportion of subjects who reported smoking was slightly higher.

8.2.2.2 Overview of Analysis Population

There were small numbers of subjects who either were not randomized by the central randomization system (n=9) or received a treatment pack other than that to which they were randomized (n=10). The applicant used the same approach as for WV15671 on handling these 19 subjects, i.e., for the safety and standard populations they were analyzed according to treatment actually received; for the

ITT and ITTI populations they were analyzed according to the treatment to which they were originally randomized.

Comment: Of the 9 subjects who were not randomized, 4 subjects were from a single center (CRTN=19264, Asgardstrand, Netherlands) where the total enrollment was merely 5.

Among all laboratory-confirmed infected subjects, 43 subjects had either a protocol violation(s) (n=17) or did not fulfill the compliance criterion required of the standard population (n=26). The types of protocol violations included an absence of baseline symptoms, symptom duration longer than 40 hours, and a violation of temperature criterion.

8.2.2.3 Subjects Withdrawn Prematurely from the Study

Table 23: Premature Study Discontinuation (WV 15670)

Reason for premature withdrawal	Placebo (n=235)	75mg bid (n=242)	150mg bid (n=242)
Premature withdrawal , total	15 (6.4%)	8 (3.3%)	15 (6.2%)
AE/int. illness	6(2.6%)	3(1.2%)	6(2.5%)
Refused treatment*	5(2.1%)	1(0.4%)	4(1.7%)
Viol. Criteria	3 (1.3%)	2 (0.8%)	1 (0.4)
Fail to return	-	-	3 (1.2%)
Admin. Reason	1 (0.4%)	1(0.4%)	-
Early improvement	-	-	1(0.4%)
Other violation	-	1 (0.4%)	-

*None was as a result of study drug intolerance.
Source: Table 8, vol. 253, page 49

Comment: The discontinuation rate and reasons for discontinuation were similar to that reported for WV15671.

A total of 15 subjects withdrew prematurely as a consequence of an adverse event or intercurrent illness. The events and relation to study drug will be discussed under Section 8.2.2.6.2 in this MOR.

8.2.2.4 Time from Symptom Onset to First Study Drug Intake

Table 24: Time Since Onset of Symptoms (WV 15670)

Time since onset of symptoms (hours)	Placebo (n=161)	75mg bid (n=158)	150mg bid (n=156)
N	161	157	155
Mean	23	23.2	23.6
SD	8.9	8.3	8
Median	23	24	25
Range	0 to 58.8	3.9 to 60	0 to 43

Source: Table 9, vol, 253, page 50

All three groups were found to be comparable with respect to time from symptom onset to first study drug intake with a mean and median approximately of 24 hours, with the exception of 6 subjects having exceeded the 40 hour symptom duration criterion.

8.2.2.5 Efficacy results

8.2.2.5.1 Primary Efficacy Parameter

Treatment with Ro 64-0796, 75 mg bid or 150 mg bid, reduced the time to alleviation of all influenza symptoms by 25% and 31% respectively, when compared with placebo. These differences were statistically significant. The median time to alleviation of all symptoms for the placebo group was slightly longer (116.5 h) than that reported for WV 15671 (103.3h). The following table depicts the analysis for the ITTI population

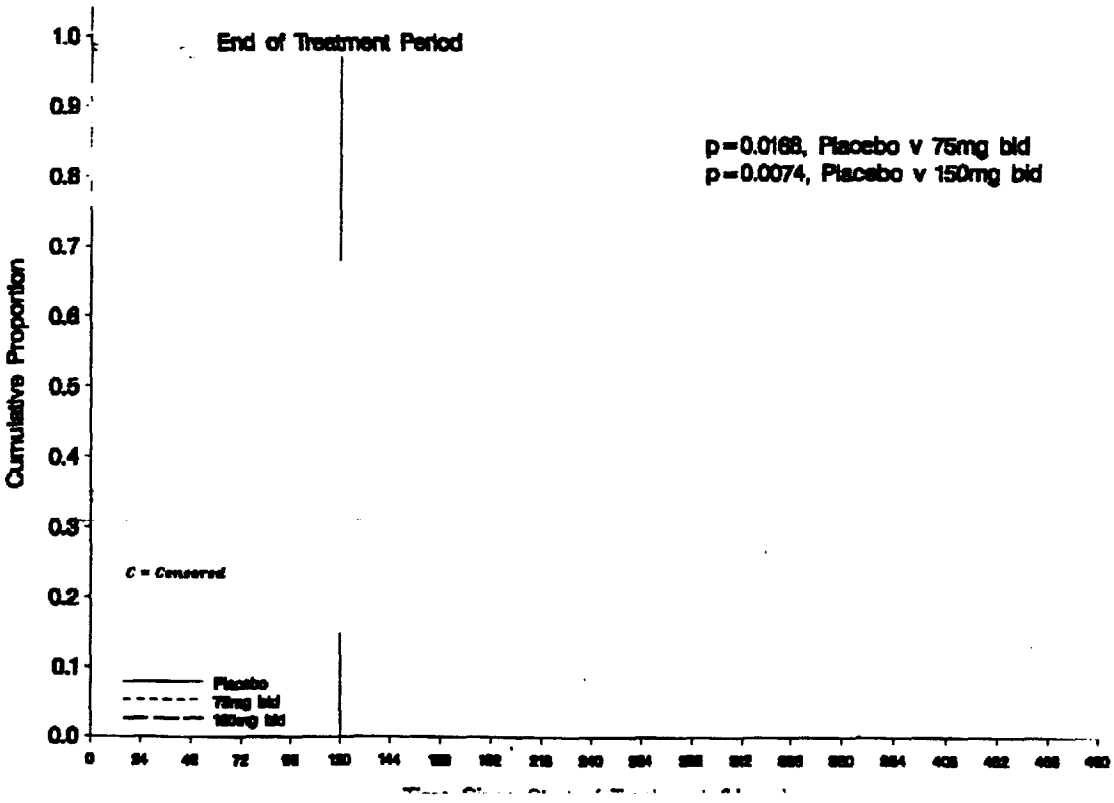
Table 25: Time to Symptoms Alleviation (ITTI) (WV 15670)

Time (hours)	Placebo (n=161)	75mg bid (n=158)	150mg bid 9n=156)
N	161	157	155
Mean	145.7	115.8	115.8
SD	9.2	7.4	8.4
Median	116.5	87.4	81.8
Range	0 to 467.1	0 to 368	0 to 467.5
95% CI for within group median	101.5 to 137.8	73.3 to 104.7	68.2 to 100
p-value	NA	0.0168	0.0074

Source: Table 11, vol. 253, page 52.

The Kaplan-Meier curve comparing the time to alleviation of all symptoms for subjects in the placebo group versus those in the 75 mg bid and 150mg bid doses from which the above information was derived is provided in the following Figure 4.

Figure 4: Time to Symptoms Alleviation (Kaplan-Meier curves) (WV 15670)



Comment: Dr. Hammerstrom reanalyzed the primary efficacy parameter for this trial similar to that for the previous trial. Although there were a number of discrepancies in the calculated alleviation times, there was no difference in the conclusions that both doses of Ro 64-0796 were statistically significantly superior to placebo and there was no discernible difference between the 75 mg and 150 mg doses. The p-values for the Wilcoxon-Gehan tests, using Dr. Hammerstrom's calculated alleviation times, were 0.008 for comparing the 75 mg dosing regimen to placebo and 0.004 for comparing the 150 mg dosing regimen to placebo.

During FDA's review, the Division of Scientific Investigation notified this Division of an anomaly involving site 19167 concerning the validity of diary entries (Please refer to Antoine El-Hage's memo dated 9/29/99). Dr. Hammerstrom therefore conducted analyses of this trial with all subjects from this center deleted. He concluded that the treatment effect of Ro 64-0976 remained statistically significant for both treatment groups even after omission of the data from site 19167.

To assess the homogeneity of the treatment effect in the ITTI population, two subgroup analyses according to 'region' or 'smoking' status were performed. The study centers were grouped into 4 regions on an approximate geographical basis (except for Region 4) as shown below.

Table 26: Subgroups by Regions (WV 15670)

Region	Countries included	Total subjects recruited (N=726)
1	Germany, Switzerland	276
2	France, United Kingdom	137
3	Belgium, Netherlands, Norway, Finland	183
4	Canada, Hong Kong	130

Source: Appendix 3, vol. 253, page 86

Results of treatment effects by regions and smoking status are shown in the Table below.

APPEARS THIS WAY
ON ORIGINAL

Table 27:Treatment Effect According to Region/Smoking Status (WV 15670)

Time (hours)	Placebo (n=161)	75mg bid (n=158)	150mg bid (n=156)
Region 1			
N	47	52	46
Mean	132	125.5	102.7
SD	12.2	12.9	13.7
Median	128	104.8	79
Range	0-403.2	10.7-128.7	0-467.5
Region 2			
N	31	31	28
Mean	155.9	131.8	153.7
SD	21.1	18.3	25.9
Median	137.8	75.7	103
Range	21.5 –462.5	25.3 –322.5	21.8 – 416.2
Region 3			
N	51	46	44
Mean	131.8	102.8	98
SD	16.7	11.5	14.4
Median	93.3	78.3	64.8
Range	0-456	0-239.6	0-404.5
Region 4			
N	32	28	37
Mean	164.9	96.3	121.9
SD	22.8	16.7	14.4
Median	109.3	80.3	94.2
Range	5 – 467.1	0-365.8	0 –299.8
Non-smokers			
N	102	103	101
Mean	130.4	119.7	125.6
SD	10	9.1	11.5
Median	109.3	88.1	81.2
Range	5 –456	0-368	0-467.5
Smokers			
N	59	54	54
Mean	170.3	112.2	93.4
SD	17.3	14	8.4
Median	135.2	80	83.4
Range	0-467.1	10.7-365.8	0-214.8

Source: Appendix 18, vol. 254, page 71

No serious imbalances were found between the numbers of subjects in each treatment group for the ITTI population following this regional grouping. There was, however, slight evidence of a lack of homogeneity of the treatment effect across regions and by smoking status. Active treatment groups demonstrated consistently lower median time to alleviation values than placebo, although for Regions 2 and 4, and the smoker group, the point estimates of treatment effects of the respective 150 mg bid groups were smaller than that of corresponding 75 mg bid group. The applicant attributed these differences to the small sample sizes following the grouping procedures.

> Comment: As Dr. Hammerstrom noted, there was an observed interaction between treatment and smoking status in study WV15671. However, there was no such interaction demonstrated in WV15670. The interaction results were inconclusive.

8.2.2.5.2 Secondary Parameters

- Total Symptom Score AUC

The following table shows the total symptom score AUC in the ITTI population.

Table 28: Total Symptom Score AUC(ITTI) (WV 15670)

Symptom AUC (Score x hours)	Placebo (n=161)	75mg bid (n=158)	150mg bid (n=156)
N	161	157	155
Mean	1149.4	902.7	903.1
SD	900.5	636.6	754.4
Median	943	773.3	708.5
Range	0-5408.2	0-3792.9	0-4797.3
p-value	NA	0.0073	0.0025

(Source: Table 14, vol. 253, page 55.

Baseline median total symptom scores were similar between the three treatment groups (15, 15, and 14 in the placebo, 75mg bid and 150 mg bid groups, respectively). The applicant concluded that a treatment effect was observed with significantly lower median AUC values being reported in both active treatment groups compared with placebo.

- Time to Cessation of Virus Shedding

The proportion of subjects in the ITTI population shedding influenza virus at baseline was similar across treatment groups (80% of placebo subjects and 86% of subjects in each of the 75mg and 150mg bid groups). The median duration of virus shedding in the active drug treatment groups was found to be only slightly lower than that of the placebo group.

Table 29: Duration of Virus Shedding (ITTI) (WV 15670)

Time (hours)	Placebo (n=161)	75mg bid (n=158)	150mg bid (n=156)
N	127	134	131
Mean	78.6	71.4	68.4
SD	3.4	3.4	3.1
Median	71	70.2	69.5
Range	0-167.3	0-166.5	0-171.7
95% CI for within group median	70.2 to 73.5	67.5-71.4	67.2-70.8
p-value	NA	0.0917	0.0213

Source: Table 15, vol.253, page 56

Comment: Although numerically the difference between the 150 mg group and placebo is statistically significant, the 1.5-hour shortening in viral shedding offered by active treatment provides no meaningful clinical benefit.

8.2.2.5.3 Tertiary Efficacy Parameters

- Viral Antibody Titers

At baseline, a similar proportion of subjects with detectable (at least 1:10) antibody titers at baseline was identified in the placebo (16%), 75mg bid (14%) and 150 mg bid (15%) treatment groups. As mentioned previously, these percentages were much lower than that of WV15671.

Approximately 90% of subjects in the ITTI population had evoked at least a 4-fold increase in viral antibody titer. There was no evidence that treatment with Ro64-0796 reduced the capacity to induce type-specific antibody rises in response to naturally acquired influenza infection.

- Time to Alleviation of Individual Symptoms and Fever

Compared to a similar analysis for WV15671, the data of ' time to alleviation' for individual symptoms were quite variable. For example, in WV15670, Ro64-0796 treatment at 75 mg bid did not shorten the symptom durations for 'nasal congestion' and 'sore throat' when compared with placebo. Except for 'nasal congestion' and 'sore throat', individual symptoms resolved faster with Ro 64-0796 than in the placebo group. The times to alleviation of individual symptoms for the placebo group were generally shorter than that of the placebo group in WV15670, except 'cough' and 'headache', despite the fact that both studies had a comparable total symptom scores at baseline (~15 scores).

The median time to afebrile state (i.e. ≤37.2 C or 98.9F) over the treatment dosing period was reduced for subjects in both active treatment groups compared with placebo.

Table 30: Time to Afebrile State (WV 15670)

Time (hour)	Placebo (n=161)	75 mg bid (n=158)	150 mg bid (n=156)
N	161	158	156
Mean	73.7	58.1	54.9
SD	3.2	3.3	3.5
Median	73.5	43.6	43.8
Range	0 to 163.5	0 to 140.6	0 to 166
95% CI for within group median	64 to 86.4	36 to 54.4	35.5 to 47

Source: Table 25, vol. 253, page 65

- Symptom Relief Medication

The total acetaminophen consumption and the total number of days during which acetaminophen was taken are summarized in the following table.

Table 31: Acetaminophen Consumption (ITTI) (WV 15670)

	Placebo (n=161)	75mg bid (n=158)	150mg bid (n=156)
Total consumption dose (gm), median	3.0	2.5	2.0
#of days with consumption, median	1.5	1.5	1.0

Source: Appendix 26, vol. 254

Table 31 shows that subjects taking Ro 64-0796 consumed slightly less amount of acetamenophen compared to placebo.

Comment: In this non-US study, subjects generally consumed less acetamenophen than those enrolled in the US (WV15671).

- Secondary Illnesses

Secondary illnesses were predefined as sinusitis, bronchitis, pneumonia and other lower respiratory tract infections. These events were considered secondary to influenza if the onset of these conditions occurred at least 48 hours after the start of study drug.

Fewer subjects reported any secondary illness in each of the two active treatment groups (13%) compared to subjects in the placebo group (19%).

Four percent, 3%, and 6% of patients were reported to have an influenza -like illness for the 75 mg bid, 150mg bid, and placebo groups, respectively. Influenza-like illness was defined as the reappearance of more then one symptom following the alleviation of influenza-like symptoms.

Analysis of the data also showed that a small number of subjects in the 75mg bid, 150mg bid, and placebo groups required antibiotics for the treatment of secondary illnesses (1, 5, and 8, respectively). Numerically, fewer subjects in the active treatment groups required antibiotics than that in the placebo group.

8.2.2.5.4. Influenza B Virus Infection

A small but similar proportion of subjects in each treatment group was diagnosed with the influenza B virus (3%, 2%, and 2% in the placebo, 75mg bid and 150mg bid treatment groups, respectively). The number was too small to allow investigation of the primary efficacy parameter for patients with influenza B infections.

8.2.2.6 Safety Results

8.2.2.6.1 Adverse Events

The majority of subjects took their study medication twice daily for 5 days, as required by the protocol, except for a small number of subjects who failed to complete the full course of medication (11, 3 and 11 in the placebo, 75mg bid and 150 mg bid treatment groups, respectively).

- On treatment adverse events

The incidence of adverse events by treatment group up to 2 days after the last day of treatment is shown in the table below.

Table 32: On-Treatment Adverse Events (ITT) (WV 15670)

Body system/AE	Placebo (n=235)	75mg bid (n=242)	150mg bid (n=242)
Gastrointestinal:			
Nausea	10(4.3%)	29(12%)	28(11.6%)
Vomiting	7(3%)	24(9.9%)	22(9.1%)
Diarrhea	10(4.3%)	13(5.4%)	11(4.5%)
Drug mouth	2(0.9%)	1(0.4%)	4(1.7%)
Abdominal pain	3(1.3%)	2(0.8%)	1(0.4%)
Abdominal pain, upper	1(0.4%)	2(0.8%)	3(1.2%)
Loose stools	2(0.9%)	-	3(1.2%)
Dyspepsia	1(0.4%)	-	3(1.2%)
General:			
Dizziness	6(2.6%)	6(2.5%)	6(2.5%)
Neurological:			
Headache	2(0.9%)	3(1.2%)	4(1.7%)
Respiratory:			
Cough	4(1.7%)	1(0.4%)	2(0.8%)
Nasal congestion	2(0.9%)	3(1.2%)	1(0.4%)
Epistaxis	-	-	3(1.2%)
Others:			
Herpes simplex	3(1.3%)	3(1.2%)	2(0.8%)
Vertigo	1(0.4%)	3(1.2%)	4(1.7%)

Source: Table 28, vol. 253, page 68

Gastrointestinal events were the most frequent events to be considered drug-related by the investigator. Most adverse events were considered to be mild or moderate in intensity.

- Off - treatment adverse events

Of the subjects reporting adverse events in the follow-up period (more than 2 days after treatment end), 32 were in the placebo group, 32 in the 75mg bid group and 28 in the 150mg bid group. Most events were considered by the investigator to be unrelated or remotely related to study medication. Four subjects reported adverse events which were considered possibly or probably related to study medications, they were: one case each of severe abdominal pain and mild dyspepsia in the placebo group and one case each of mild diarrhea and mild nausea in the 150 mg bid group.

8.2.2.6.2 Premature Discontinuation Due to Adverse Events

A total of 15 subjects withdrew prematurely as a consequence of one or more adverse events or intercurrent illness. The events for each treatment arm are listed in the following table.

Table 33: Premature Discontinuation due to Adverse Events (WV 15670)

Events+	Placebo (n=235)	75mg bid (n=242)	150mg bid (n=242)
Vomiting	-	2	2
Abdominal pain	1	-	2
Dermatitis	1	0	1
Diarrhea	0	0	1
Others*	4	1	4

+ One subjects could have more than one event.
*Vertigo, ear infection, anxiety, insomnia, palpitations, sore throat, hypersensitivity, pain in jaw
Source: Appendix 52, vol. 255, page 165

Of these events, vomiting and abdominal pain were the only 2 symptoms assessed by the investigator as remotely, possibly, or probably related to study medication.

8.2.2.6.3 Deaths

There were no deaths reported during the study, or up to 4 weeks following the study.

8.2.2.6.4 Serious Adverse Events

There were 4 serious adverse events recorded during the treatment period. None of these events was considered by the investigator as being related to trial treatment (1 case each of herpes zoster, neutropenia, and sepsis in the placebo group; 1 case of peritosillar abscess in the 75mg bid group.)

8.2.2.6.5 Clinical Laboratory Data

Because of the low incidence of clinical laboratory abnormalities or changes as presented by the applicant, these abnormalities will be discussed under the Integrated Summary of Safety for the pooled database.

8.2.3 Reviewer's Assessment and Conclusions

Study WV15670 was a naturally acquired influenza treatment trial conducted during the 1997-1998 influenza season in Northern Hemisphere outside the US. The predominant influenza type during this trial was type A/H3N2. A total of 726 subjects were recruited. The infection rate was approximately 65% which resulted in 475 subjects in the ITTI population.

The primary outcome of the study was a reduced time to alleviation of symptoms. A significant reduction in the duration of illness was observed in subjects treated with Ro 64-0796 (75 mg bid and 150 mg bid) when compared with placebo. The

clinical benefit can be expressed as a reduction in illness duration of 1.2 days (29.1 hours) for the 75 mg bid group and 1.4 days (34.7 hours) for the 150 mg bid group compared with placebo. The treatment effect was demonstrated in both smokers and non-smokers. This conclusion was further supported by the FDA's analyses.

The study shares similar weaknesses as described for WV15671 with respect to insufficient number of cases infected with influenza type B, inconsistent use of second diary cards, and intermittent collection of virological data.

In general, treatment with Ro 64-0796 was well tolerated and there were no reports of drug-related serious adverse events. Non-serious adverse events occurring with greater frequency in subjects receiving active drug were GI events such as nausea, and vomiting. However, the total number of subjects discontinuing study medication due to GI events was low (<2%).

Based on the above, it is concluded that study WV15670 is an adequate pivotal study in support of the indication for treatment of influenza type A infection in otherwise healthy subjects of 18 to 65 years of age. The effectiveness of Ro 64-796 in treatment of influenza type B infection has not been demonstrated in this study alone due to an insufficient number of cases.

8.3 Protocol WV15730

Title: **A double-blind, stratified, randomized, placebo controlled study of Ro64-0796 (GS 4104) in the treatment of influenza infection in adults**

8.3.1 Study Design

This Southern Hemisphere multicenter study was conducted in 9 centers in Australia and 3 centers in South Africa. The planned sample size was 500 subjects. However, because the study began in the declining weeks of the season, there were only 60 subjects enrolled.

The study population, stratification, blinding, assessments, compliance and study parameters were identical to that of WV 15670 and WV15671. However, two design features differed from previous two trials: 1. There was only 1 active treatment group, i.e. 75 mg b.i.d, and, 2. No viral culture was performed for centers in South America.

Due to the small sample size, the applicant's presentation focused on summaries and graphical presentations of the data without formal statistical testing.

8.3.2 Results

8.3.2.1 Patient disposition and demographics

Sixty subjects were enrolled and randomized. Fifty-eight subjects received at least one dose of study drug. Four subjects withdrew prematurely from the study. Among them, two withdrew consent prior to receiving the first dose of study drug, one in the 75 mg group failed to return to the clinic and one in the placebo group withdrew prematurely due to vomiting and diarrhea, leaving 58 subjects in the ITT population. The demographic data for the ITT population are summarized below.

Table 34: Patient Demographics (WV 15730)

	Placebo (n=27)	75mg bid (n=31)
Sex: males	14(52%)	16(52%)
Females	13(48%)	15(48%)
Age (yr.):mean	36.4	34.1
SD	12.1	9.9
Median	34	32
Range	18-65	18-54
Weight (kg):mean	70.6	73.4
SD	12.7	14.4
Median	70	72
Range	51-98	48-109
Race: Caucasian	25(93%)	29(94%)
Black	1(4%)	0
Asian	0	2(6%)
Hispanic	0	0
Other	1(4%)	0

Source: Table 3, vol. 272, page 35

The two treatment groups were comparable with regard to the proportion of subjects with infection. The majority of subjects were infected with influenza A (H3N2).

Table 35: Infection in the ITT Population (WV 15730)

Infection	Placebo (n=27)	75mg bid (n=31)
Yes	19 (70%)	19(61%)
A (H1N1)	2(7%)	1(3%)
A (H3N2)	16(59%)	17(55%)
Unknown type	1(4%)	1(3%)
No	8(30%)	12(39%)

Source: Table 5, vol. 272, page 37

8.3.2.2 Efficacy results

8.3.2.2.1 Primary efficacy parameter

As shown in the following table, there was a numerical reduction in the time to alleviation of all symptoms for subjects receiving Ro 64-0796 treatment compared with those receiving placebo.