Table 36: Time to Symptoms Alleviation (WV 15730)

Time (hours)	Placebo (n=19)	75mg bid (n=19)
Mean	134.2	108.2
SD	12	26.6
Median	143.9	78.2
Range	31 to 510.7	3.8 to 373.8
95% CI for within group median	101 to 179.8	37.5 to 101.8

Source: Table 6, vol. 272, page 38

8.3.2.2.2 Secondary Efficacy Parameter

The secondary efficacy parameter assessed was the total symptom score (AUC) from initiation of treatment to the time at which all symptoms were first alleviated. The median AUC for all symptoms was 758.7 hours in the 75 mg bid group as compared to 1215.2 hours in the placebo. This trend was consistent with the results from WV 15671 and WV15670.

8.3.2.3 Safety

All subjects but one completed the twice daily 5-day course of study medication. One subject in the placebo group stopped treatment on day 2 due to aggravated diarrhea.

The most common adverse events that occurred during the 'on-treatment' period were nausea and vomiting. The frequency of reporting of nausea as an adverse event was 14.8% and 16.1% for the placebo and 75 mg bid, respectively.

Six subjects reported adverse events in the follow-up period, including cough, dermatitis, rib fracture, dysuria, and pilonidal sinus infection. The majority of adverse events were considered by the investigator to be unrelated to treatment; however, one subject in the placebo group reported dermatitis which was classified as possibly related to treatment.

There were no deaths reported during the study.

There were no serious events recorded during the study.

8.3.3 Reviewer's Assessment and Conclusions

Study WV15730 was a naturally acquired influenza treatment trial conducted during the 1998 July-September influenza season in the Southern Hemisphere (Australia and 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.

Due to the small sample size, the data were analyzed without formal statistical testing.

The infection rate was approximately 65%, which resulted in 38 subjects in the ITTI population. The predominant strain was influenza type A/H3N2.

There was a reduction in the time to alleviation of all symptoms in subjects receiving Ro 64-0796 75 mg bid treatment compared with placebo. The median time was 78.2 hours in the 75 mg bid group as compared to 143.9 hours in the placebo group. These results are consistent with those of the previous two pivotal studies.

All treatments were well tolerated. Nausea and vomiting were reported more frequently in the active treatment group.

It is concluded that study WV15630, with insufficient sample size, can be considered as a supportive study to the pursued indication for treatment of influenza type A infection in otherwise healthy subjects of 18-65 years of age. There was no case of influenza type B infection in this study.

8.4 Protocol WV15819
Title: **A double-blind, stratified, randomized, placebo controlled study of Ro 64-0796 in the treatment of influenza infection in the elderly adults**

The objectives of the study were to investigate the clinical and antiviral efficacy of Ro 64-0796 in elderly patients with influenza and to investigate the safety and tolerability of the drug in this elderly population.

This was a double-blind, placebo-controlled multicenter study conducted during the 1998-1999 influenza season in the Northern Hemisphere. The applicant's preliminary report was submitted in 7/99 in order to provide additional evidence of safety and efficacy of Ro 64-0796 in elderly patients.

Patients, $\geq$ 65 years of age, presenting within 36 hours of onset of symptoms of influenza ($\geq$ 37.5 C temperature, plus one respiratory symptom, plus one constitutional symptom) were eligible to enroll. Subjects were excluded if they presented with unstable or uncontrolled renal, cardiac, pulmonary, vascular, neurologic, metabolic disease, or significant liver dysfunction associated with jaundice.

Eligible patients were randomized in a 1:1 ratio to receive either 75 mg Ro 64-0796 or placebo twice daily for 5 days. There were two pre-randomization stratification variables: current vaccination (yes or no) and chronic obstructive airways disease (yes or no).

Schedule of assessment, diary entry and definition of endpoints were identical to that applied in the previous trials.

The trial had originally planned to enroll 500 subjects on the assumption that 50% of subjects would prove to have confirmed influenza infection. In this preliminary report, 172 subjects were enrolled.

8.4.1 Results

8.4.1.1 Overview of Analysis Populations

A total of 172 subjects were enrolled. 4 subjects did not have safety data recorded after randomization (2 in each treatment groups). These subjects were excluded from both the safety and ITTI populations. The disposition of the remaining subjects is shown in Table 37.

Table 37: Disposition of Subjects (WV 15819)

	Evaluable for:				
	Safety	Efficacy(ITT)	Withdrawal due to:		Deaths
			AE's	Other	
Placebo	91	69	1	3	0
75 mg b.i.d.	77	52	2	4	0

Source: Fig. 2 and Table 1, Amendment 7/20/99.

8.4.1.2 Demograhic Data and Baseline Characteristics

The demographic data and baseline characteristics are summarized in the following table.

Table 38: Demographics and Baseline Characteristics (ITTI) (WV 15819)

Parameter	Placebo (n=69)	75 mg bid (n=52)
Age: Mean	73.97	73.73
(yr.) Median	73	73
SD	6.84	7.15
Range	65-92	65-96
Sex: Female	42 (61%)	26 (50%)
Race: Caucasian	66(96%)	50(96%)
African American	2(3%)	2(4%)
Other	1(1%)	
Vaccination: yes	34(49%)	22(42%)
COAD: no	65(94%)	49(94%)
Baseline symptom scores		
Median	13	12
Influenza virus type		
Type A	62(90%)	47(90%)
Type B	7(10%)	5(10%)
Baseline antibody titer		
<1:40	44(64%)	36(69%)
≥1:40	23(33%)	15(29%)
unknown	2(3%)	1(2%)
Region: USA	11(16%)	6(12%)
Non-USA	58(84%)	46(88%)

Source: Table 2, page 13, Amendment 7/20/99

Comment: All demographic parameters and baseline characteristics were comparable between treatment groups. There was a preponderance of female participants which is to be expected for an elderly population. The proportion of Type B infection for the 1998-1999 season appeared to be higher than that of the preceding year.

The HAI titer of 1:40 is a threshold level for defining 'protective' antibody.

8.4.1.3 Efficacy Results

- Primary Efficacy Parameter

Table 39: Primary Efficacy Analysis (WV15819)

Time (hour)	Placebo (n=69)	75 mg bid (n=52)
Mean	215.5	215.2
SD	16.3	22.1
Range	0-512	4.8-506.1
Median	213.2	161.8
95% CI for within group	152 –262	103.4-243.9
Median difference	51.4	NA
95% CI for median difference	-52.6 – 131.5	NA

Source: Table 7, page 19, Amendment 7/20/99.

As shown above, treatment with Ro 64-0796 in otherwise healthy influenza-infected elderly subjects was associated with a shorter duration of symptoms which was consistent with the results from the previous trials.

This numerical difference was also demonstrated in a subgroup analysis including subjects infected with influenza type B, however the number of subjects infected with influenza type B was very small (7 and 5 in the placebo and Ro64-0796 groups, respectively).

- Time to Afebrile State

The median duration of fever, measured as the time to return to the afebrile state ($\leq 98.6^{\circ}$ F in elderly, $\leq 98.9^{\circ}$ F in adults), was lower in the active treatment group. The median time to becoming afebrile was reduced from 100 hours in the placebo group to 88.8 hours on active treatment.

- Time to Cessation of Virus Shedding

No information was available for this parameter.

- Use of Symptom Relieving Medication

The total consumption of acetaminophen over the duration of dosing was 5.5 gm in the placebo group and 5 gm in the active treatment group.

- Incidence of Secondary Illnesses Requiring Antibiotics

  A slightly lower proportion of subjects reported secondary illnesses requiring antibiotic intervention in the active treatment group (12%) compared with the placebo group (16%). The recorded secondary illnesses included bronchitis, lower respiratory tract infection, pneumonia and sinusitis.

- Proportion of Subjects Hospitalized

  The number of subjects hospitalized during the trial was low. There were 4 subjects in the placebo group hospitalized compared with 1 subject in the 75 mg bid treatment group. In the placebo group, two subjects were hospitalized due to pneumonia, one due to aggravation of asthma and the other due to a femoral hernia. The subject receiving active treatment was hospitalized as the result of a fall.

8.4.1.4 Safety Results

- Adverse Events Leading to Premature Withdrawal

  Three subjects withdrew prematurely from the study due to adverse events. One subject from the 75 mg bid group withdrew on Day 3 as a result of nausea and abdominal pain, which were considered by the investigator to be probably related to study treatment. The other two events (asthma in the placebo group and pneumonia in the active treatment group) leading to premature withdrawal were not considered related to study treatment.

- On-Treatment Adverse Events

Table 40: On-Treatment Adverse Event (WV 15819)

Events	Placebo (n=91)	75 mg bid (n=77)
Nausea	7(7.7%)	11(14.3%)
Vomiting	2 (2.2%)	6(7.8%)
Abdominal pain	0	2(2.6%)
GI disorder	0	2(2.6%)
Bronchitis	7(7.7%)	8(10.3%)
Sinusitis	1(1.1%)	1(1.3%)
Pneumonia	3(3.3%)	2(2.6%)
Lower Respiratory Tract Infection	2(2.2%)	0
Headache	3(3.3%)	0
Diarrhea	8(8.8%)	4(5.2%)

Source: Table 6, page 18, Amendment 7/20/99.

In this elderly population, nausea and vomiting were the two most frequent adverse events.

- Off-Treatment Adverse Events

  There was no evidence to suggest a higher incidence of gastrointestinal disorders during the off-treatment period in subjects receiving active treatment, compared to those receiving placebo.

8.4.2 Reviewer's Assessment and Conclusions

Study WV15819 was a double-blind, placebo-controlled multicenter study of Ro 64-0796 in the treatment of influenza infection in elderly subjects (≥65 years of age). In this preliminary report, a total of 172 subjects were enrolled, of them, 121 subjects were in the ITTI population and 168 subjects were included in the safety population.

Treatment with Ro 64-0796 in otherwise healthy influenza-infected elderly subjects was shown to be associated with a shorter duration of symptoms. Although the reduction did not reach statistical significance due to inadequate sample size, the differences between treatments were consistent with the results from the previous trials.

In general, Ro 64-0796 given at 75 mg bid for 5 days was well tolerated by this small number of otherwise healthy elderly subjects (only 6% had COAD as underlying disease). Nausea and vomiting were the two most frequent adverse events.

It is concluded that study WV15819 can serve as supportive evidence of good tolerability of Ro 64-0796 in a small number of elderly subjects given at the 75 mg bid dosing regimen. Preliminary efficacy analyses showed results that were consistent with the two pivotal trials.

8.5 Protocol WV15812
Title: **A double-blind, stratified, randomized, placebo controlled study of Ro 64-0796 in the treatment of influenza in chronically ill adults**

This multicenter study was designed to enroll subjects with chronic cardiac disease (excluding chronic idiopathic hypertension) and/or respiratory diseases (including bronchopulmonary dysplasia, and asthma but excluding cystic fibrosis); aged ≥ 13 years presenting with symptoms of influenza defined similarly as the previous treatment trials. Eligible patients were to be randomized to receive either 75 mg Ro64-0796 or placebo as a b.i.d. regimen for a period of 5 days.

The study was stratified according to the status of COAD (yes or no). Prior to randomization and initiation of study drug, subjects' cardiac and/or respiratory diseases status was to be classified by ECG and FEV_1 assessments. Patients with COAD stage III (FEV_1 <35%) were to be excluded from the study. These two

assessments were repeated at each visit (days 2, 4, 6, 8 and 21) and any time during the study if deemed necessary.

Concomitant mediations allowed during the study included a preprepared supply of acetaminophen and medications for chronic conditions. The use of immuno-suppressants was prohibited except treatment with steroids at doses ≤ 5mg/day of prednisolone.

The schedule of assessments, diary entries and definitions of endpoints were identical to that for the previous trials.

The trial had originally planned to enroll 500 subjects. In this preliminary report, 304 subjects were enrolled.

8.5.1 Results

8.5.1.1 Overview of Analysis Populations

A total of 304 subjects were enrolled. Three subjects, (2 in placebo, 1 in active treatment group) had no safety assessments recorded. These subjects were excluded from the safety population. The disposition of the remaining subjects is shown in Table 41.

Table 41: Disposition of Subjects (WV15812)

	Evaluable for:				
	Safety	Efficacy (ITT)	Withdrawal due to:		Deaths
			AE's	Other	
Placebo	150	104	4	2	1
75 mg bid	151	97	2	1	0

Source: Fig. 2 and Table 1, Amendment 7/20/99

8.5.1.2 Demographic Data and Baseline Characteristics

The demographic data and baseline characteristics are summarized in the following table.

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Table 42: Demographics and Baseline Characteristics (WV15812)

Parameter	Placebo (n=104)	75 mg bid (n=97)
Age: Mean	52.55	52.72
(yr.) Median	54	53
SD	15.14	17.51
Range	13-83	15-86
Sex: Female	54 (52%)	68(70%)
Race: Caucasian	96(92%)	91(94%)
African American	3(3%)	1(1%)
Other	5(5%)	5(5%)
Smoking: yes	21(20%)	16(16%)
Vaccination: yes	30(29%)	30(31%)
COAD: yes	70(67%)	69(71%)
Baseline symptom scores		
Median	13	14
Influenza virus type		
Type A	86(83%)	79(81%)
Type B	18(17%)	18(19%)
Baseline antibody titer		
<1:40	75(72%)	66(68%)
≥1:40	25(24%)	27(28%)
unknown	4(4%)	4(4%)
Region: USA	19(18%)	22(23%)
Non-USA	85(82%)	75(77%)

Source: Table 3, page 14, Amendment 7/20/99

Comment: This was the only treatment trial presented by the applicant in which adolescent subjects (13 to 17yrs of age) were recruited. However, the number enrolled was too small (n=4) to perform subgroup analyses for adolescents.

Sixty-nine percent (69%) of subjects had a COAD condition at baseline. However, it was unclear as to what proportion of subjects had cardiac conditions.

The proportion of type B virus infection during the 1998-1999 season was 18%, higher than that observed in the seasons during the preceding year.

8.5.1.3 Efficacy Results

- Primary Efficacy Parameter

Table 43: Primary Efficacy Analysis (WV 15812)

Time (hour)	Placebo (n=104)	75 mg bid (n=97)
Mean	208.3	209.6
SD	14.8	15.6
Range	0-568.5	18.3 to 546
Median	161	170.6
95% CI for within group	108.5 to 235	115.2 to 208.5
Median Difference	-9.6	NA
95% for median difference	-72.9 to 78.5	NA

Source: Table 7, page 24, Amendment 7/20/99

In this population, comprising influenza-infected subjects with underlying chronic respiratory and cardiac illness, treatment with 75 mg bid Ro 64-0796 **did not reduce** the median time to alleviation of <u>all</u> symptoms compared with the placebo group.

However, when time to alleviation of <u>individual</u> symptoms was compared, treatment with active drug resulted in reduced median time to alleviation compared to placebo for all symptoms with the only exception for the 'fatigue' component (Appendix 25, page 87-97, Amendment 7/20/99). The time to alleviation of illness required all symptoms to be alleviated, i.e., defined by the slowest to alleviate. In this study, 'fatigue' was the last symptom alleviated in a sizable proportion of patients in both treatment groups. The applicant explained that fatigue, being a co-morbidity in those with a history of chronic respiratory disease, might have contributed to the negative outcome of the study.

Eighteen subjects in each treatment group were infected with influenza type B. In a subgroup analysis in subjects with influenza B, there was no reduction in the median time to alleviation of symptoms.

- Time to Afebrile State

An afebrile state was defined for this population as $\leq 98.9^{\circ}F$. The results showed that duration of fever was reduced with active treatment from 69 to 52.7 hours.

- Use of Symptom-Relieving Medication

The median consumption was reduced from 5.8 gm in the placebo group to 3.5 gm on active treatment.

- Time to Cessation of Virus Shedding

  No information was available for this parameter.

- Incidence of Secondary Illnesses Requiring Antibiotic Intervention

  The incidence of secondary illnesses requiring antibiotic intervention in the active treatment group compared with placebo was slightly higher (20% on active treatment compared to 18% of subjects on placebo).

- Proportion of Subjects Hospitalized

  One subject in each of the placebo and active treatment groups was hospitalized. The patient receiving Ro 64-0796 was hospitalized for pneumonia and the one receiving placebo was hospitalized as a result of an intestinal obstruction.

8.5.1.4 Safety Results

- Adverse Events Leading to Premature Withdrawal

Six subjects withdrew as a consequence of an adverse event (4 subjects in the placebo group and 2 in the 75 mg bid group). Events leading to withdrawal in the placebo group were pneumonia, dermatitis, palpitations and a mild elevation in SGPT. The two subjects receiving active treatment withdrew as a result of bronchitis and nausea. Only the case of dermatitis and nausea were assessed by the investigators as possibly related to study drugs.

- On-Treatment Adverse Events

Table 44: On-Treatment Adverse Event (WV 15812)

Event	Placebo (150)	75 mg bid (n=151)
Nausea	10(6.7%)	13(8.6%)
Vertigo	1(0.7%)	3(2%)
Bronchitis	10(6.7%)	13(8.6%)
Otitis media	1(0.7%)	2(1.3%)
Tonsillitis	1(0.7%)	2(1.3%)
COAD	2(1.3%)	1(0.7%)
Insomnia	2(1.3%)	1(0.7%)
Pneumonia	3(2%)	2(1.3%)
Vomiting	4(2.7%)	3(2%)
Abdominal pain	5(3.3%)	2(1.3%)
Dizziness	6(4%)	3(2%)
Asthma aggravated	6(4%)	2(1.3%)
Sinusitis	7(4.7%)	3(2%)
Diarrhea	22(14.7%)	7(4.6%)

Source: Table 6, page 18, Amendment 7/20/99

Comment: The event rates of nausea and vomiting were quite similar between the placebo and active treatment groups. Consistent with all previous treatment trials, there was a higher incidence of diarrhea reported in subjects receiving placebo.

- Off-Treatment Adverse Events

There was no evidence to suggest a higher incidence of gastrointestinal events during the off-treatment period in subjects receiving active treatment compared with those receiving placebo.

8.5.2 Reviewer's Assessment and Conclusions

Study WV15812 was a naturally acquired influenza treatment trial in subjects with chronic cardiac and/or respiratory diseases. A total of 304 subjects were recruited, among them 69% of subjects had a COAD condition at baseline.

dilution schemes employed. This criterion was intended to minimize variability in virus titer at the time of infection.

- Because the challenge strains were attenuated, the symptoms associated with experimental infection were generally milder than that observed with naturally acquired influenza infection. For this reason, 'duration of symptoms' was not chosen as the primary efficacy parameter.
- The chosen primary efficacy parameter was 'change in viral load' which was defined as the virus titer over time and calculated as an AUC up to and including 7 days after the first dose of treatment. Change in viral load was measured by quantitative viral cultures of nasal lavage fluid collected once or twice daily for a period of 8 days following inoculation of the challenge strain.
- Because there were few sites (1 to 4 sites) participating in each study and the individual virology laboratories processing the specimens were located in close proximity with the trial site, the performance of quantitative viral cultures was therefore relatively easier to standardize than that for the pivotal treatment trials.

9.1 Protocol GS 97-801

Title: **Safety, tolerability, and activity of oral Ro 64-0796 in the treatment of subjects experimentally inoculated with human influenza Type A**

The objectives of this single center, double-blind, randomized study were to assess the safety, tolerability and antiviral activity of Ro 64-0796 (20 mg bid, 100mg bid, 200mg qd, or 200 mg bid) compared to placebo and, to assess trough plasma concentrations of Ro 64-0796 and its active metabolite Ro 64-0802 in subjects experimentally inoculated with human influenza A/Texa/36/91 virus. To maintain blinding, those subjects receiving active drug 20 mg bid received two 10mg capsules of active compound at each dosing. Subjects receiving 100 mg bid received one capsule containing 100 mg active compound and a matching placebo. Subjects receiving doses of 200 mg bid received two 100 mg active drug. Subjects receiving 200 mg qd received two capsules of matching placebo in the morning dose and two capsules of 100 mg active compound at the evening dose. The 10-mg, 100-mg strengths and the placebo were all size 4 capsules.

Eighty subjects, who were sero-susceptible to influenza A virus (defined as HAI antibody titer of $\leq$ 1:8), were randomized in an equal ratio to the 5 study groups. Administration of either drug or placebo began 24 hours after intranasal inoculation with 10^6 50% tissue culture of a safety-tested pool of human A/Texas/36/91 (H1N1) influenza virus strain. Of 80 subjects randomized, 69 (86%) became infected and were thereby eligible for efficacy analyses.

Efficacy measurements included quantitative virus titers, serum HAI antibody determination, nasal discharge weight and composite influenza symptom scores. Blood for pk measurements was collected at intervals throughout the study. The potential effect of food on exposure to the active drug was assessed following drug administration to half of the subjects in each treatment group under fasting

conditions and administration to the other half in close temporal proximity to a meal.

9.1.1 Efficacy results

All 69 subjects who developed infection with the inoculated influenza virus were included in the standard population.

Prior to virus inoculation of Day 1 all subjects who entered the study had a negative virus titer. At the baseline timepoint (immediately prior to first dose), all groups had similar virus titers, mean ranging from 0.6 to 1.0 log_{10} TCID50/ml.

The following table shows the AUC data over time obtained from subjects from individual treatment groups as well as the pooled active treatment groups.

Table 46:Virus Titer AUC (GS 97-801)

Virus titer AUC Log_{10}/TCID50 x hour	Placebo N=13	20mg bid n=15	100mg bid n=14	200mg bid n=14	200mg qd n=13	Pooled Ro64-0796 N=56
Mean	214.9	104.9	65	103.2	142	103.1
SD	136.1	121.4	58.3	88	128.9	103.7
Median	273.1	51.4	53.7	84.8	143.3	79.5
Range	0 – 351.7	0-432.7	0-185.3	9.7-348	0-441.4	0-441.4
p-value	NA	NA	NA	NA	NA	0.0204

Source: Table 5, vol. 223, page 41.

As shown in Table 46, over the entire study period, data obtained from subjects in the pooled active treatment groups were associated with a significantly lower AUC of virus titer compared to subjects in the placebo group.

Analyses of two secondary efficacy parameters also showed similar results:

The duration of virus shedding was reduced in all active treatment groups. The mean and median duration of virus shedding in the pooled active treatment groups were 58.8 and 55.7 hours compared to placebo (103.5 and 106.6 hours, respectively). The difference between the pooled treatment groups and placebo was found to be statistically significant (p=0.003).

All individual treatment groups demonstrated a shorter mean and median time to alleviation of the composite symptom scores. When individual treatment groups were pooled (median time to alleviation: 52.6 hours) and compared with placebo (median time to alleviation 94.8 hours), the difference in median time to alleviation between the two groups was found to be statistically significant (p=0.034).

9.1.2 Pharmacokinetic Results

Given the variability inherent within the assays used, the study was not of sufficient size to support analysis for the selection of a dosage regimen for later studies against naturally acquired influenza infection. For all bid dosing regimens, trough levels of Ro64-0796 observed were above concentrations associated with *in vitro* antiviral activity against influenza A and B strains. Consequently, the once daily dosing was not investigated further.

The food effect on the absorption of R064-0796 had not been evaluated in a formal cross-over design. In this study, approximately half of the subjects received the drug under fasting conditions, while the other half received drug in close temporal proximity to a meal. The results indicate that within each dose group, mean plasma concentrations of Ro 64-0796 and its active metabolite Ro 64-0802 were similar in both fasted and fed subjects. Consequently, no requirement of the timing of drug administration in relation to food was specified for subsequent trials.

9.1.3 Safety Results

All treatment doses were generally well tolerated. No relationship between the incidence of adverse events and dose of Ro 64-0796 was identified. The most common adverse event deemed by the investigator as being possibly associated with drug administration was nausea. There were no serious adverse events reported during the study and no patients were withdrawn from the study as a result of any adverse event.

9.1.4 Reviewer's Assessment and Conclusions

Study GS97-801 was a single center, double-blind, randomized study designed to assess the safety, tolerability and antiviral activity of Ro 64-0796 (20 mg bid, 100mg bid, 200 mg qd, or 200 mg bid) compared to placebo. Because the study was not of sufficient sample size, the study was not intended to support selection of a dosage regimen for later treatment trials.

The primary efficacy parameter employed was AUC of virus titer. This endpoint was significantly lower for subjects receiving Ro64-0796 than for those receiving placebo.

The compound was well tolerated with mild nausea being the most frequently noted adverse event. The results of an informal assessment of the food effect of Ro 64-0796 suggested that mean plasma concentrations of the prodrug and its active metabolite were similar in both fasted and fed subjects and that nausea and vomiting could be ameliorated by administering the drug with or shortly following a meal.

It is concluded that study GS 97-801 has provided convincing evidence that Ro 64-0796 significantly reduces the viral load associated with influenza, following experimental infection of subjects with influenza A/Texas/36/91 (H1N1) virus.

9.2 Protocol NP15717

Title: **Study of the phamacodynamics and pharmacokinetics of the neuraminidase inhibitor Ro 64-0796 in the treatment of volunteers experimentally infected with human influenza B virus**

This was a single center study conducted in New Zealand. The study design consisted of twice daily, oral administration of Ro 64-0796 or placebo commencing 24 hours after virus inoculation and continuing for 5 days. The dosing regimens studied were 75 mg or 150 mg or Ro 64-0796 bid for 5 days.

Sixty subjects were screened for sero-susceptibility to influenza B virus. Subjects were inoculated intranasally with 10^7 $TCID_{50}$ of influenza B/Yamagata/16/88 virus (supplied by NIAID, NIH), 24 hours prior to the start of study drug. Nasal washes were collected for quantitative viral culture prior to the start of study drug, twice per day for the next three days and then once per day until day 8 following inoculation. Type specific HAI antibody levels were measured on Day –1 and Day 21. Full pk profiles were taken on day 1 and day 5 with trough sampling on day 2, day 3, and day 4.

9.2.1 Efficacy Results

During the trial, a problem with the HAI assay procedure was discovered. An error was made in the initial viral antigen preparation. It made the applicant conclude that the assay procedure employed initially was insensitive for influenza B type specific antibody. The applicant then retested, prior to unblinding all blood samples, with a corrected assay procedure. As a result, a small number of subjects (3, 2, and 2 subjects in the placebo, 75 mg bid and 150 mg bid groups, respectively) with baseline HAI antibody titers of >1:10 (sero-positive) were found. In order to reconcile differences between these two sets of data, the applicant decided to use the data derived from the original antibody assay method for the primary efficacy analysis and the data derived from the retesting for an exploratory efficacy analysis.

- Primary efficacy analysis

In the pooled active treatment group the mean AUC virus titer was 102.5 with a standard deviation of 159.2, compared to 182.2 in the placebo group with a standard deviation of 241.6. Although the AUC of virus titers was substantially reduced in the pooled active treatment group the difference was not statistically significant (p=0.249) due to the high degree of variability between subjects as reflected by a higher standard deviation compared to mean values. Similarly,

analysis of the individual treatment groups revealed no statistically significant differences between the active treatment groups and placebo.

- Exploratory efficacy analysis

Since the applicant believed that the inclusion of subjects with influenza B/Yamagata/16/88 HAI antibody titers >1:10 could be responsible for the high variability of treatment effects. An exploratory analysis of the primary efficacy analysis was conducted using data only from those subjects with HAI antibody titer ≤1:10 at baseline. A total of 13 subjects in each group fulfilled the criterion. In the pooled active treatment group, the median (note: this is not a 'mean') AUC of virus titer was reduced by the administration of active drug. In the pooled active treatment group the median AUC of virus titer was 5.9 log 10 TCID 50x hours/ml compared to 149.7 in the placebo group. The difference in median AUC between the two groups approached statistical significance (p=0.086).

9.2.2 Safety Results

All treatments were well tolerated. Nausea was the most common adverse event that was considered possibly related to treatment. There were no serious adverse events or deaths during the study.

9.2.3 Reviewer's Assessment and Conclusions

Study NP15717 was a single center, double-blind, randomized study designed to assess the safety, tolerability and antiviral activity of Ro 64-0796 (75 mg bid or 150 mg bid) against influenza type B compared to placebo. Sixty subjects were screened for sero-susceptibility to the influenza B virus by an assay procedure which was later discovered to be insensitive. The applicant then retested, prior to unblinding all blood samples, with an improved assay procedure. With these two sets of data, the applicant conducted two efficacy analyses: primary (original) and exploratory (retested).

The efficacy parameter employed was AUC of virus titers. For the primary efficacy analysis, this endpoint was slightly lower for subjects receiving Ro64-0796 than for those receiving placebo but the reduction was not statistically significant (p=0.249). For the exploratory efficacy analysis, the reduction in median AUC value between the pooled active treatment groups and the placebo group was approaching statistical significance (p=0.086).

The compound was well tolerated with mild nausea being the most frequently noted adverse event.

It is concluded that study NP15717, employing an insensitive HAI antibody assay for sero-susceptibility screening, did not demonstrate conclusive antiviral activity

of Ro 64-0796 in subjects experimentally infected with influenza B/Yamagata/16/88 virus.

9.3 Protocol NP15827

Title: **Study of the pharmacodynamics of the neuraminidase inhibitor Ro 64-0796 in the treatment of volunteers experimentally inoculated with human influenza B virus**

This repeat study was prompted by the results from the preceding study in which a statistically significant difference in antiviral activity between active treatment and placebo had not been demonstrated.

The design of this trial deviated slightly from that of study NP15717 in 3 aspects:

- There were only two treatment groups: placebo and Ro 64-0796 75 mg bid
- Subjects were randomized 2:1 to receive Ro 64-0796 or placebo respectively. It was planned to enroll a minimum of 90 subjects.
- To be eligible, the HAI antibody titer to influenza B/Yamagata/16/88 must have been $\leq$ 1:8 at baseline employing the 'corrected' assay procedure.

9.3.1 Efficacy Results

There were 117 subjects enrolled and randomized. Following inoculation with influenza B/Yamagata/16/88, 86 of the 117 subjects were diagnosed as infected and were therefore included in the efficacy analysis.

As shown in the following table, the viral titer (VT) data prior to study drug administration appeared slightly imbalanced between 2 treatment groups.

Table 47: Viral Titers Prior to Treatment (NP15827)

Virus titer(log10 TCID50/ml)	Placebo (n=29)	75 mg bid (n=57)
Mean	1.3	1.1
SD	1.1	1.2
Range	0-4.3	0-5
Median	1.5	0.8

Source: Table 7, page 34, Amendment 7/30/99

The primary endpoint was therefore analyzed after adjusting for this apparent imbalance. The baseline viral titer was divided into two strata, baseline VT$\leq$1.5 and baseline VT >1.5 where 1.5 was the median value for the placebo group. Table 48 summarizes the analysis adjusted for baseline viral titer.

Table 48: Virus Titer AUC (NP15827)

Virus titer(log10 TCID50 x hr/ml)	Placebo (n=29)	75 mg bid (n=57)
Mean	201.9	73.5
SD	215.6	120
Min	0	0
Lower quartile	27.9	8.9
Median	131.1	22.7
Upper quartile	298.2	58.9
Difference between medians	NA	75.9
Max	687.3	458.5
95% CI for difference	NA	15.9 to 148.1
p-value	NA	0.0207

Source: Table 8, page 35, Supplement 7/30/99

The above analysis shows that treatment with Ro 64-0796 at 75 mg bid significantly decreased the AUC of viral titer compared to placebo.

9.3.2 Safety Results

All treatments were generally well tolerated. The majority of adverse events in both treatment groups were gastrointestinal events including nausea and vomiting. There were no serious adverse events or death recorded during the study. No subject withdrew prematurely due to adverse events.

9.3.3 Reviewer's Assessment and Conclusions

Study NP15827 was a 4-center, double-blind, randomized study designed to assess the safety, tolerability and antiviral activity of Ro 64-0796 (75 mg bid) against influenza type B compared to placebo. One hundred seventeen (117) subjects were enrolled and randomized. Following inoculation with influenza B/Yamagata/16/88 virus, 86 of the 117 subjects were diagnosed as infected.

The efficacy parameter was AUC of virus titer. The applicant's analysis showed that treatment with 75 mg Ro 64-0796 bid significantly decreased the AUC of viral titer compared to placebo.

All treatments were generally well tolerated. The majority of adverse events in both treatment groups were gastrointestinal events including nausea and vomiting.

It is concluded that study NP15827 has provided convincing evidence that Ro 64-0796 significantly reduced the viral load associated with influenza, following experimental infection of subjects with influenza B/Yamagat/16/88 virus. This conclusion is deemed as supportive evidence for allowing a general claim of Ro 64-0796 for treatment of influenza A and B in the absence of a sufficient number of influenza B-infected subjects enrolled into treatment trials.

10 Prophylaxis Studies in Naturally Acquired Influenza

10.1Protocols WV15673 and WV 15679

Title: **Double-blind, randomized placebo controlled studies of Ro 64-0796 for prophylaxis against human influenza virus**

Although the applicant did not request a prophylaxis indication for naturally acquired influenza in the present submission, results of these studies were included for long-term safety information.

The decision to combine data from studies WV15673 and WV15679 was made before unblinding the database. When designing the trials, the sample sizes for each of the two studies were calculated to demonstrate clinical efficacy of Ro 64-0796 provided that the incidence of influenza was at least 10% and the drug was at least 70% effective. This assumption would have required 39 laboratory confirmed cases of clinical influenza in each study. As it turned out, the number of subjects with laboratory confirmed clinical influenza in the 1997/1998 season was less than 39 in each study. Therefore, the studies were combined in order to give sufficient power for an efficacy analysis.

10.1.1 Overall Study Design

Both studies were conducted in the U.S. Three sites in Virginia participated in study WV15673. Two sites in Texas and 1 in Kansas City participated in study WV15679.

Both studies were double-blind, randomized, and placebo-controlled. Qualified subjects were identified before the start of the influenza season. Eligible subjects were healthy adults, age 18 to 65 years, and had not received influenza vaccine after 11/30/96. The eligible subjects were requested to return to the clinic when the principal investigators determined that influenza was present in the community. On the day of this return clinic visit (study day 1), subjects were assigned one of the three treatment groups as follows:

- Ro 64-0796 75 mg q.d.
- Ro 64-0796 75 mg b.i.d.
- Placebo b.i.d.

Study treatment was to continue for 6 weeks.

All subjects were to return to the clinic at week 3, week 6 and week 8. In addition, 'illness visits' were designed for subjects who, in between any scheduled visits, developed fever or any symptoms of influenza.

Influenza virus antibody titers were performed on study day 1 and week 8.

Nose/throat swabs for influenza virus culture were performed on study day 1 and whenever a subject developed fever or symptoms of influenza. (nasal washes in selected centers.)

Compliance was assessed from the quantity of study mediation returned by the subjects at the week 6 visit.

Blood samples were collected for hematology and biochemistry test at screening , week 3, and week 6.

The primary efficacy parameter was the incidence of laboratory confirmed clinical influenza during the 6-week treatment period. Laboratory confirmed influenza was defined as a clinical influenza-like illness that was confirmed to be influenza virus infection through either detection of influenza virus shedding within 2 days of the occurrence of symptoms meeting the criteria for clinical influenza, or a 4-fold increase in antibody to influenza virus. Clinical influenza was defined as an oral temperature $\geq$ 99°F (37.5° C) plus one respiratory symptom and one constitutional symptom.

The secondary efficacy parameters were the incidences, during the 6-week treatment period, of

- Asymptomatic influenza infection (virus shedding or a 4-fold increase in antibody to influenza virus in the absence of clinical symptoms of influenza.)
- Non-clinical influenza (symptoms not meeting the criteria for clinical influenza but confirmed to be influenza virus infection through detection of influenza virus shedding or a 4-fold increase in antibody to influenza virus.
- Influenza-like illness not caused by influenza virus

10.1.2 Efficacy Results

10.1.2.1 Demographics

The intent to treat (ITT) population consisted of all subjects who were randomized to treatment and who took at least one dose of study medication. Demographic data for the ITT population are summarized in Table 49.

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Table 49: Demographics (WV 15673 & WV 15679)

	Placebo (n=519)	75 mg qd (n=520)	75 mg bid (n=520)
Gender, male	185(36%)	204(39%)	188(36%)
Age, yr.			
Mean	35	34.4	34.3
SD	10.7	10.5	10.5
Median	34	33	32
Range	18-64	18-65	18-63
Race			
Caucasian	407 (78%)	421 (81%)	419 (81%)
African American	68(13%)	54 (10%)	58(11%)
Asian American	8(2%)	9(2%)	12(2%)
Hispanic	13 (3%)	13(3%)	15 (3%)
Other	25 (4%)	23 (4%)	16(3%)
HAI titer ≥ 1:40			
A H1N1	331 (63.8%)	325 (62.5%)	322 (61.9%)
A H3N2 Sidney	136 (26.2%)	132 (25.4%)	127(24.4%)
A H3N2 Wuhan	257(49.5%)	236 (45.4%)	234 (45%)
B	182(35%)	178 (34.2%)	166 (31.9%)

Source:Table 3 and 4, vol. 298, page 25 and 26.

The demographic characteristics of the three treatment groups were similar. There were no important differences between the groups with regard to the proportion of subjects with detectable antibodies to the predominant circulating influenza virus strain (influenza A H3N2- Sydney) at baseline.

10.1.2.2. Primary Efficacy Parameter: Laboratory Confirmed Clinical Influenza

Table 50: Primary Efficacy Parameter (WV 15673 & WV 15679)

	Placebo (n=519)	75 mg qd (n=520)	75mg bid (n=520)
Clinical influenza	25 (4.8%)	6 (1.2%)	7(1.3%)
Treatment effect:			
Placebo vs. 75mg qd	-	76%	-
Placebo vs. 75 mg bid	-	-	72%
P value*	NA	0.00055	0.00125

* Fisher exact test (comparisons against placebo adjusted using bootstrap method.)
Source: Table 18, vol. 298, page 45.

Of note, 7 subjects (2 in placebo, 1 in 75 mg qd, 4 in 75 mg bid) developed laboratory confirmed clinical influenza after the end of study treatment and before the final clinic visit at week 8. The applicant explained that the protective effect of Ro 64-0796 did not persist after elimination of the drug from the body at the end of treatment.

10.1.2.3Secondary Efficacy Parameters

- Asymptomatic influenza

Table 51: Asymptomatic Influenza (WV 15673 & WV 15679)

	Placebo (n=519)	75 mg qd (n=520)	75mg bid (n=520)
Asymptomatic influenza	19 (3.7%)	13 (2.5%)	12 (2.3%)
Treatment effect: Placebo vs. 75mg qd Placebo vs. 75 mg bid	- -	32% -	- 37%
P value*	NA	0.288	0.208

*Fisher exact test (comparisons against placebo, unadjusted.)
Source: Table 20, vol. 298, page 47.

- Non-clinical influenza

Table 52: Non-Clinical Influenza (WV 15673 & WV 15679)

	Placebo (n=519)	75 mg qd (n=520)	75mg bid (n=520
Non-clinical influenza	11(2%)	9 (1.7%)	8 (1.5%)
Treatment effect: Placebo vs. 75mg qd Placebo vs. 75 mg bid	- -	18% -	- 27%
p-value *	NA	0.66	0.499

*Fisher exact test (comparisons against placebo, unadjusted.)
Source: Table 19, vol. 298, page 47.

- Influenza-like illness

Table 53: Influenza-Like Illness (WV 15673 & WV 15679)

	Placebo (n=519)	75mg qd (n=520)	75mg bid (n=520)
Influenza-like illness	7 (1.3%)	5 (1%)	6 (1.2%)
Treatment effect: Placebo vs. 75mg qd Placebo vs. 75 mg bid	- -	29% -	- 14%
p-value *	NA	0.578	0.789

*Fisher exact test (comparisons against placebo, unadjusted.)
Source:Table 21, vol.298, page 48.

Results of the above tables show that the overall proportion of subjects with asymptomatic or non-clinical influenza infection was lower in the two active treatment groups, although there was no significant difference between either of the active treatment group and placebo.

10.1.3 Safety Results

10.1.3.1 Extent of Exposure to Study Medication

Most of the subjects took their study medication for at least 42 days as required by the protocol. The median duration of treatment was 43 days in all three groups.

Compliance was similar in all three study groups with >90% of subjects taking more than 80% of prescribed medication.

10.1.3.2 Subjects Prematurely Withdrawn from the Study

A total of 54 subjects were withdrawn from the study prematurely. Reasons for their withdrawal are summarized in the following table.

Table 54: Premature Withdrawal (WV 15673 & WV 15679)

Reason for premature withdrawal	Placebo (n=519)	75mg qd (n=520)	75 mg bid (n=520)
AE/intercurrent illness	10(1.9%)	8(1.5%)	7(1.3%)
Failure to return	4(0.8%)	5(1%)	6(1.2%)
Refused treatment	6 (1.2%)	9(0.4%)	9(0.6%)
Other violation	-	2(0.4%)	-
Administrative	1 (0.2%)	-	-
Total	21 (4%)	17 (3.3%)	16(3.1%)

Source: Table 5, vol 298, page 27

Twenty-five subjects were withdrawn prematurely because of adverse events. 7 subjects (4 in 75 mg qd group; 3 in 75 mg bid) discontinued treatment because of gastrointestinal adverse events (nausea, vomiting, abdominal pain). Three subjects in the placebo group withdrew because of skin rashes or dermatitis. Two subjects withdrew because of pregnancy, one each in the active drug treatment groups.

10.1.3.3.On-Treatment Adverse Events

The on-treatment window was defined as the time from the start of study treatment up to and including 2 days after the last day of study treatment.

Nonspecific headache was the most frequent adverse events. It was reported by more than 40% of the subjects. A higher percentage of individuals reported headache in the active treatment groups (placebo 38.9%, 75 mg od 43.3%, 75 mg bid 46.5%). Gastrointestinal disorders were more frequent among the active treatment groups than with placebo (22.9% and 25% with Ro 64-0796 given once and twice daily, respectively, compared to 17.3% in the placebo group). For the other body systems, the incidence of adverse events was not noticeably different between the three study groups. Most of the adverse events were rated by the investigator as mild or moderate in intensity.

10.1.3.4 Off-Treatment Adverse Events

The off-treatment period was defined from day 3 after the end of treatment until the end of the 2-week follow up.

The most frequent off-treatment events were similar in nature to the events seen most commonly on-treatment (headache and upper respiratory symptoms), but were of lower incidence. Most of the off-treatment events were mild or moderate and were considered to be unrelated to study treatment.

10.1.3.5 Serious Adverse Events

There were 10 events that fulfilled the criteria for a serious event. Nine of the ten events were thought by the investigator to be unrelated to study treatment (pelvic inflammatory diseases, tinea pedis, breast cancer, skull fracture, adenocarcinoma and 4 cases of pregnancy). One case of angina pectoris in a subject receiving 75 mg bid was judged to be remotely related.

10.2 Prophylaxis Study in Elderly: Protocol WV 15708D

Title: **A double-blind, randomized, placebo controlled study of Ro 64-0796 used in elderly subjects for the prevention of clinical influenza during the influenza season**

This was a multicenter, stratified and randomized, double-blind placebo-controlled parallel group study carried out in Elderly Persons Residential Homes in the Southern Hemisphere (Australia, New Zealand, South America, Brazil). The stratification factors were vaccine status and presence or absence of chronic obstructive airway disease. After eligibility screening, subjects were allocated to one of two treatment groups:

- 75 mg Ro 64-0796 q.d. for 6 weeks
- matching placebo q.d. for 6 weeks.

Randomization was initiated when influenza appeared in the community. Study treatment was initiated immediately after the baseline assessment. Subjects were instructed to report any illness to the residential home staff, and to make an illness visit should influenza-like symptoms occur. Adverse events were recorded throughout the study. Clinical laboratory tests and vital signs were recorded at the screening assessment, at baseline, at any illness visits, at the week 3 and 6 visits and at follow-up (2 weeks after the final dose of study treatment). Nose/throat swabs were taken for influenza virus culture at baseline, at any illness visits, at the week 3 and 6 visits and at the follow-up assessment. Blood samples for determination of influenza virus antibody titers were taken at baseline, on day 14 following the onset of influenza symptoms, and at follow-up.

10.2.1 Efficacy Results

A total of 385 subjects were randomized to treatment. Of them, a total of 323 completed the study, 13 took no study treatment, and 49 withdrew prematurely. The number of enrolled subjects was fewer than the originally planned 500 subjects because the peak of the influenza season had passed when the study treatment started.

The primary efficacy parameter was laboratory confirmed clinical influenza. Only 1 subject in the placebo group satisfied the definition of laboratory confirmed clinical influenza. This subject had not been vaccinated against the circulating strain during the flu season when the study was conducted.

The overall incidence of asymptomatic influenza infection in this study was also very low (17/385, 4.4%).

The applicant therefore concluded that no statistical analysis could be conducted due to the very low incidence of influenza for this trial.

10.1.2 Safety Results

A high proportion (90%) of the subjects had other pre-existing diseases. Hypertension was the most frequent co-existing disease reported. The two treatment groups did not differ significantly in terms of co-existing illnesses overall (44.5% and 51.6% for the placebo and 75mg q.d. group, respectively). However, it was noted that diabetes mellitus was more common in the Ro 64-0796 group than the placebo group (17.4% and 8.8%, respectively).

Similarly, the most frequently used concomitant mediations were antihypertensives, followed by analgesic/anti-inflammatory agents and benzodiazepines.

The median duration of treatment was 42 days for both groups. A similar distribution of subjects in both groups took <80% study medication (12% and 11% for the placebo and 75mg q.d. group).

The number of subjects reporting at least one adverse event during the 6 weeks of treatment was comparable for the two treatment groups (approximately 70% of subjects in each group). However, 30% more adverse events were reported in the 75 mg q.d. group compared with the placebo group.

The overall safety profile of Ro 64-0796 in this elderly population was similar to that previously noted in trials in younger subjects. Gastrointestinal events were most noticeably different between the placebo and active drug group. Elderly subjects appear to be more likely to report vomiting while on drug than subjects in younger age groups. In subjects taking Ro 64-0796, diarrhea occurred more frequently in the active drug group than the placebo (7.4% vs. 2.7%). This was not observed in the treatment studies where diarrhea occurred more frequently in the placebo group.

Serious adverse events occurred more frequently in this population than in previous studies. The events were frequently exacerbation of underlying disease states.

There were 2 deaths in the study population: 1 subject (placebo) died of bladder carcinoma; 1 subject (75 mg q.d.) died of hepatic neoplasm. Both deaths occurred over 30 days after the last dose of trial treatment and were considered by the investigator to be unrelated to trial treatment.

11 Integrated Evaluation of Efficacy

The applicant conducted an Integrated Evaluation of Efficacy (IEE) for Ro 64-0796 in order to show effectiveness data from all controlled studies having internal consistency with respect to important variables; and to test the strength of their conclusions by conducting various types of exploratory analyses on the pooled database.

The applicant's description of IEE encompassed a wide range of topics from an overview of the clinical program to development of resistant virus. Among them, 4 sections are felt critical to the applicant's overall conclusions on efficacy of Ro 64-0796. They are:

- Key efficacy results from the individual pivotal studies
- Pooled efficacy analyses
- Efficacy in subgroups of subjects
- Clinical and *in vitro* development of virus resistance

Efficacy results from individual pivotal studies that have been reviewed and presented in Section 8 of this MOR are not repeated in this section. For a discussion of virus resistance, please refer to Dr. Narayana Battula's Microbiology review.

The applicant's pooled efficacy database comprised of 3 treatment trials: WV15670, WV15671, and WV15730. WV15670 and WV15671(both Northern Hemisphere) were two pivotal trials. Although WV15730 (Southern Hemisphere) contributed only 4.2% of the pooled database, its inclusion in the pooled analyses was an attempt to present the data with a wide geographical representation. WV15891 and WV15812 were completed after this report, therefore they were not included in the integrated summary.

> Comment: Since identical protocols were followed by these trials and the time periods when the trials were conducted were in close proximity, combining data from three distinct trials is justified. Based on previous reviews of individual trials, the data quality and directions of efficacy results were sufficiently similar to support a pooling strategy.

A total of 1415 subjects were enrolled into these three trials. Of them, 887 subjects were classified in the pooled ITTI population.

11.1 Baseline Infection Type

At least 60% of the subjects, who entered these studies with a clinical diagnosis of influenza-like illness during an outbreak of influenza, were subsequently confirmed to be infected with the influenza virus. The proportion of subjects in the pooled ITTI population with each type of influenza virus is summarized in the following table.

Table 55: Summary of Virus Types (IEE)

Infection	Placebo (n=309)	75mg bid (n=301)	150 mg bid (n=277)
A (not specified)	-	1	1
A-H1N1	7(2%)	9(3%)	12(4%)
A-H3N2	288(93%)	275(91%)	248(90%)
B	8(3%)	7(2%)	8(3%)
Unknown type	6(2%)	9(3%)	8(3%)

Source: Table 10, vol 171, page 50

At least 90% of the subjects were infected with influenza A-H3N2 type.

11.2 Primary Efficacy Parameter: Time to alleviation of all symptoms in ITTI population

Table 56: Time to Alleviation of All symptoms (ITTI) (IEE)

Time (Hour)	Placebo (n=309)	75mg bid (n=301)	150 mg bid (n=277)
N	308	297	274
Mean	138.4	105.6	107.6
SD	6.1	5.2	5.9
Range	0 – 510.7	0 – 487.5	0 – 467.5
Median	112.5	78.2	78.5
95% CI within group median	101.5-119.9	72-88	68.2-88.7
p-value (vs. placebo)	NA	<0.0001	< 0.0001
95% CI for difference	NA	19.5 to 45.0	19.5 to 47.5

Source: Table 20, vol. 171, page 65

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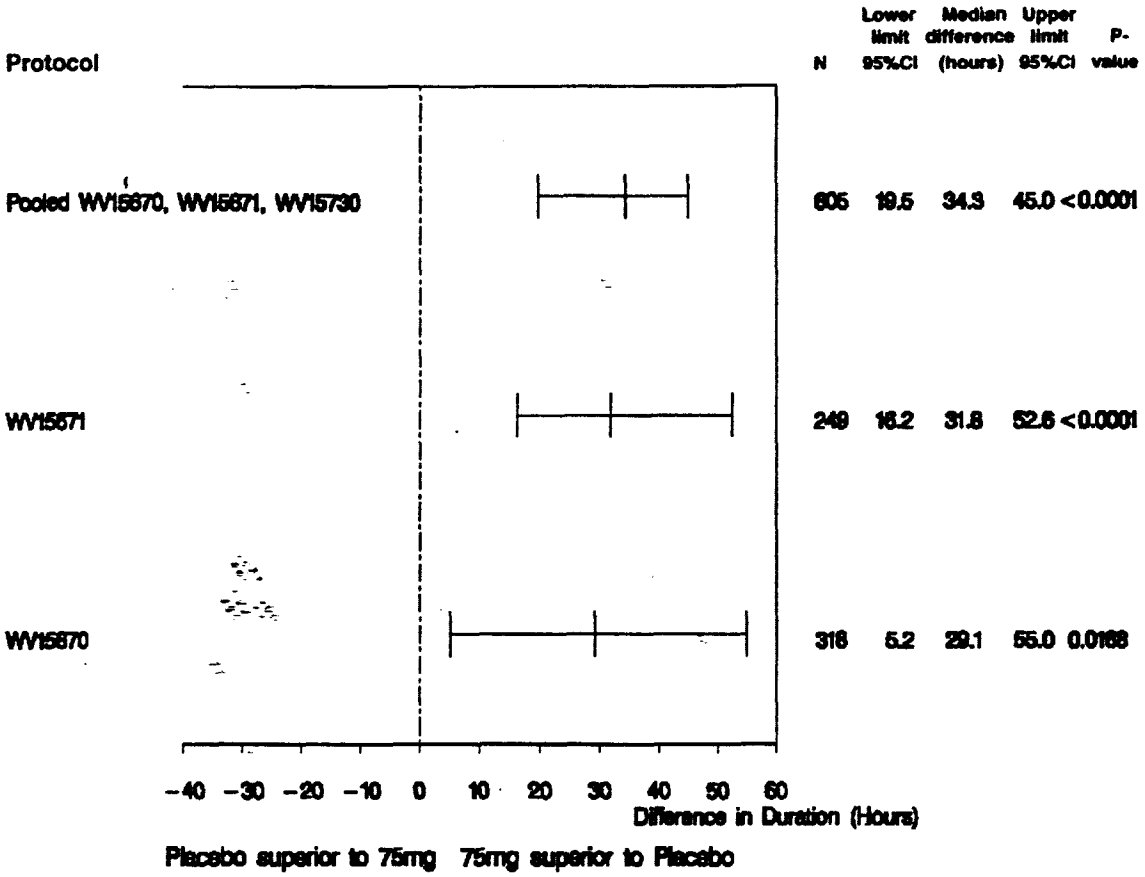
The above table shows that administration of Ro 64-0796 at a dose of 75 mg bid reduced the duration of the clinical symptoms of influenza by 30% when given within the first 2 days after the onset of symptoms. There was no additional clinical benefit gained by increasing the dose to 150 mg bid.

To illustrate the consistency of the results between the efficacy analyses of individual pivotal trials and the pooled database, the following figure displays the 95% confidence intervals of these analyses.

Figure 5: Summary of Confidence Intervals



Data for WV15730 alone are not included because of the small number of subjects in the study

Source:Fig. 9, Vol. 171, page 67

The above figure shows that the results of the analysis of the primary efficacy parameter (time to alleviation of all symptoms) in subjects treated with Ro 64-0796 75 mg bid for both the pooled dataset and the individual pivotal studies are fairly consistent. The pooled dataset provides a more precise estimate of efficacy as shown by the narrowest confidence intervals.

11.3 Robustness Analyses

The analysis of 'time to alleviation of all symptoms' as presented above could potentially be influenced by subjects for whom data were censored. In all three study groups, the majority of censoring occurred at 168 hr (morning of Day 8), when there was a changeover of diary cards. That is, the subjects whose data were censored on day 8 did not receive a second diary card, despite the fact they should have been issued according to protocol instructions. There were a total of 99 such censored subjects.

Therefore, the applicant performed 3 additional analyses to test the impact of censored observations.

(1) Subjects with censored data were assigned the longest observed duration of illness:

Table 57: Robustness Analysis (1)

Time (Hour)	Placebo (n=309)	75mg bid (n=301)	150 mg bid (n=277)
N	308	297	274
Mean	172.1	128.5	129
SD	159.2	139.9	138.3
Range	0 – 510.7	0 – 510.7	0 – 510.7
Median	114.1	78.2	79
p-value (median difference vs. placebo)	NA	<0.0001	< 0.0001
95% CI for difference	NA	16.3 to 41.4	15.3 to 41.1

(2) Only subjects in the active treatment groups with censored data were assigned the longest duration of illness:

Table 58: Robustness Analysis (2)

Time (Hour)	Placebo (n=309)	75mg bid (n=301)	150 mg bid (n=277)
N	308	297	274
Mean	126.6	128.5	129
SD	90.3	139.9	138.3
Range	0 – 510.7	0 – 510.7	0 – 510.7
Median	111.3	78.2	79
p-value (median difference vs. placebo)	NA	<0.0001	0.0049
95% CI for difference	NA	10 to 33.3	8.1 to 32

(3) Subjects with data censored before day 10 were assigned a duration of 216 hours (=day 9):

Table 59: Robustness Analysis (3)

Time (Hour)	Placebo (n=309)	75mg bid (n=301)	150 mg bid (n=277)
N	308	297	274
Mean	133.7	102.5	105
SD	92.9	80.2	84
Range	0 – 510.7	0 – 487.5	0 – 467.5
Median	114.1	78.2	79
p-value (median difference vs. placebo)	NA	<0.0001	<0.0001
95% CI for difference	NA	16 to 40	15 to 39.4

Source of Tables 57,58,59: Appendix 57, vol 171, page 166-167.

The results of these three robustness analyses show that:

- Administration of Ro 64-0796 at either a dose of 75 mg bid or 150 mg bid for 5 days significantly reduced the duration of the clinical symptoms of influenza similar to the primary analyses.
- There was no treatment difference between the 75 mg and 150 mg groups.

11.4 Exploratory Analyses

The applicant performed a number of exploratory analyses which are summarized below:

(1) Half-day Interval analysis

This was requested by the FDA to use nominal time-points of 12 hours instead of actual clock times in the calculation of time to alleviation of all symptoms. To do so, time to alleviation was divided into ½ day windows, pushing exact times to the end of the ½ day, e.g. 6, 28, 30, 42....hours.

The applicant performed this half-day interval analysis on both pooled and individual datasets of pivotal studies.

The results of these analyses, together with the analysis using the original clock time approach, are summarized in the following table.

Table 60: Time to Alleviation of All Symptoms (actual clock time vs. ½ day interval)

		Time to alleviation (hr)									
		Placebo		75 mg bid		150 mg bid		Placebo – 75mg bid		Placebo-150 mg bid	
Approach	Protocol	N	Median	N	Median	N	Median	Median (95% CI)	p-value	Median (95% CI)	p-value
Original	Pooled dataset	308	112.5	297	78.2	274	78.5	34.3 (19.5-45)	<0.0001	34(19.5-47.5)	<0/0001
½ day interval	Pooled dataset	308	114	297	90	274	90	24 (12-48)	<0.0001	24 (12-48)	<0.0001
	WV15671	128	114	121	78	119	78	36 (12-60)	<0.0001	36 (12 – 48)	<0.007
	WV15670	161	126	157	90	155	90	36 (0-48)	0.0125	36 (12-60)	0.0027

Source: Appendix 58, vol. 171. Page 168; facsimile 6/11/99.

The results obtained by the half-day analyses indicate a consistent and statistically significant median reduction in the duration of illness between the active drug and the placebo treated patients in both the pooled dataset and in individual pivotal trials.

(2) Impact of temperature and /or use of symptom relief medication

In order to assess the impact of 2 factors, temperature and use of symptom relief medication, either singly or in combination, the effect of Ro 64-0796 treatment on the duration of illness was further explored by conducting the analysis using 3 different definitions of symptoms alleviation:

(A) Absence of symptoms, as originally defined, plus absence of fever during the first period of at least 21.5 hr in which all symptom scores were ≤ 1.
(B) Absence of symptoms plus no use of symptom relief medication during the first period of at least 21.5 hr. in which all symptom scores were ≤ 1.
(C) Absence of symptoms plus absence of fever *and* no use of symptom relief medication during the first period of at least 21.5 hr in which all symptom scores were ≤ 1.

The results are shown in Table 61.

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Table 61: Exploratory Analyses

Definition of Alleviation	Time to alleviation (hr)									
	Placebo (n=309)		75 mg bid (n=301)		150 mg bid (n=277)		Placebo – 75 mg bid		Placebo – 150 mg bid	
	N	Median	N	Median	N	Median	Median (95% CI)	p-value	Median (95% CI)	p-value
Original	308	112.5	297	78.2	274	78.5	34.3 (19.5-45)	<0.0001	34 (19.5-47.5)	<0.0001
(A)	308	113.8	297	78.8	274	79.5	35 (19.3-45.7)	<0.0001	34.3 (20-47.4)	<0.0001
(B)	308	120.4	297	92	274	89.4	28.4 (15.9-47.7)	<0.0001	31 (13.8-51)	<0.0001
(C)	308	120.4	297	93	274	89.8	27.4 (16.2-47)	<0.0001	30.6 (13.3-50.4)	<0.0001

Source: Table 21, vol. 171, page 69

The results of the above analyses of the primary endpoint, requiring either or both absence of fever/rescue mediation, did not appear to change the conclusions of the primary analysis.

11.5 Duration of Illness in the ITT Population

Table 62: Time to Alleviation of All Symptoms (ITTI and ITT)

Population	Time to alleviation (hr)									
	Placebo		75 mg bid		150 mg bid		Placebo – 75 mg bid		Placebo – 150 mg bid	
	N	Median	N	Median	N	Median	Median (95%CI)	p-value	Median (95% CI)	p-value
ITTI	308	112.5	297	78.2	274	78.5	34.3 (19.5-45)	<0.0001	34 (19.5-47.5)	<0.0001
ITT	462	105.3	475	83.2	443	81	22.1 (9-35.8)	0.0002	24.3 (10.3-38.5)	0.0002
Influenza-negative	154	90.9	178	108.6	169	89	-17.7 (-40-16.5)	0.6576	1.9 (-24.1-29.1)	0.4425

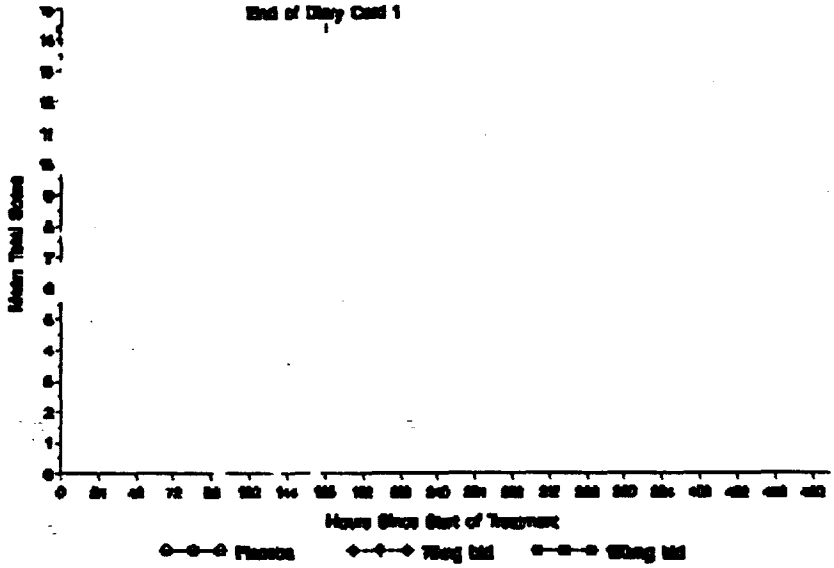
Source: Table 22, vol. 171, page 70.

There was a statistically significant benefit of Ro 64-0796 treatment in the ITT population. However, the observed benefit was entirely driven by the efficacy of the compound in the influenza-infected group since there was no evidence that Ro 64-0796 had any impact on the duration of illness in influenza-negative subjects (p=0.4425).

11.6 Reduction of Total Symptom Score Over Time

The results are depicted in the following figure.

Figure 6: Total Symptom Scores Over Time



Source:Fig. 10, vol. 171, page 71

The above figure displays the mean total symptom scores for each timepoint. It shows an early benefit with Ro 64-0796 administration, with lower mean scores in the active treatment groups. In all treatment groups there was a small increase in the mean total symptom score at 168 hours, when diary card 1 was completed and the second diary card was begun. The small increase in the mean score could be an artifact resulting from the protocol procedure that only patients who were symptomatic completed a second diary card.

11.7 Virology

The effect of Ro 64-0796 on viral replication was investigated in a subset of subjects who had nose and throat swabs taken at days 2, 4, and 6, and who were culture positive at baseline (day 1). This subset represents approximately 67% of the pooled ITTI population.

The major virologic endpoint in the treatment studies was the duration of viral shedding.

The time to cessation of virus shedding was measured from the start of study medication to the time of the first negative culture with no subsequent positive

cultures. The results, which were provided in the 9/1/99 response, are presented in Table 63.

Table 63: Duration of Virus Shedding (ITTI)

Time (hr)	Placebo N=309	75 mg bid n=301	150 mg bid n=277
N	245	257	237
Mean	76.9	70.7	69.2
SD	2.4	2.6	2.6
Range	0-167.3	0-220.6	0-171.7
Median	70.6	68.9	69.5
95% CI for within group median	70.1-71.9	67.3-70.3	67.8-70.8
	Median difference(a)	p-value (b)	95% CI for difference (a)
Placebo –75mg bid	1.7	0.0296	0.3-3.8
Placebo –150 mg bid	1.1	0.0310	-0.2-3.2

(a)Bootstrap estimates, (b) Weighted Mantel-Haenszel test

The above results show that there was a statistcally significant reduction (1.1 h – 1.7 h) in the active treatment groups with respect to the duration of virus shedding, although the reduction is hardly of any clinical significance.

11.8 Serology

The majority of subjects in the pooled database did not have a protective level of antibody titer (<1:40 HAI) at baseline. But the proportion of subjects with 'protective' baseline levels of antibody to the infecting virus type was similar in each treatment group: 17% in the placebo group; 16% in the 75mg treatment group; 17% in the 150 mg group. For those who were diagnosed as infected, the geometric mean change from baseline was around 20-fold in both active treatment groups and placebo. These data suggested that Ro 64-0796 did not suppress the antibody response to the influenza virus.

11.9 Symptom Relief Medication Usage

The applicant analyzed the acetaminophen usage data in many different ways, including the total cumulative dose, AUC of consumption over time, number of days on which rescue medication was taken from the pack provided, and number of occasions per day on which rescue medication was taken from the pack. The following table summarizes the 'total dose' and 'number of days used' data without presenting the 'AUC' and 'number of occasions/day' data since the latter two analyses were felt to offer little additional information.

Table 64: Summary of Acetamenophen Usage

Parameter	Placebo (n=309)		75mg bid (n=301)		150 mg bid (n=277)		Placebo-75mg bid		Placebo-150 mg bid	
	N	Median	N	Median	N	Median	Median difference (95%CI)	p-value	Median difference (95%CI)	p-value
Total dose (g)	309	5	301	4	277	3	0.5 (0-1)	0.067	1 (0.5-2)	0.0006
# days used	309	2	301	1.5	277	1.5	0.5 (0-0.5)	0.0312	0.5(0-0.5)	0.0006

Source: Table 29, vol. 171, page 79.

Overall, acetaminophen usage was lower during Ro 64-0796 treatment than during placebo administration. There was less consumption in the group treated with the higher dose of Ro 64-0796 than in the group receiving the lower dose. The differences from placebo were statistically significant for every parameter with the 150 mg group, and approached statistical significance with the 75 mg bid group.

11.10 Secondary Illnesses and Associated Antibiotic Use

Secondary illnesses were prespecified as bronchitis, otitis media, sinusitis and pneumonia. These selected illnesses were considered secondary to influenza if the onset was at least 48 hours after the start of study treatment. The overall incidence of the 4 selected secondary illnesses was 10% in the placebo group, 7% in the 75 mg bid group and 6% in the 150 mg bid group.

The proportion of subjects given antibiotics for the predefined illnesses, was reduced from 7% in the placebo group to 4% in the 75 mg bid and 3% in the 150 mg bid group.

11.11 Efficacy and Subject Characteristics (Age, Gender, Race)

The ITTI population was divided into subjects <35 years vs. ≥35 years of age. The analysis of time to symptom alleviation in these subgroups showed no difference between the two groups in effects of Ro 64-0796. However, the duration of illness was longer in the older age group.

The analyses by gender showed that the efficacy of Ro 64-0796 was comparable in both genders.

The majority of subjects in the treatment trials were Caucasian. Although there were small numbers of non-Caucasians, analyses by race showed a trend towards a beneficial effect of Ro 64-0796 treatment on illness duration.

12 Integrated Summary of Safety[3]

The core of safety data was presented for a pooled group which included all treatment studies in naturally acquired influenza (WV15671, WV15670, WV15730, and WV15707[4]) in which the recommended dose of 75 mg bid for 5 days was studied. Additional supportive long-term data were obtained from the prophylaxis trials in which the recommended dose given for 6 weeks was studied.

Because study WV15891 and study WV15812 were completed after this report, adverse events observed in these two trials were not integrated in the summary.

Although adverse events observed during the human experimental influenza and clinical pharmacology studies were not integrated in the summary, the event profile was reported to be similar to that from the core dataset.

12.1 Demographics

The demographic data for the 'core' studies and 'supporting studies' are presented as follows.

Table 65: Demographics (Core and Supporting Studies)

Parameter	Core (treatment studies)	Supporting (prophylaxis studies)
N	1418	1931
Age: Mean	35.91	43.08
Median	34	37
Range	18-65	18-95
SD	12.19	20.06
Sex: male	714(50%)	730(38%)
Female	704(50%)	1201(62%)
Race: Caucasian	1255(89%)	1616(84%)
Asian	40(3%)	47(3%)
African American	61(4%)	183(9%)
Other	62(4%)	85(4%)
Smoking:yes	442(31%)	-
No	950(67%)	-
N/A	26(2%)	1931 (100%)
Vaccination*: Yes	NA	255(69%)
No		117(31%)

*Data for vaccination obtained from study WV15708D.
Source: Tables 12 and 13, vol 172, page 47-48.

[3] After finalization of the study reports of WV15671 and WV15670, the applicant noted a programmatic error in the production of tabular outputs of adverse events for 'on-' and 'off-' treatment. Because the number of these uncorrected adverse events was small, the individual reports were not amended. Rather, an 'errata' page stating the precise error were compiled alongside each appropriate study report in the NDA. However, the corrected outputs were utilized for this integrated summary of safety. As such, there were minor discrepancies between the outputs presented for these studies in this summary and the equivalent ouputs presented in the corresponding final study reports.

[4] WV15707 had a small enrollment, therefore it was not individually reviewed in this MOR.

In both datasets, the majority of subjects enrolled were of Caucasian background. There was a predominance of female gender in the pooled prophylaxis trials which was to be expected of in elderly population.

12.2 Core Safety Studies

12.2.1 Adverse Events

In the pooled treatment studies, there was no evidence for a dose relationship in the frequency of reporting adverse events. Therefore, the overall adverse events were summarized and reviewed only for the 75 mg bid dose level and placebo, unless otherwise specified. Presented below is an overall event rate table in which a cut-off incidence rate of 2% (sum of column frequencies) was used.

Table 66: Adverse Events

Adverse event	Placebo (n=475)	75mg bid (n=496)
Vomiting	15(3.2%)	**59(11.9%)**
Nausea	31(6.5%)	**73(14.7%)**
Insomnia	3(0.6%)	**7(1.4%)**
Headache	11(2.3%)	**13(2.6%)**
Abdominal pain	11(2.3%)	**12(2.4%)**
Sore throat	6(1.3%)	6(1.2%)
Fatigue	7(1.5%)	6(1.2%)
Herpes simplex	6(1.3%)	4(0.8%)
Cough	10(2.1%)	8(1.6%)
Nasal congestion	10(2.1%)	6(1.2%)
Diarrhea	40(8.4%)	37(7.5%)
Dizziness	17(3.6%)	11(2.2%)

Source: Table 14, vol. 172, page 51.

Five adverse events (bold print) were more commonly reported by subjects receiving Ro 64-0796 (75 mg bid) than placebo. However, the excess reporting of headache and abdominal pain in the active treatment group compared with placebo is marginal. The applicant investigated these 5 events in more depth which are summarized as below.

12.2.2 Events According to Dose and Influenza Status

Table 67: Events More Commonly Reported in the Treatment Groups

	Influenza (+)			Influenza (-)		
	Placebo N=313	75mg bid n=306	150mg bid n=276	Placebo N=162	75mg bid n=190	150mg bid n=171
Vomiting	9(2.9%)	41(13.4%)	40(14.5%)	6(3.7%)	18(9.5%)	13(7.6%)
Nausea	21(6.7%)	41(13.4%)	44(15.9%)	10(6.2%)	32(16.8%)	24(14%)
Insomnia	2(0.6%)	5(1.6%)	8(2.9%)	1(0.6%)	2(1.1%)	0
Headache	9(2.9%)	8(2.6%)	5(1.8%)	2(1.2%)	5(2.6%)	8(4.7%)
Abdominal pain	6(1.9%)	9(2.9%)	4(1.4%)	5(3.1%)	3(1.6%)	5(2.9%)

Source: Table 17, vol 172, page 54.

The data suggest that vomiting was frequent among subjects receiving Ro 64-0796 if they were proven to have influenza infection. There was no evidence for a substantial difference in the incidence according to dosing regimen.

12.2.3 Intensity of Adverse Events, Relationship to Study Treatment

These 5 events were assessed mainly as mild or moderate in intensity regardless of treatment received. Headache and abdominal pains were the two events more commonly reported as severe. In subjects reporting vomiting, there is a suggestion of a shift in intensity from mild intensity to moderate intensity in the active dose groups. However, there was no evidence of an intensity shift between the two dose groups.

Nausea and vomiting were the two events with a higher proportion being classified as possibly or probably related to treatment in the Ro 64-0796 groups than in the placebo group.

12.2.4 Incidence of Adverse Event by Sex, Age, Race, Region and Smoking Status

- Vomiting

Vomiting was reported in twice as many females than males. This was apparent in both the placebo (4.1% and 2.2% in females and males, respectively) and Ro 64-0796 (75 mg bid) treated groups (16.5% and 7% in females and males, respectively). The mechanism for this difference is unclear.

There was no obvious effect of age, race or region (US vs. non-US) on the incidence of vomiting. However, it was noted that smokers reported vomiting less frequently than non-smokers (8.9% and 4.5%, respectively).

- Nausea

Similarly, females were more likely to report nausea than males. In the placebo group 9.5% of females reported nausea compared with 3.4% of males. In the Ro 64-0796 treated subjects, 18.5% of females experienced nausea compared with 10.7% of males.

There were no obvious differences in the incidence of nausea depending on age, region or smoking status in either the placebo or active drug treatment groups.

- Insomnia, Headache, and Abdominal Pain

Because the numbers of subjects reporting insomnia, or headache, or abdominal pain were low, an assessment of demographic interactions was not performed.

12.2.5 Recrudescence of Influenza-Like Illness

The diagnosis of influenza-like illness was solely based on the investigators' judgement and was recorded on the 'secondary illness form'. Although the

investigators were instructed only to report 'influenza-like illness' following the cessation of diary recording (meaning having achieved alleviation of all symptoms), this instruction was not uniformly followed.

At some sites, influenza symptoms and influenza-like illness were incorrectly reported on the 'adverse event' pages.

Since the reporting of influenza-like illness was inconsistent among sites, it is felt that the data provided in the submission were insufficient for a complete assessment of recrudescence of influenza-like illness.

To further explore the adequacy of these data, the applicant, in response to this reviewer's request, compiled a list of all cases reported to have a recrudescence of influenza-like illness from the two pivotal treatment trials. The following table compares the onset of influenza-like illness in relation to the timing of symptom alleviation (primary efficacy parameter). For ease of comparison, the time to alleviation was presented in days rather than using the original data in hours.

Table 68: Summary of 'Recrudescence' Cases

Pt. ID(treatment group)	WV15671		WV15670	
	Start day of 2nd illness (day)	Time to symptoms alleviation(day)	Start day of 2nd illness (day)	Time to symptoms alleviation (day)
1125 (placebo)	13	3		
1331(150 mg bid)	4	5(censored)		
1211(placebo)			13	6
1246(placebo)			6	7(censored)
1258(placebo)			4	5
1262(placebo)			8	7(censored)
1392(Placebo)			3	9
1406(Placebo)			5	6
1408(Placebo)			1	0
1415(placebo)			6	16
8271(placebo)			2	15
1225(75 mg bid)			1	9
1245(75mg bid)			8	6
1405(75mg bid)			8	3
1407(75mg bid)			8	4
1414(75mg bid)			4	9
1450(75 mg bid)			1	1
8434(75mg bid)			6	3
1442(150mg bid)			6	10
3105(150mg bid)			20	10
1412(150 mg bid)			4	8
8484(150 mg bid)			5	6

Source: submission 6/11/99

In WV15671, 2 subjects were reported to have influenza-like illness on the secondary illness form. For Subject 1125 the event had occurred after the alleviation of all initial symptoms; but for subject 1331, the rationale for reporting the event of recrudescence of influenza-like illness before the symptom alleviation is unclear.

In WV15670, 20 subjects were reported to have influenza-like illness recorded as secondary illness. Of these 20 cases, 12 subjects were reported to have influenza-like illness documented prior to the alleviation of initial symptoms.

There was only one subject whose influenza-like illness was recorded as an adverse event (subject 7141, placebo) in WV15670.

In conclusion, because the documentation of influenza-like illness as secondary illness to the initial influenza infection was erratic and in some cases not interpretable, it is felt that data presented in this NDA are inadequate to assess the incidence of recrudescence of influenza-like illness for the pooled analysis.

12.2.6 Adverse Events in Treatment Studies in the Elderly

Study WV15707 was a small treatment trial in elderly subjects (n=27). Although the study was not reviewed in detail, the safety profile of Ro 64-0796 appeared to be similar to that observed in younger (18-65 year) adults, with gastrointestinal events such as diarrhea and vomiting being the most common adverse events reported more frequently in the active treatment group.

Similarly, in study WV15819 where 77 elderly subjects were enrolled, the safety profile of Ro 64-0796 given at 75 mg bid for 5 days was similar to that observed in younger adults. There was an excess of nausea and vomiting in subjects receiving active treatment. There were no unexpected events reported in this elderly population.

Comment: Pharmacokinetic data from the ascending dose studies indicated that for a given dose of Ro 64-0796, exposure to Ro 64-0796 and its active metabolite, Ro 64-0802, was approximately 25% higher in elderly subjects compared to adults <65 years of age. This extent of increase in exposure does not seem to have any impact on the incidence of adverse events reported for elderly patients receiving the 75 mg bid dose of Ro 64-0796 treatment.

12.3Supporting Safety Data

12.3.1 Pooled Prophylaxis Studies

The pooled prophylaxis studies included WV15673, WV15697 (both in adults) and WV15708 (elderly).

In the prophylaxis studies subjects were exposed to Ro 64-0796 for 42 days (in contrast to 5 days for treatment studies) at doses of 75 mg q.d. or 75 mg bid. These prophylaxis studies provide information allowing a comparison of the nature and

frequency of adverse events between long-term exposure (42 days) versus short-term (5-day) exposure of Ro 64-0796.

The following table summarizes the adverse events in pooled prophylaxis studies by event and by dose. Presented in the lower section of the table is a partial list of events which occurred during the prophylaxis studies but were not reported in the treatment studies.

Table 69: Adverse Event (Pooled Prophylaxis Studies)

Events	Placebo (n=701)	75 mg bid (n=520)	75 mg od (n=710)
Vomiting	5(0.7%)	**14(2.7%)**	**22(3.1%)**
Nausea	39(5.6%)	**76(14.6%)**	**80(11.3%)**
Insomnia	11(1.6%)	10(1.9%)	16(2.3%)
Headache	228(32.5%)	242(46.5%)	263(37%)
Abdominal pain	17(2.4%)	21(4%)	23(3.2%)
Sore throat	67(9.6%)	57(11%)	74(10.4%)
Fatigue	84(12%)	60(11.5%)	92(13%)
Herpes simplex	6(0.9%)	4(0.8%)	10(1.4%)
Cough	64(9.1%)	27(5.2%)	68(9.6%)
Nasal congestion	92(13%)	53(10.2%)	85(12%)
Diarrhea	27(3.9%)	23(4.4%)	38(5.4%)
Dizziness	12(1.7%)	7(1.3%)	11(1.5%)
Myalgia	19(2.7%)	29(5.6%)	17(2.4%)
Dymenorrhea	47(6.7%)	47(9%)	47(6.6%)
Rigors	8(1.1%)	12(2.3%)	9(1.3%)
Sinus headache	13(1.9%)	15(2.9%)	11(1.5%)
Pain in the limb	5(0.7%)	8(1.5%)	15(2.1%)
Allergic rhinitis	3(0.4%)	6(1.2%)	4(0.6%)
Pain	32(4.6%)	27(5.2%)	45(6.3%)

Vomiting was reported by more Ro 64-0796 (75 mg bid) treated subjects compared with placebo (2.7% vs. 0.7%, respectively). A slightly higher percentage of subjects (3.1%) reported vomiting on 75 mg q.d. even though they were taking the drug at half the dosing frequency.

Nausea was experienced by 5.6% of subjects on placebo, 11.3% of subjects on 75 mg q.d. and 14.6% of those receiving 75 mg bid.

Headache was the most common adverse event recorded in the pooled prophylaxis studies and was reported by 32.5%, 37% and 46.5% of subjects in the placebo, 75 mg q.d. and 75 mg bid groups, respectively. Dosing frequency seems to have a bearing on this event in long term therapy.

Insomnia did not show any consistent differences in rates between the placebo and treatment groups.

Abdominal pain showed modest differences between placebo, 75 mg q.d., and 75 mg bid, reported as 2.4%, 3.2% and 4%, respectively.

Other adverse events that occurred only in the pooled prophylaxis studies did not appear to show significant differences in frequencies between treatment groups.

When comparing adverse events recorded by subjects receiving Ro 64-0796 at 75 mg bid for treatment (5 days) and to those receiving the same dose for prophylaxis (42 days), the results can be summarized as the following:

- The proportion of subjects reporting vomiting was noticeably lower in the prophylaxis studies than in treatment studies at the 75 mg bid dose (2.7% vs. 11.9%).
- The incidence of nausea was almost identical in both the treatment and prophylaxis studies at the 75 mg bid dose (14.6% vs.14.7%)

12.3.2 Adverse Events in the Prophylaxis Study in the Elderly

Information on the safety of Ro 64-0796 in the elderly was derived from WV15708, a seasonal prophylaxis study. Elderly subjects living in residential care homes were randomized to receive either 75 mg q.d. Ro 64-0796 or placebo for 42 days.

The events most frequently reported in the active drug treated groups were gastrointestinal events. In this population, vomiting occurred in 4.7% (9/190) of the 75 mg q.d. group compared to 0.5% (1/182) in the placebo group. Nausea occurred in 8.9% (17/170) of the 75 mg q.d. group and 1.1% (2/182) of the placebo group.

12.4 Time to Event Analysis for Selected Adverse Events

The 5 principal adverse events chosen for this analysis were vomiting, nausea, abdominal pain, insomnia, and headache.

The time to first occurrence of selected adverse events relative to the start of study treatment was investigated for both the treatment and prophylaxis study datasets. The following table summarizes the comparison.

Table 70: Time to Adverse Event (Treatment and Prophylaxis Studies)

Adverse event	Treatment studies (5 days)	Prophylaxis studies (42 days)
Vomiting Nausea Abdominal pain	Mostly reported on day 1 or day 2	Mostly reported on day 2 or day 3 in the active treatment groups and >7days in the placebo group.
Insomnia	Mostly reported between day 1 and day 3	Sporadically during the first 7 days
Headache	No particular pattern throughout the treatment period	No particular pattern throughout the treatment period

As shown in Table 70, vomiting and nausea were mostly reported on day 1 or day 2 of treatment in both study types.

The duration of adverse events was also investigated. In the treatment studies, all events were relatively short-lived (~2 days) in the active treatment group. In the prophylaxis studies, vomiting was found to last for up to a day longer than it did in the treatment studies. The duration of nausea and insomnia were similar in both study types.

12.5 Clinical Laboratory Data

The applicant presented summaries of mean shifts from baseline in hematological and biochemical parameters, comparing placebo with Ro 64-0796 (75 mg bid, 150 mg bid) treated subjects in the pooled treatment studies and prophylaxis studies. Changes were defined as differences between last valid post baseline value and baseline value. (Note: Blood and urine were sampled at only 3 timepoints: Days 1, 6, and 21±4.) Hematological laboratory parameters included hemoglobin, WBC counts, hematocrit, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils, MCV, and MCHC. Biochemical laboratory parameters included BUN, potassium, carbon dioxide, chloride, total bilirubin, fasting glucose, sodium, uric acid, SGOT, SGPT, GGT, alkaline phosphatase, albumin, creatinine, and total protein.

There were no clinically relevant changes in baseline for any of the laboratory parameters tested.

12.6 Serious Adverse Events Including Pregnancies

The numbers of serious adverse events reported from pooled treatment studies and pooled prophylaxis studies are summarized in the following table.

Table 71: Serious Adverse Events

	Pooled treatment studies	Pooled prophylaxis studies
On-treatment:		
Number of events	12(4 placebo, 8 active treatment)	25(13 placebo, 12 active treatment)
Number of events considered unrelated to study drug	10	23
Off-treatment:		
Number of events	3(all placebo)	14(5 placebo, 9 active treatment)
Number of events considered unrelated to study drug	3	14

Sources: vol. 173, appendices 46, 47, 48, and 50

In summary, there were no important differences in the reporting of serious adverse events in any of the active treatment groups compared with placebo.

In the treatment studies, a case of pseudomembranous colitis and abdominal pain in subject 20705/3616 (75 mg bid) and one case of pregnancy in subject

20673/1456 (150 mg bid) were considered by the investigator possibly related to treatment.

Subject 20705/3616 was a 39 years old male who underwent a laparoscopic appendectomy on study day 7. Post-operatively he was on ampicillin/sulfabactam and developed diarrhea which was later confirmed to be due to *Clostridium difficile*. The applicant assessed the *C. difficile* colitis to be unlikely related to study drug, as opposed to investigator's assessment. This reviewer agrees to the applicant's assessment.

Subject 20673/1456 became pregnant during the study. As of the submission of this application, the pregnancy was still ongoing. The investigator's assessment of this pregnancy to be possibly related to treatment is questionable.

A total of 4 pregnancies were recorded during clinical trials of Ro 64-0796. All pregnancies were recorded as serious adverse events as stipulated by the protocol. None of the pregnancies occurred in subjects who were taking oral contraceptives. Except for one normal outcome, no further information is available for the remaining 3 pregnancies as of 9/1/99.

12.7 Adverse Events Leading to Premature Withdrawal

A partial list of adverse events associated with premature withdrawal from studies of the treatment and prophylaxis of naturally acquired influenza is presented in the following table.

Table 72: Premature Withdrawal Due to Adverse Event

	Pooled treatment studies			Pooled prophylaxis studies		
	Placebo N=475	75mg bid n=496	150mgbid n=447	Placebo N=701	75mg bid n=520	75mg qd n=710
Nausea	0	1(0.2%)	1(0.2%)	1(0.1%)	3(0.6%)	5(0.7%)
Vomiting	1(0.2%)	3(0.6%))	2(0.4%)	0	0	4(0.5%)
Abdominal pain	1(0.2%)	0	2(0.4%)	0	1(0.2%)	3(0.4%)
Headache	0	0	1(0.2%)	7(1%)	0	0
Dermatitis	0	0	2(0.4%)	2(0.3%	0	0
Pneumonia	0	0	3(0.7%)	0	0	0
Diarrhea	0	0	1(0.2%)	0	0	3(0.4%)

Source: Table 64, vol. 172, page 136

The numbers of patients who discontinued study medication because of adverse events were 25 in the pooled treatment studies and 37 in the pooled prophylaxis studies. Overall, the proportion of subjects withdrawing prematurely due to adverse events from both short-term (5 days) and long-term (42 days) studies was low (62/3349; 1.7%). Withdrawal due to gastrointestinal adverse events occurred at a very low rate in the treatment studies and prophylaxis studies, 0.8% (11/1418) and 0.9% (17/1931), respectively.

12.8 Electrocardiogram Changes

In the multiple ascending dose study in the elderly, WP15647, the ECGs of 3 subjects (all 200 mg bid) showed changes during the treatment period. One subject (19010/0025) had T wave fattening and inversion and prolongation of an already prolonged QTc interval. An independent cardiological assessment stated that QTc interval seen in subject 19010/0025 was probably within the bounds of normal. The T wave changes seen in all 3 subjects could have been the result of non-specific patho-physiology such as seen with vaso-vagal reactions and hypotension. At the end of the treatment period, the configurations of the ECGs of all 3 subjects were similar to those at baseline.

ECGs were not routinely performed in the treatment nor prophylaxis studies.

12.9Pharmacokinetic Study in Renally Impaired Subjects (WP15648)

Ro 64-0796 is eliminated largely as the active compound, Ro 64-0802, via the kidney. WP15648 was a single-center, open-label study in which 20 subjects (18-59 years) with various degrees of renal dysfunction received Ro 64-0796 100 mg bid for 4 days, with single doses on Days 1 and 6. They were divided into 4 groups according to creatinine clearance (ml/min):

- Group 1 :CLcr <30
- Group 2: CLcr >30≤60
- Group 3: CLcr >60≤90
- Group 4: CLcr >90 (normal)

Ro 64-0796 was well tolerated in all groups. However the frequency of reported adverse events was higher in the three renally impaired groups than Group 4 as shown in the following Table.

Table 73: Adverse Event in Renally Impaired

Adverse event	Group 1 (n=5)	Group 2(n=5)	Group 3(n=5)	Group 4(n=5)
#subjects with at least 1 AE	4	3	4	3
Total # Aes	16	9	12	5
#subjects with				
Nausea	2(40%)	0	0	2(40%)
Vomiting	0	1	0	0

Most of adverse events were considered by the investigator to be associated with the subjects' underlying conditions and not likely to be drug-related. Nausea and vomiting, the commonly reported adverse events from the treatment trials, occurred at similar frequency between the three renally impaired groups and the group with normal renal function. Therefore, the applicant concluded that there was no evidence to suggest renal impairment would impact on the safety profile of Ro 64-0796.

Comment: Although nausea and vomiting occurred at a similar rate between groups, the rate (40%) appeared to be higher than that observed in the treatment studies. However, the number of subjects in each subgroup is too small to draw a conclusion.

Even though creatinine clearance was not measured in subjects enrolled in both the treatment and prophylaxis trials, the applicant did subgroup analyses by estimating the creatinine clearance value using the Cockroft and Gault equation. There were 2 subjects in the <30 ml/min CrCL group and 43 subjects in the 30-60 ml/min of CrCL group from the pooled treatment dataset (4-month safety update). The general pattern of adverse experiences within the 30-60 ml/min group was the same as that of the higher (normal) CrCL group. Vomiting and nausea were reported at a slightly higher rate (20%) for the <30% ml/min group based on a very small number of subjects. These findings seem reasonable to support the labeling recommendation of no dose adjustment for patient with creatinine clearance above 30 ml/min.

12.10 Drug Interaction Studies

12.10.1Acetaminophen (WP15676)

WP15676 was a study designed to investigate the effects of Ro 64-0796 on the safety, tolerability and pharmcokinetics of acetaminophen. The following treatment sequences were studied.

- Ro 64-0796 200 mg bid for 5 days, single doses of Ro 64-0796 200 mg and acetaminophen 500 mg on day 6, a washout period of 5 days followed by a single dose of acetaminophen 500 mg.
- A single dose of acetaminophen 500 mg, a washout period of 5 days followed by Ro 64-0796 200 mg bid for 5 days, with single doses of Ro 64-0796 200 mg and acetaminophen 500 mg on day 6.

Ro 64-0796 was well tolerated in the 3 treatment phases: Ro 64-0796 200 mg bid, Ro 64-0796 200 mg + acetaminophen 500 mg, and acetaminophen 500 mg. Results showed that administration of Ro 64-0796 in conjunction with acetaminophen did not yield any increase in number of adverse events recorded with either Ro 64-0796 or acetaminophen alone.

12.10.2Cimetidine, Probenicid (NP15728)

Clinical studies have indicated that renal excretion is the primary elimination pathway of Ro 64-0796 and its metabolite and that renal tubular secretion contributes to its clearance via this pathway. There are two pathways leading to the renal clearance, anionic and cationic. In order to investigate which pathway

Ro 64-0796 is eliminated, the applicant conducted an interaction study with cimetidine and probenicid.

Cimetidine is known to compete for active tubular secretion with some drugs, primarily those that are basic, resulting in a decrease of renal clearance, and a possible increase of serum concentration of those drugs when given with cimetidine.

Probenecid is known to inhibit the renal tubular transport of many acidic drugs. At the proximal and distal tubules, probenicid competitively inhibits the secretion of many weak organic acids, thus substantially increasing plasma concentrations of acidic drugs eliminated principally by renal secretion.

NP15728 was a study design to investigate the pathway of renal secretion of Ro 64-0796 and its metabolite by assessing the effect of plasma concentrations of cimetidine and probenecid on the pk of Ro 64-0796.

Subjects were randomized to receive each of the following three treatments, with washout intervals of 9 to 12 days:

- Ro 64-0796 150 mg single dose alone
- Ro 64-0796 150 mg single dose during multiple dosing with cimetidine 400 mg q6h
- Ro 64-0796 150 mg single-dose during multiple dosing with probenecid 500 mg q6h

The results showed that cimetidine had no apparent effect on the pharmacokinetics of either the prodrug or its active metabolite. In contrast, steady-state concentrations of probenecid caused decreased renal clearance of Ro 64-0802 indicating that renal tubular secretion of Ro 64-0802 occurred via the anionic pathway.

Adverse events were reported more frequently in subjects receiving the combination of Ro 64-0796 and cimetidine or probenecid than single administrations of individual drugs as shown in table below.

Table 74: Incidence of Adverse Events (NP 15728)

Drug regimen	No. subjects	Adverse events	
		No. subjects with AE	No. of events
Ro 64-0796 150 mg	18	5(28%)	6
Cimetidine 400 mg qid	18	2(11%)	3
Probenecid 500 mg qid	20	5(25%)	5
Cimetidine 400 mg qid + Ro 6-0796 150 mg	18	9(50%)	15
Probenecid 500 mg qid +Ro 64-0796 150 mg	19	9(47%)	15

Source: Table 57, vol. 172, page 114

The most frequently reported events were nausea, bruising and headache as shown in the table below.

Table 75: Adverse Events (NP 15728)

Adverse event	Ro 64-0796 150 mg (n=18)	Cimetidine 400 mg qid (n=18)	Probenecid 500 mg qid (N=20)	Ro 64-0796 + Cimetidine (n=18)	Ro 64-0796+ Probenecid (n=19)
Nausea	3(17%)	0	0	1(6%)	4(21%)
Bruising	2(11%)	0	1(5%)	4(22%)	1(5%)
Headache	1(6%)	0	1(5%)	1(6%)	4(21%)

Source: Table 7, vol. 199, page 38

Comment: According to Dr. Rajagopalan's assessment, there was no evidence of a pharmacokinetic interaction between cimetidine and Ro 64-0796. The interaction with probenecid suggested that Ro 64-0796 was renally cleared via the anionic pathway. This finding has subsequently prompted the applicant to conduct an interaction study with Amoxicillin which is ongoing.

The report of the brusing event in this cimetidine study as well as in a pediatric pharmacokinetic study (NP15826) is worth noting. A placebo group was not utilized in either study, thereby making it difficult to draw conclusions on the etiology of the bruising. The applicant believed this was an artifact and related to frequent blood draws in these two pk studies. In the treatment and prophylaxis studies evaluated to date, bruising has been reported rarely (0.3% and 0.2%, respectively in the active treatment groups; 0% and 0.1%, respectively in the placebo groups.) The bruising event should be kept in mind during post-marketing surveillance.

13. Reviewer's Overall Assessment:

The clinical section of this NDA submission is deemed generally well organized and clearly presented. The electronic submissions have provided added convenience to this review.

To support the indication of Ro-64-0796 for treatment of influenza infection, the applicant has completed two phase 3 pivotal studies (WV 15670 and WV 15671) conducted during the winter of 1997-98. Each trial examined the efficacy of Ro 64-0796 given for 5 days at doses of 75 mg bid and 150 mg bid vs. placebo in the treatment of naturally acquired influenza infection, when given within 40 hours of the onset of symptoms. In both studies, the time to alleviation of all symptoms was reduced by about 1.3 days with either dose. This degree of reduction is statistically significant and its robustness has been verified by multiple sensitivity analyses. The applicant's primary efficacy analyses were fully supported by the FDA's reanalyses.

The safety database consists of treatment and prophylaxis trials, allowing an adequate assessment of the toxicity profile of Ro 64-0796 under the conditions of

short- and long-term drug exposures in healthy adults. The drug was well tolerated. The most common adverse events were nausea and vomiting which were generally reported of mild to moderate in intensity. The safety profile of Ro 64-0796 was further supported by two ongoing studies in elderly and high risk patients.

During the labeling review, several issues were discussed, either within the review team or with the applicant, about the extent to which certain aspects of the efficacy data reported by the applicant could be incorporated into the package insert for Tamiflu. The following is a summary of these discussions.

1. Evidence of effectiveness against influenza B

   Since only 3% of the infected patients diagnosed with influenza B enrolled in the two pivotal trials, evidence for the effectiveness of Ro 64-0796 against influenza B is limited. At the pre-NDA meeting with the applicant, the division recognized both the practical limitations of recruiting sufficient numbers of patients with influenza B into trials and the unavailability of commercial rapid kits for distinguishing Types A and B viruses by laboratories in physicians' offices. The division's intent was to allow a broad treatment claim (including both influenza A and B) based on the totality of the available information, including *in vitro* data, animal models, human challenge trials and treatment trials. In this NDA, despite the lack of a sufficient number of influenza B cases from both treatment trials, the data provided by the applicant's *in vitro* studies, animal studies, and human challenge trials, collectively, have provided consistent and supportive evidence for the effectiveness of Ro 64-0796 against influenza B. Nevertheless, the effectiveness of Ro 64-0796 against influenza B in clinical settings will require continued investigation.

2. Severity of illness

   It is the division's consensus that the applicant's analyses of the severity of symptoms in terms of AUC of symptom scores can not be fully supported by the methodology employed for the two pivotal trials. Therefore, to present such data in the package insert could be misleading. The symptom scores were represented by arbitrarily chosen numbers, without giving considerations to the differing clinical significance (i.e. score weight) conferred by individual symptoms. Thus, these scores merely convey qualitatively that a subject who has a score of 10 is sicker than a subject with a score of 5. To quantify these scores as expressed by the AUCs is deemed not strictly appropriate.

3. Duration of viral shedding

   It is the division's consensus that the applicant's analyses of the duration of viral shedding can not be adequately supported by the data derived from the

two pivotal trials. The viral shedding status was fluctuated in most patients, possibly a reflection of inadequate sampling, delay in sample transporting, and/or inherent variability and insensitivity of the virus isolation procedure. In addition, a design flaw of both trials was that the sampling schedules were intermittent and irregular.

The magnitude of treatment effect (1.3 days), as shown by Ro 64-0796 in the NDA, is deemed modest. Given the fact that the untreated course of influenza infection in healthy subjects is self-limited and of relatively short duration, it would be difficult to expect any new therapies to demonstrate larger treatment effects in clinical trials. Therefore, a 1.3-day of reduction in illness duration is deemed reasonable to be translated into clinical benefits in otherwise healthy adults.

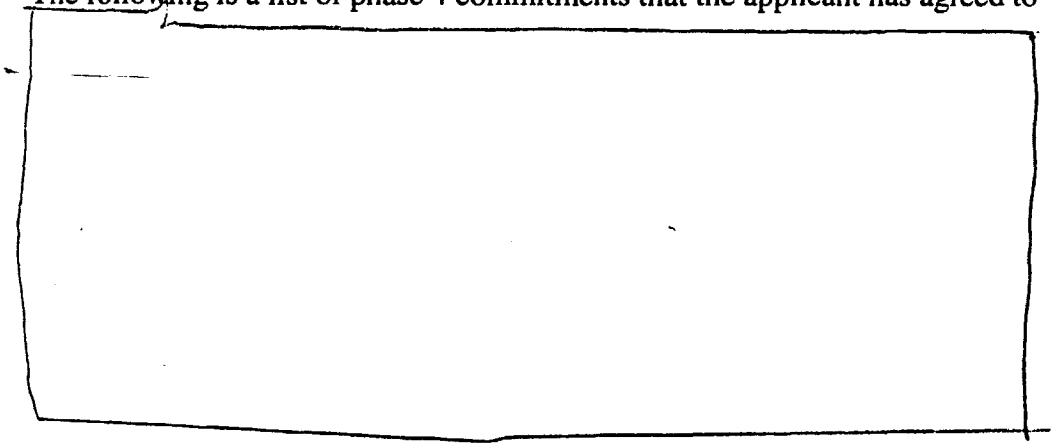
However, several questions remain to be answered. Studies are ongoing to assess the efficacy of Tamiflu in young children and persons over 65 years of age who are at increased risk of complications and deaths. The field experience and results of several ongoing clinical trials concerning the effectiveness of Tamiflu against influenza B are awaited to determine if the initial successes seen *in vitro*, in animal models and in human challenge trials will be confirmed. The potential for development of viral resistance to Ro 64-0796 and its clinical and epidemiological significance will also require continued investigation.

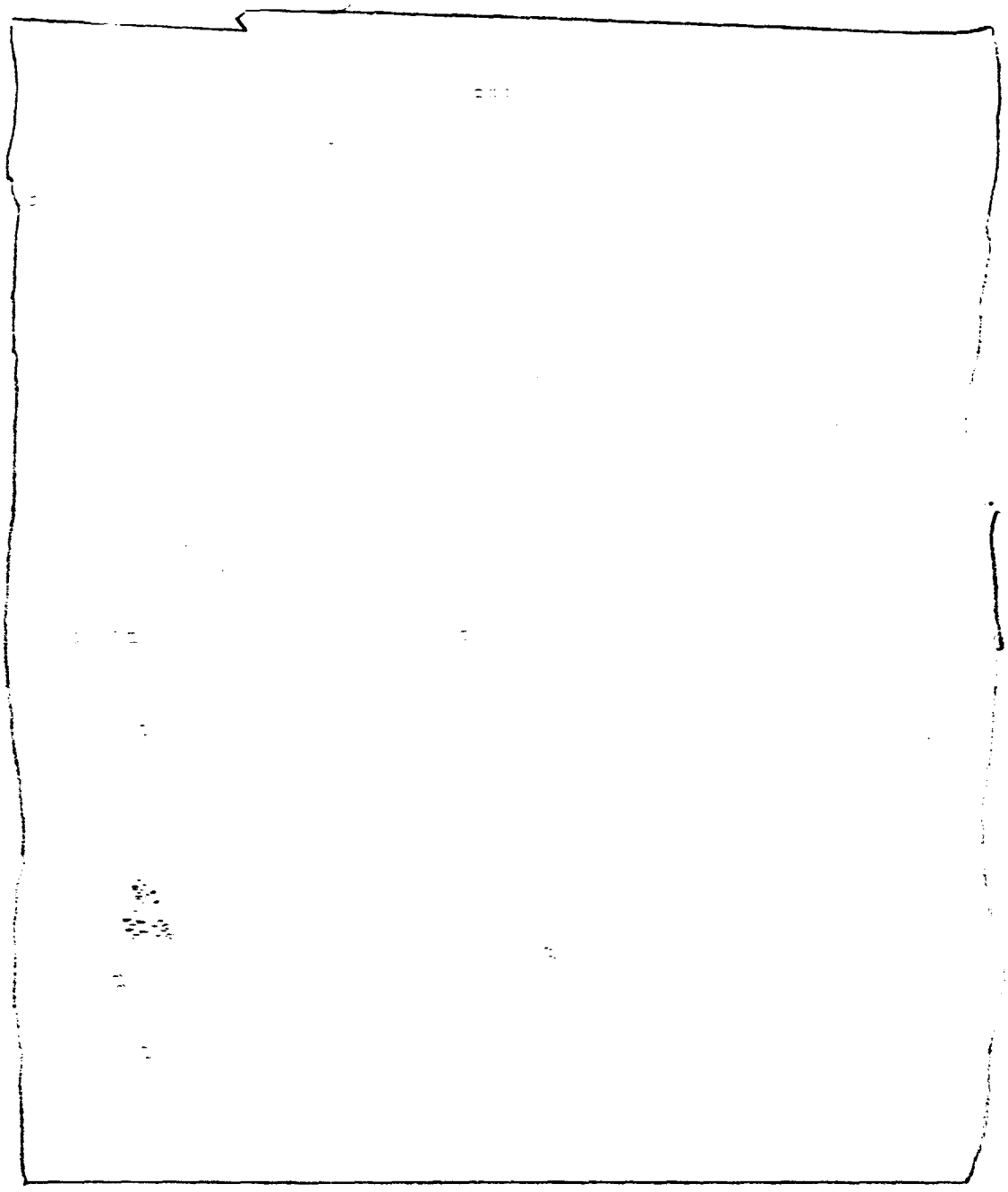
14. Package Insert and Patient Package Information

Comments brought up by the review team were discussed extensively with the applicant during the labeling review. The applicant accepted and incorporated all the recommendations in the final version of package insert as suggested by the review team.

15. Phase 4 Commitments

The following is a list of phase 4 commitments that the applicant has agreed to





16. Regulatory Recommendation

Based on this reviewer's assessment, the applicant has demonstrated the effectiveness and safety of Tamiflu for the treatment of influenza infection. It is recommended that this NDA be approved for treatment of uncomplicated acute illness due to influenza infection in adults.

/S/ 11/24/99

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Concurrences:

/S/

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CC
Orig NDA
HFD-340
HFD-530
MO/WuT
Chem/Boring
Pharm/Yuen
Micro/Narayana
Biophar/Rajagopalan
Stat/Hammerstrom
PM/Carmouze

APPEARS THIS WAY
ON ORIGINAL