CENTER FOR DRUG EVALUATION AND RESEARCH

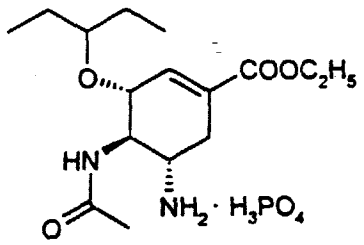
APPLICATION NUMBER for: 021087

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

REVIEWER	: Prabhu Rajagopalan, Ph. D.
NDA (FORMULATION)	: 21087 (Capsule)
TYPE	: 1P
APPLICANT	: Hoffmann-La Roche
DRUG	: Oseltamivir (Ro 64-0796)
STRENGTH	: 75 mg
SUBMISSION DATE	: April 29, 1999
DRAFT REVIEW	: September 3, 1999
FINAL REVIEW	: November 3, 1999

BACKGROUND



Oseltamivir phosphate

Oseltamivir (also referred to Ro 64-0796) is an ethyl ester prodrug of Ro 64-0802, an inhibitor of the neuraminidase enzyme of influenza virus. This enzyme catalyzes the cleavage of terminal sialic acid residues resulting in the release of the virus from infected cells. It is anticipated that inhibition of the neuraminidase enzyme may result in a decrease in the duration of illness.

A preclinical pharmacokinetic study indicated that the oral bioavailability of Ro 64-0802 is low. In order to improve the bioavailability of Ro 64-0802, an ethyl ester prodrug (Ro 64-0796) was synthesized. Upon oral administration of Ro 64-0796, this compound undergoes ester hydrolysis by esterases to yield the active species, Ro 64-0802.

Two major Phase III clinical trials have been conducted in support of this application. Studies WV15670 (non-USA) and WV15671 (USA) were conducted in patients with naturally acquired influenza. Patients enrolled in these studies were randomized to receive placebo or Ro 64-0796 at doses of 75 mg BID or 150 mg BID for a period of 5 days. The treatments were started within 36 hours of the appearance of symptoms. Partly based on the results of these studies, the Applicant recommends a dosing regimen of 75 mg BID of oseltamivir for 5 days for the treatment of influenza.

SYNOPSIS

The important features in the pharmacokinetics and disposition of oseltamivir are presented here. The question based review approach has been used in writing the synopsis section. Unless specified otherwise, in all subsequent sections of the synopsis, the variation in the mean is represented by percent coefficient of variation associated with the mean and is shown as mean (%CV). A detailed review begins on page 6.

Is Ro 64-0802 bioavailable upon oral administration of Ro 64-0796? If yes, what is the absolute bioavailability?
Following oral administration, extensive conversion of Ro 64-0796 to Ro 64-0802 takes place. The average absolute bioavailability of Ro 64-0802, upon oral administration of Ro 64-0796, was estimated to be 79% (15) in twelve healthy male subjects.

When administered orally, what are the disposition characteristics of Ro 64-0796?
About 75% to 85% of orally administered Ro 64-0796 is absorbed. Mean C_{max} values of approximately 1.0 hour and 4.0 hours were observed for Ro 64-0796 and Ro 64-0802, respectively. Plasma concentrations declined with a mean half-life of 1 hour and 6.5 to 7.5 hours for Ro 64-0796 and Ro 64-0802, respectively. On the average, approximately 5% of the administered drug was recovered in the urine as unchanged drug and 80% was recovered as Ro 64-0802. The renal clearance of Ro 64-0802 was greater than glomerular filtration rate indicating that the active species undergoes active tubular secretion.

By radioactivity measurements, an average of 74% and 17% of orally administered radioactivity was eliminated in the urine and feces, respectively.

Are the steady-state pharmacokinetic parameters in adult subjects independent of dose? What are the multiple dose pharmacokinetic features of Ro 64-0796 and Ro 64-0802?
In healthy male adult subjects, over the dose range of 50 to 500 mg BID, statistically significant deviation from dose proportionality was not seen in steady-state Ro 64-0802 C_{max} and AUC_{12}. Percent of administered drug eliminated as Ro 64-0796 and Ro 64-0802 was comparable in this dose range. At steady-state, ratio of Ro 64-0802 to Ro 64-0796 AUC_{12} ranged from 25 to 29 indicating extensive conversion of the prodrug. Following administration of multiple doses of Ro 64-0796 twice daily for seven days, a 60% to 80% increase in Ro 64-0802 AUC_{12} was observed, which is consistent with the reported half-life.

The Applicant has estimated key pharmacokinetic parameters of Ro 64-0796 and Ro 64-0802 in Phase III studies. The mean (%CV) values after five days of dosing are reported below.

	Ro 64-0796		Ro 64-0802	
	75 mg BID	150 mg BID	75 mg BID	150 mg BID
n	24	20	24	20
C_{max}, ng/mL	84.7 (58)	141 (51)	398 (26)	772 (18)
AUC(0-12), ng.h/mL	148 (31)	266 (26)	3447 (30)	6518 (20)
Half-life, h	1.7 (31)	1.8 (23)	7.9 (36)	7.4 (39)

Are the steady-state pharmacokinetic parameters in elderly subjects (age > 65 years) independent of dose? Is the disposition of Ro 64-0796 different in elderly subjects when compared to adult subjects?
At steady-state, significant deviations from dose proportionality was not seen in Ro 64-0796 and Ro 64-0802 C_{max} and AUC_{12} in the dose range 100 to 200 mg BID. In general, exposure to Ro 64-0802 was 25% higher in the elderly subjects when compared to adult subjects. In part, this may be attributed to reduced renal function.

Knowing that renal clearance of Ro 64-0802 involves active tubular secretion, what is the pathway of active tubular secretion?
Concomitant administration of Ro 64-0796 and cimetidine did not have a significant effect on the pharmacokinetics of Ro 64-0802. However, concomitant administration of Ro 64-0796 and probenecid increased the average Ro 64-0802 C_{max} and AUC by 83% and 145%, respectively. This was also accompanied by a 53% decrease in Ro 64-0802 renal clearance. These data indicate that Ro 64-0802 is partly cleared by the anionic tubular secretion pathway in the kidneys.

Does renal impairment affect the pharmacokinetics of Ro 64-0796 and Ro 64-0802?
The pharmacokinetics of Ro 64-0796 and Ro 64-0802 are altered in subjects with renal impairment. While the impact on Ro 64-0796 C_{max} and AUC was modest, renal impairment significantly affected the pharmacokinetics of Ro 64-0802. The average Ro 64-0802 AUC_{12} increased by 2.4-, 3.6- and 10.3- fold in subjects with mild (CLcr between 60 and 90 mL/min), moderate (CLcr between 30 and 60 mL/min) and severe (CLcr between 10 and 30 mL/min) renal impairment, respectively.

Knowing that acetaminophen was widely used as a relief medication in Phase 3 studies, is there a pharmacokinetic interaction between Ro 64-0796 and acetaminophen?
A small study conducted in six healthy male subjects indicates that multiple doses of Ro 64-0796 does not have a significant effect on the single dose pharmacokinetics of acetaminophen.

Is there a relationship between exposure to Ro 64-0802 and response?
Two studies were conducted in healthy subjects experimentally inoculated with influenza A and B virus. The activity of placebo and four doses of Ro 64-0796 (20 mg BID, 100 mg BID, 200 mg BID and 200 mg QD) were evaluated against influenza A. The activity of placebo and two doses of Ro 64-0796 (75 mg BID and 150 mg QD) were evaluated against influenza B. A clear exposure-response relationship was not apparent in these two studies. However, viral AUC (a response parameter) for Ro 64-0796 treated groups was lower when compared to placebo providing preliminary evidence for antiviral activity.

What impact does food have on the pharmacokinetics of Ro 64-0802?
When Ro 64-0796 was administered immediately after a high-fat breakfast, a 19% decrease in mean Ro 64-0802 C_{max} was observed. The geometric mean ratio [90% CI] for fed to fasted comparison was 0.81 [0.76 – 0.86]. However, this decrease in C_{max} was

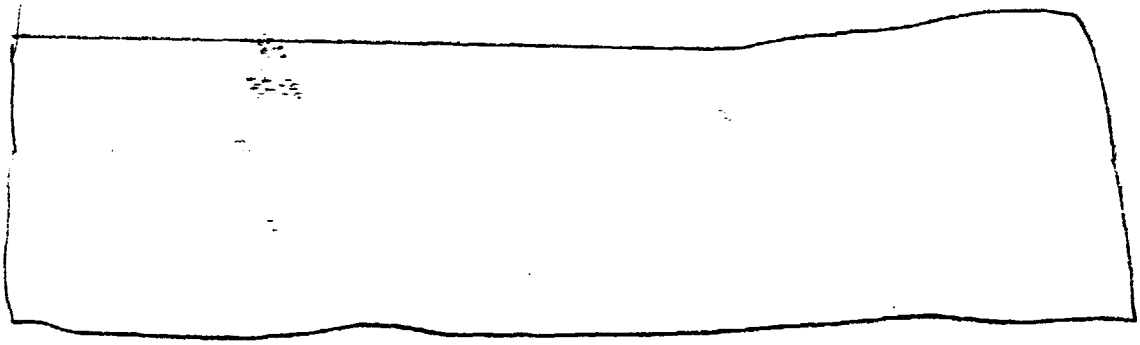
associated with only a minor (~3%) decrease in AUC_{∞}. In Phase III clinical trials, Ro 64-0796 was dosed without regard to meal consumption.

Is the proposed market formulation bioequivalent to the clinical trial formulations?
The Applicant conducted two bioequivalency studies. In the first study, the market formulation was compared to the clinical trial formulation and in the second study, the market formulation was compared to an early clinical trial formulation. A single dose of 150 mg of Ro 64-0796 was administered to healthy subjects under fasted conditions in these two studies. The results of these studies are shown below.

PK parameter of Ro 64-0802	Formulation	Arithmetic mean (%CV)	Geometric mean	% point estimate [90% CI]
C_{max}, ng/mL	Clinical trial	543 (45)	508	100
	Market	551 (37)	526	103.6 [97 – 111]
$AUC_{0-\infty}$, ng.h/mL	Clinical trial	6155 (16)	6083	100
	Market	6218 (12)	6176	101.5 [98 – 106]

PK parameter of Ro 64-0802	Formulation	Arithmetic mean (%CV)	Geometric mean	% point estimate [90%CI]
C_{max}, ng/mL	Market	550 (17)	541	100
	Early clinical trial	560 (19)	552	101.9 [94 – 111]
$AUC_{0-\infty}$, ng.h/mL	Market	6200 (22)	6050	100
	Early clinical trial	6339 (17)	6249	103.3 [98 – 109]

These results indicate that the market formulation is bioequivalent to the clinical trial formulations with respect to Ro 64-0802.



CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS BRIEFING
The briefing was held on September 21, 1999 and was attended by Drs. Rajagopalan, Wu, Reynolds, Bashaw, Selen, Lazor, Chen, Mehta, Sun and Suarez.

RECOMMENDATION

The human pharmacokinetic studies submitted under NDA 21087 provide an understanding of the pharmacokinetics of oseltamivir (Ro 64-0796) and fulfills the requirements of Section 320 of the Code of Federal Regulations (21 CFR). Adequate pharmacokinetic information has been provided to support approval of TAMIFLU™.

/S/ 11/3/99

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Concurrence: /S/ 11/3/99

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cc: HFD-530 /NDA 21087
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HFD-880 /Rajagopalan
/Reynolds
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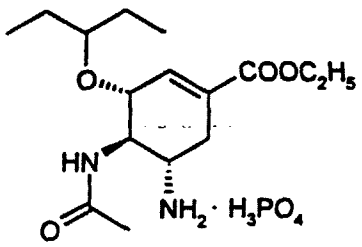
I. CHEMISTRY OVERVIEW

Chemical name: Ethyl-(3R, 4R, 5S)-4-acetylamino-5-amino-3(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid ethyl ester, phosphate.

Structure:



Molecular Formula : $C_{16}H_{28}N_2O_4$
Molecular weight: : 312.4
Solubility : > 250 mg/mL in water.

II. FORMULATION

The composition of the proposed market formulation is given below:

Ingredient	mg/tablet
Oseltamivir phosphate*	
Starch	
Croscarmellose sodium	
Povidone K30	
Talc	
Sodium stearyl fumarate	
Total weight	

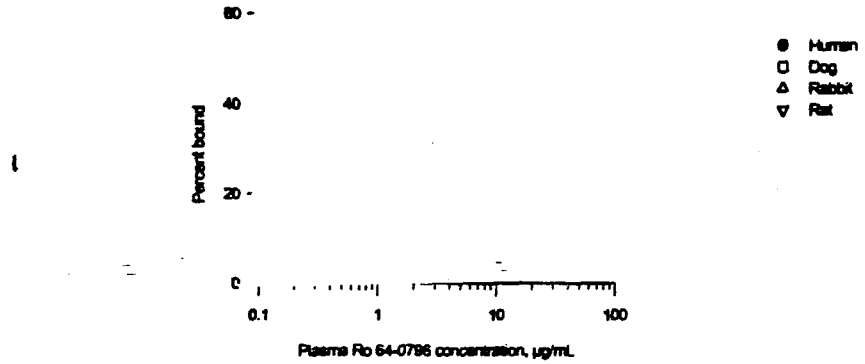
III. INDICATION (as per proposed label)

Oseltamivir is indicated in the treatment of influenza.

IV. DOSAGE AND ADMINISTRATION (as per proposed label)

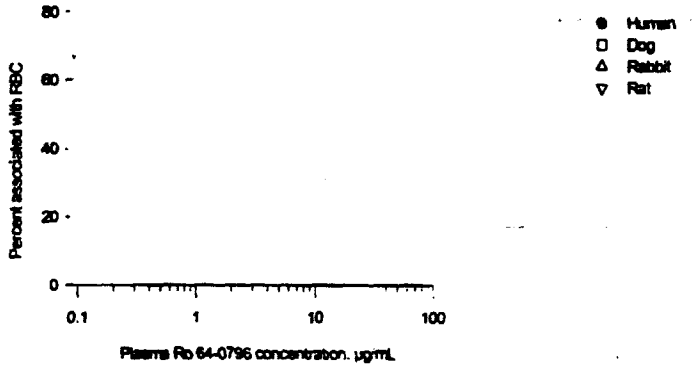
The proposed recommended oral dose of Oseltamivir for adults is 75 mg twice daily for 5 days. Dose adjustment is recommended for patients with severe renal dysfunction.

Protein binding: Plasma protein binding of Ro 64-0796 and Ro 64-0802 was determined by ultrafiltration technique. 14C radiolabeled Ro 64-0796 and Ro 64-0802 were incubated at concentrations ranging from 0.1 to 5 µg/mL in human plasma. At steady-state, mean Ro 64-0796 and Ro 64-0802 Cmax values at a dose of 100 mg BID were approximately 65 and 440 ng/mL, respectively in healthy adult subjects. It is noted that the concentration range chosen does not cover clinically relevant Ro 64-0796 concentrations. In rat, rabbit and dog plasma, Ro 64-0796 and Ro 64-0802 concentrations ranged from 0.1 to 100 µg/mL. The percent of Ro 64-0796 bound to plasma proteins is shown in the following figure.



In human plasma, Ro 64-0802 was largely unbound to plasma proteins. Percent of Ro 64-0802 bound to proteins was highest (approximately 6%) at a concentration of 0.1 µg/mL. At concentrations of 0.2, 0.5 and 1 µg/mL, protein binding was less than 1.5%. The binding of Ro 64-0802 to plasma proteins was low and averaged less than 4% in all other species. Some negative values observed in this study have been attributed to imprecise bioanalytical measurements.

Red blood cell partitioning study: ^{14}C radiolabeled Ro 64-0796 and Ro 64-0802 were incubated at concentrations ranging from 0.1 to 5 µg/mL in human whole blood. In rat, rabbit and dog whole blood, Ro 64-0796 and Ro 64-0802 concentrations ranged from 0.1 to 100 µg/mL. Based on initial studies, an incubation time of 10 minutes was chosen as the optimum time for red blood cell partitioning studies. The results of the erythrocyte partitioning studies are shown below.



When compared to Ro 64-0796, significant partitioning of Ro 64-0802 into red blood cells was not observed. Percent of Ro 64-0802 associated with red blood cells (in human whole blood) was 17.8 and 16.6% at a concentration of 0.1 and 0.2 µg/mL. Negative values were calculated for percent associated with red blood cells at other concentrations and in samples obtained from other species. Approximately, mean percent associated with red blood cells from human, rat, dog and rabbit was 14%, 13%, 7% and 7%, respectively.

Based on preliminary studies, dichlorvos (an inhibitor of esterase activity) was added to rat blood and plasma samples to prevent conversion of Ro 64-0796 to Ro 64-0802. The Applicant has conducted a study to examine the stability of Ro 64-0796 and Ro 64-0802 in human blood, plasma and urine and plasma samples obtained from rat, marmoset, mouse, rabbit and ferret.

An investigation of the stability of Ro 64-0796 and Ro 64-0802 in biological fluids (Volume 72)

Human, rat, marmoset, mouse, rabbit and ferret blood and plasma samples were spiked with Ro 64-0796 to obtain concentrations of 5 and 200 ng/mL. Human urine samples were spiked to obtain concentrations of 25 and 800 ng/mL. Similarly, human, rat, marmoset, mouse, rabbit and ferret blood and plasma samples were spiked with Ro 64-0802 to obtain concentrations of 50 and 8000 ng/mL. Human urine samples were spiked to obtain concentrations of 150 and 24000 ng/mL.

Long term stability studies involved storing four or five aliquots at 4° C and –20° C for 7 days and 6 months, respectively. Since previous studies have shown rapid conversion of Ro 64-0796 in rat and mouse plasma, long-term studies were not conducted for these matrices. Experiments were also conducted to measure stability of Ro 64-0796 and Ro 64-0802 at room temperature in human plasma and urine (incubation time: 1 hour) and at room temperature and 4° C in whole blood (incubation time: 4 hour).

The following observations were made. Ro 64-0796 and Ro 64-0802 were stable when stored at -20° C for 6 moths in human plasma and urine. These compounds were also stable in plasma obtained from various species at this temperature. In human plasma, conversion of Ro 64-0796 to Ro 64-0802 occurred at 4° C. The Applicant has calculated a half-life of 7.4 days and 8.8 days for the 5 and 200 ng/mL concentrations. However, both these compounds were stable in plasma samples from other species.

At room temperature, rapid conversion of Ro 64-0796 to Ro 64-0802 was observed in mouse and rat plasma with average half-life values of 60 and 20 minutes, respectively. Conversion of Ro 64-0796 was not significant in plasma samples obtained from other species (including human). Ro 64-0796 (particularly at the low concentration of 5 ng/mL) appears to be sufficiently stable in whole blood at room temperature and at 4°C for between 1 to 2 hours. Ro 64-0802 is stable in whole blood at room temperature and at 4°C for up to 2 hours.

In vitro metabolism of Ro 64-0796. Main metabolites formed in plasma, liver S-9, microsomes and hepatocytes from rats and man (Volume 66).

Relevant results from this study are presented here.

Incubation in human plasma

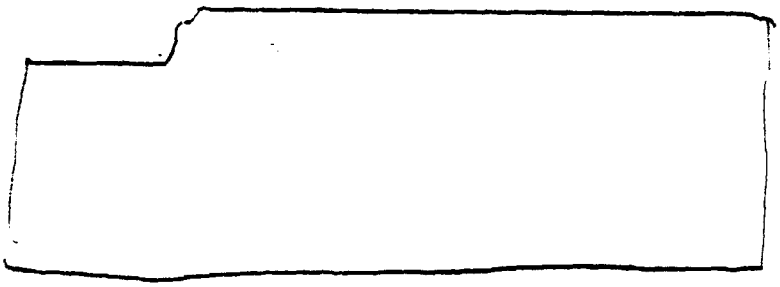
Ro 64-0796 was found to be stable when incubated in human plasma.

Incubation in human microsomes

In control incubation with human microsomes, Ro 64-0796 was hydrolyzed to Ro 64-0802. In incubation of Ro 64-0796 with NADPH, no other species other than Ro 64-0802 was seen. In incubation of Ro 64-0796 with UDP-GT, formation of glucuronic acid conjugate of Ro 64-0796 was seen. Incubations of Ro 64-0802 under the above three conditions did not result in further metabolism

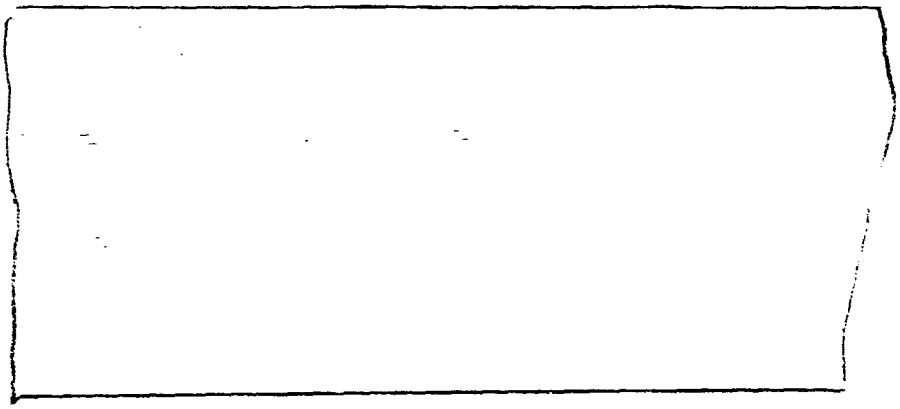
Incubation in human liver homogenate S9

When incubated in human liver homogenate S9, Ro 64-0796 was hydrolyzed to Ro 64-0802.



Incubation with human hepatocytes

In incubation with human hepatocytes, rapid conversion of Ro 64-0796 to Ro 64-0802 occurred within 2 minutes.



An investigation of the potential inhibitory effect of Ro 64-0796 and Ro 64-0802 on the metabolism of cytochrome P450 model substrates (Volume 66).

The inhibitory effect of Ro 64-0796 and Ro 64-0802 on human cytochrome P450 1A2, 2C9, 2C19, CD6, 2E1, 3A4 and 4A were investigated in this study. Details on the biochemical reaction monitored for each of the seven CYP450 enzymes are provided in the following table.

CYP enzyme	Substrate (concentration)	Reaction monitored	Positive control
1A2	Ethoxyresorufin (0.4 µM)	7-ethoxyresorufin O-deethylation	7, 8-benzoflavone
2C9	Tolbutamide (100 µM)	Tolbutamide 4-hydroxylation	Sulfaphenazole
2C19	S-mephenytoin (100 µM)	S-mephenytoin 4-hydroxylation	Tranylcypromine
2D6	Bufuralol (10 µM)	Bufuralol 1-hydroxylation	Quinidine
2E1	Chlorzoxazone (100 µM)	Chlorzoxazone 6-hydroxylation	–
3A4	Testosterone (65 µM)	Testosterone 6-hydroxylation	Triacetyloleandomycin
4A	Lauric acid (20 µM)	Lauric acid 12-hydroxylation	–

Pooled human liver microsomes were used in this in vitro study. In general, the concentrations of the model substrates were in the acceptable range with respect to their Km values. This Reviewer noted that the concentration of tolbutamide was lower when compared to its Km value of ~ 350 µM. Inhibition of cytochrome P450 enzyme activity was determined at 20 µg/mL of Ro 64-0796 and Ro 64-0802. At steady-state, mean Ro 64-0796 and Ro 64-0802 C_{max} values at a dose of 100 mg BID were approximately 65 and 440 *ng/mL*, respectively in healthy adult subjects. The concentration chosen for this study, 20 *µg/mL*, is much greater when compared to the clinically relevant concentrations. Appropriate positive controls (as mentioned in the above table) were used in this study. Percent enzyme inhibition is reported below:

	Percent inhibition by	
CYP enzyme	Ro 64-0796	Ro 64-0802
1A2	3.8	< 0
2C9	19.7	< 0
2C19	11.8	< 0
2D6	19.2	< 0
2E1	< 0	< 0
3A4	8.8	< 0
4A	< 0	< 0

Negative numbers for percent inhibition are uninterpretable but indicate no inhibition of the cytochrome P450 enzymes. The results of this study indicate that it is unlikely that Ro 64-0796 or Ro 64-0802 will inhibit the cytochrome P450 enzymes examined in this study at the proposed recommended dose of 75 mg BID. Significant pharmacokinetic interactions are not expected when Ro 64-0796 is concomitantly administered with drugs that are metabolized by the cytochrome P450 enzymes examined in this study.

Study of the pharmacokinetics and absolute bioavailability of the neuraminidase inhibitor Ro 64-0796/Ro 64-0802 (Protocol NP15719) (Volume 80)

OBJECTIVE: To determine the absolute bioavailability of Ro 64-0802 after oral administration of Ro 64-0796 with respect to intravenous infusion of Ro 64-0802.

SUBJECTS: 13 healthy male subjects (mean age: 26 years; mean weight: 78 kg) were enrolled in this study. 12 subjects completed the study. One subject was prematurely withdrawn from the study due to lack of cooperation.

STUDY DESIGN: The subjects enrolled in this study received the following two treatments in a randomized crossover fashion.
Treatment A: Oral dose of 150 mg of Ro 64-0796
Treatment B: Intravenous infusion of 150 mg of Ro 64-0802 (infusion time: 3 hour)

The treatments were separated by a washout period of 7 to 10 days. On the morning of each dosing day, a standard breakfast was given approximately 30 minutes prior to dosing.

FORMULATIONS: Ro 64-0796 capsules (75 mg, /V01, batch number GMZ0067) and Ro 64-0802 solution (20 mg/mL) were used in this study.

SAMPLE COLLECTION: Blood samples were obtained at predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 18, 24, 36, 48 and 72 hours after oral administration and initiation of infusion. In addition, two samples were obtained at 3.16 and 3.33 hours after initiation of infusion. Urine samples were collected during 0-4, 4-8, 8-12, 12-24, 24-48 and 48-72 hours after drug administration.

PHARMACOKINETIC DATA ANALYSIS: Pharmacokinetic parameters of Ro 64-0796 and Ro 64-0802 were estimated by non-compartment methods. Absolute bioavailability was calculated as the ratio of Ro 64-0802 AUC_∞ for the oral route to that of the intravenous route (after adjusting for dose). The mean Cp-t profiles are shown in Figure 1 and the pharmacokinetic parameters are summarized in Table 1.

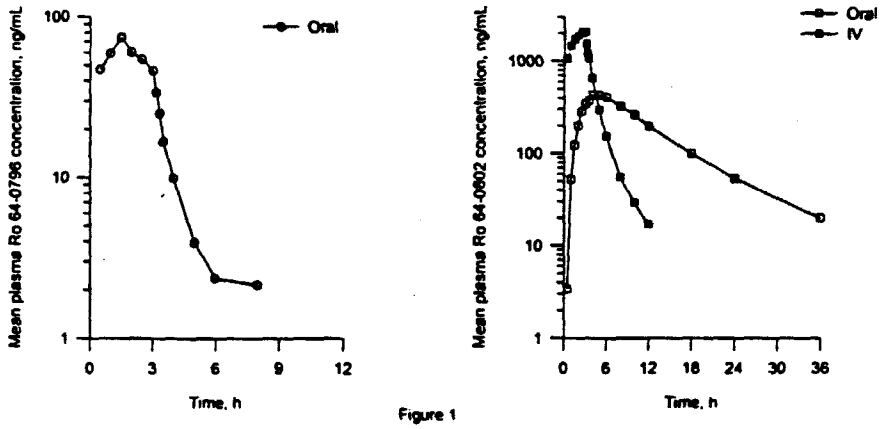


Figure 1

Table 1. Mean (%CV) Ro 64-0796 and Ro 64-0802 pharmacokinetic parameters

Species	Ro 64-0796	Ro 64-0802	
PK parameter	Oral	Oral	Intravenous (Dose = 136.54 mg)*
C_{max}, ng/mL	111 (31)	456 (14)	2091 (9)
AUC_{last}, ng.h/mL	247 (25)	5225 (21)	6796 (11)
$AUC_{0-\infty}$, ng.h/mL	253 (24)	5436 (24)	6834 (11)
CL, L/h/kg	7.96 (26)	0.33 (22)	0.26 (14)
Vss, L/kg			0.33 (23)
Half-life, h		6.81 (33)	1.79 (70)
Bioavailability, %		78.9 (15)	

*The Applicant has dose normalized the plasma concentrations to 136.54 mg (equivalent to the amount of Ro 64-0802 in 150 mg of Ro 64-0796) prior to calculation of pharmacokinetic parameters.

Following oral administration of Ro 64-0796, plasma samples had quantifiable concentrations of Ro 64-0802 from the first sampling time point of 30 minutes. Maximum plasma Ro 64-0802 concentrations were observed 5 hours after oral administration of Ro 64-0796, which subsequently declined in a monoexponential fashion. The ratio of Ro 64-0802 to Ro 64-0796 AUC was more than 21 indicating extensive first pass metabolism of Ro 64-0796 to Ro 64-0802. After intravenous administration, the mean Ro 64-0802 clearance was 0.26 L/h/kg and the steady-state volume of distribution was 0.33 L/kg. The mean absolute bioavailability of Ro 64-0802 following administration of Ro 64-0796 averaged 79%.

The mean apparent terminal phase half-life of Ro 64-0802 was calculated to be 6.8 and 1.8 hours after Treatments A and B, respectively. The Applicant states that three possible mechanisms exist for this observation. The most likely of the three explanations is the possibility of a change in the volume of distribution of Ro 64-0802 following oral administration of Ro 64-0796. The Applicant states that Ro 64-0796 is highly lipophilic and preclinical studies indicate that it readily distributes into the liver. In humans, the Applicant hypothesizes that Ro 64-0796 may be sequestered in the liver and may bind to p-glycoprotein in the intestine. The overall result could be delayed release (from one of these compartments) and formation of Ro 64-0802 leading to an apparent increase in half-life. In support of this theory, the Applicant points out that the clearance (apparent and systemic after oral and intravenous administration, respectively) of Ro 64-0802 is similar after Treatments A and B. To account for the increase in half-life, the volume of distribution of Ro 64-0802 should be higher in Treatment A and the increase in the volume may be due to distribution of Ro 64-0802 into another compartment (liver).

The mean cumulative urinary elimination of Ro 64-0802 following oral and intravenous administration of Ro 64-0796 are shown in Figure 2 and the relevant pharmacokinetic parameters are presented in Table 2.

Table 2. Mean (%CV) Ro 64-0796 and Ro 64-0802 urinary pharmacokinetic parameters

Species	Ro 64-0796	Ro 64-0802	
PK parameter	Oral	Oral	Intravenous (Dose = 136.54 mg)*
Percent eliminated	4.60 (21)	74.5 (25)	93.0 (22)
Renal clearance, L/h/kg	0.37 (26)	0.25 (27)	0.24 (23)
Bioavailability, %		80.0 (11)	

Reviewer's remarks: The total percent urinary recovery (as Ro 64-0796 and Ro 64-0802 or Ro 64-0802 alone) was greater than 100% in 2 to 3 subjects. The Applicant has not given an explanation for this anomalous observation.

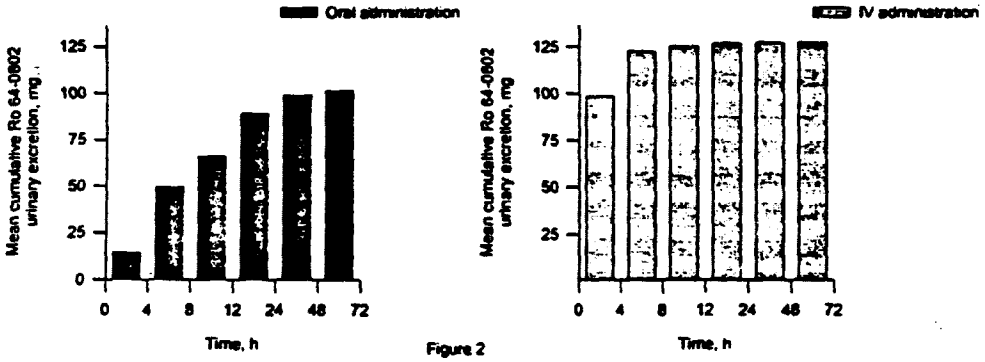


Figure 2

Based on the calculated renal clearance of 0.25 L/h/kg (~ 325 mL/min) for Ro 64-0802, it appears that part of renal elimination is via tubular secretion. The Applicant has conducted a study (NP15728) to characterize the pathway involved in the tubular secretion of Ro 64-0802.

In addition to the above-mentioned pharmacokinetic analyses, the Applicant has carried out additional analyses using average data. The Applicant has used the following equation to calculate the fractional metabolic conversion, i.e., the fraction of the absorbed drug that is metabolized.

$$(fm)_{oral} = \left[\frac{(AUCm)_{oral} * (CLm)_{iv}}{(AUCp)_{oral} * (CLp)_{oral}}\right] / F_{p,abs} \qquad \text{(Equation 1)}$$

where the subscripts m and p refer to Ro 64-0802 and Ro 64-0796, respectively and $F_{p,abs}$ denotes the fraction of the oral dose of Ro 64-0796 that was absorbed. For the sake of clarity, the above equation was simplified (by the Reviewer) as follows. Since $(AUCp)_{oral} * (CLp)_{oral}$ = Dose of Ro 64-0796 administered, substitution and rearrangement yields,

$$(fm)_{oral} = \left[\frac{(AUCm)_{oral} * (CLm)_{iv}}{\text{Dose of parent drug} * F_{p,abs}}\right] \qquad \text{(Equation 2)}$$

Since a true estimate of the clearance of the metabolite is available from the intravenous dose $(CLm)_{iv}$, the numerator is the amount of metabolite in circulation. The denominator is the amount of orally administered Ro 64-0796 that is absorbed and, therefore, $(fm)_{oral}$ is the fraction of the absorbed Ro 64-0796 that is converted to Ro 64-0802.

The Applicant has also calculated fractional metabolic clearance using the formula,
$(fm)_{oral}$ = % Ro 64-0802 in urine / (% Ro 64-0796 in urine + %Ro 64-0802 in urine)
(Equation 3)

The Applicant has used the mean data for all four parameters in Equation 1 and an estimate of 0.79 for $F_{p,abs}$. The estimate of $F_{p,abs}$ is based on the percent of Ro 64-0796 and Ro 64-0802 eliminated in the urine (0.046 + 0.745 = 0.791, see Table 2). Using these mean values, $(fm)_{oral}$ was calculated to be 87%. Also, substituting the relevant parameters in Equation 3, the Applicant has obtained a value of 94% for $(fm)_{oral}$.

Reviewer's remarks: The values for parameters in the denominator in Equation 1, $(AUC_p)_{oral}$ and $(CL_p)_{oral}$, are only estimates of the true AUC and clearance of Ro 64-0796. However, Equation 2, as simplified by this Reviewer, contains dose of Ro 64-0796 in the denominator, which is a known quantity (and is less variable). Using mean values for the numerator and 150 mg as the dose of Ro 64-0796, this Reviewer has calculated a value of 93% for $(fm)_{oral}$, which is in agreement with the value calculated from urinary excretion data (Equation 3).

This Reviewer also calculated $(fm)_{oral}$ values for individual subjects. The mean[%CV] $(fm)_{oral}$ value was calculated to be 95% [23%] and the individual values ranged from 0.6 to 1.4. Values greater than 1 for $(fm)_{oral}$ may be attributed to incomplete or missed urine samples resulting in a lower estimate for $F_{p,abs}$.

CONCLUSIONS: The results of this study indicate that the absolute bioavailability of Ro 64-0802 following administration of Ro 64-0796 is approximately 80%. Absolute bioavailability values calculated using plasma data and urinary excretion data were in agreement. Following oral administration of Ro 64-0796, this prodrug is extensively converted to Ro 64-0802 and 80% of the administered drug was recovered in the urine as Ro 64-0796 and Ro 64-0802. The renal clearance of Ro 64-0802 was greater than glomerular filtration rate indicating that the drug undergoes renal tubular secretion. It is not known if Ro 64-0796 and Ro 64-0802 undergo tubular reabsorption.

An excretion balance and pharmacokinetic study of Ro 64-0796 after single oral doses of ^{14}C-labelled Ro 64-0796 and intravenous doses of ^{14}C-labelled Ro 64-0802 in healthy male subjects (Protocol NP15718) (Volume 78)

OBJECTIVE: To examine the absorption, distribution, metabolism and elimination of orally administered Ro 64-0796 and intravenously administered Ro 64-0802.

SUBJECTS: 12 (6 per treatment) healthy male subjects (mean age: 57 years; mean weight: 76 kg) were enrolled in this study.

STUDY DESIGN: The subjects in this study received *one* of the following *two* treatments.
Treatment A: Single oral dose of 75 mg of Ro 64-0796 solution containing ~ 50 µCi of ^{14}C-labelled Ro 64-0796
Treatment B: Single intravenous infusion of 75 mg of Ro 64-0802 containing ~ 25 µCi of ^{14}C-labelled Ro 64-0802 (infusion time: 1 hour).

On the morning of each dosing day, breakfast was given approximately 30 minutes prior to dosing.

FORMULATIONS: Ro 64-0796 solution (~1 mg/mL in orange juice) and Ro 64-0802 solution in normal saline for intravenous infusion were used in this study.

SAMPLE COLLECTION: Blood samples were obtained at predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72, 84, 96, 108 and 120 hours after oral administration. After Treatment B, blood samples were obtained prior to infusion and at 0.25, 0.5, 0.92, 1.08, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72, 84, 96, 108 and 120 hours after initiating infusion. Samples of urine and feces were collected during the time periods 0-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-60, 60-72, 72-84, 84-96, 96-108 and 108-120 hours.

PHARMACOKINETIC DATA ANALYSIS: Pharmacokinetic parameters of Ro 64-0796 and Ro 64-0802 were estimated by non-compartmental methods. The mean Cp-t profiles of Ro 64-0796, Ro 64-0802 and radioactivity (converted to equivalents of Ro 64-0796) following Treatment A are shown in Figure 1.

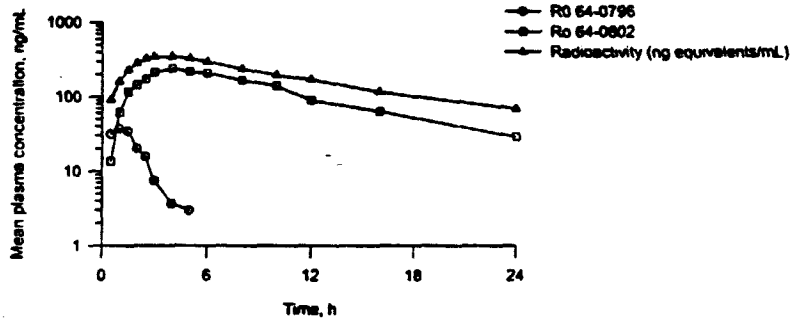


Figure 1

Concentrations of Ro 64-0796 and Ro 64-0802 and radioactivity were measurable in plasma from the first sampling time point of 30 minutes. Comparison of concentration-time profiles indicates that Ro 64-0796 is extensively converted to Ro 64-0802 upon to oral administration of Ro 64-0796. The ratio of AUC of Ro 64-0796 to that of Ro 64-0802 was approximately 3%. Pharmacokinetic parameters of all the three species are summarized in Table 1.

Table 1. Mean (%CV) pharmacokinetic parameters after Treatment A (n=6).

Species	Ro 64-0796	Ro 64-0802	Radioactivity[1]
C_{max}, ng/mL	45.7 (42)	252 (23)	357 (19)
T_{max}, h	1.01 (44)	4.17 (24)	3.50 (16)
$AUC_{0-\infty}$, ng.h/mL	84.1 (16)	2870 (18)	5290 (19)
Half-life, h	1.01 (55)	6.34 (19)	9.02 (24)
% eliminated in urine	4.75 (10)	80.6 (3)	74.0 (4)
% eliminated in feces			17.2 (14)

[1] Expressed as ng equivalent of Ro 64-0796

Reviewer's remarks: It was noted that in the calculation of $AUC_{0-\infty}$ for radioactivity, the percent of are under the curve that was extrapolated ranged from 10 to 22% with a mean of 15%. While all subjects had measurable radioactivity at 24 hours after dosing, only 2 out of 4 subjects had measurable radioactivity at the next sampling time point of 36 hours. A blood sample between 24 and 36 hours would have decreased the percent of area that has been extrapolated.

The Applicant points out that circulating drug related radioactivity in the plasma could not be accounted for by Ro 64-0796 and Ro 64-0802 alone. However, the amounts of Ro 64-0796 and Ro 64-0802 eliminated in the urine do not suggest the existence of significant amounts of unknown metabolites. An explanation for this paradoxical observation is not apparent. The Applicant states that such observations have been made in preclinical studies and may be due to presence of unstable metabolites.

The urine samples were analyzed for the 'cold' species of Ro 64-0796 and Ro 64-0802 and urine and fecal samples were analyzed for radioactivity. After oral administration of Ro 64-0796, less than 5% was recovered as unchanged species in the urine while approximately 80% was recovered as Ro 64-0802. By radioactivity measurements, a total of 91% was recovered in urine and feces. Approximately, an average of 74% and 17% of orally administered radioactivity was eliminated in the urine and feces, respectively (see Figure 2). Radioactivity data indicate that about 75% of orally administered Ro 64-0796 is absorbed. The fraction that was eliminated in the feces could represent (a) unabsorbed drug, (b) biliary excretion or (c) hydrolysis of Ro 64-0796 to Ro 64-0802, which is known to be poorly absorbed, within the GI tract.

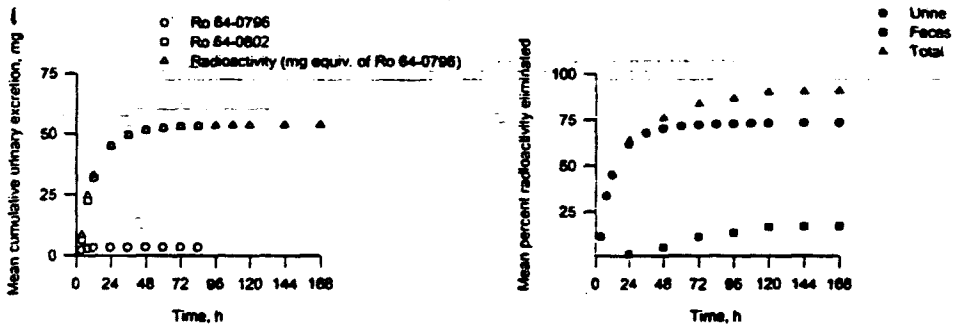


Figure 2

The mean Cp-t profiles of Ro 64-0802 and radioactivity (converted to equivalents of Ro 64-0802) following Treatment B are shown in Figure 3 and the pharmacokinetic parameters are summarized in Table 2.

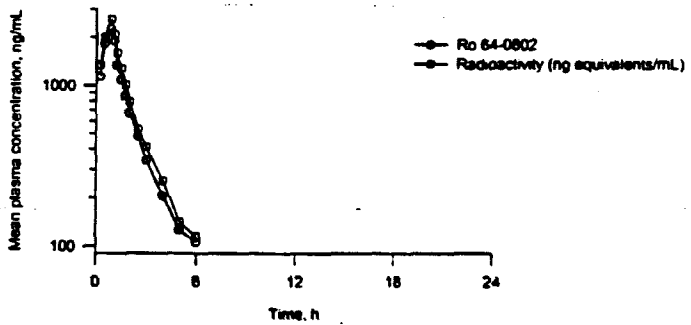


Figure 3

Table 2. Mean (%CV) pharmacokinetic parameters after Treatment B (n=6)

Species	Ro 64-0802	Radioactivity[1]
C_{max}, ng/mL	2290 (21)	2590 (20)
AUC_{0-z}, ng.h/mL	3920 (29)	4520 (30)
Half-life, h	1.11 (19)	1.13 (25)
Vss, L/kg	0.276 (10)	
CL, L/h/kg	0.234 (20)	
Renal clearance, L/h/kg	0.241 (22)	
% eliminated in urine	99.9 (4)	97.2 (3)
% eliminated in feces		0.30 (47)

[1] Expressed as ng equivalent of Ro 64-0802

Eight hours after initiation of infusion, plasma Ro 64-0802 and radioactivity concentrations were below the limit of quantitation in four (out of six subjects studied) subjects. The mean plasma elimination half-life of Ro 64-0802 was 1.1 hours. The values for mean Ro 64-0802 clearance and steady-state volume of distribution estimated in this study are comparable to the values estimated in Study NP15719.

As with the Treatment A, urine samples were analyzed for the 'cold' species of Ro 64-0802 and urine and fecal samples were analyzed for radioactivity. An average of 97% of the radioactivity was recovered in the urine, with approximately 80% being recovered within 3 hours after completion of infusion. Less than 0.5% of the radioactivity was recovered in the feces (see Figure 4).

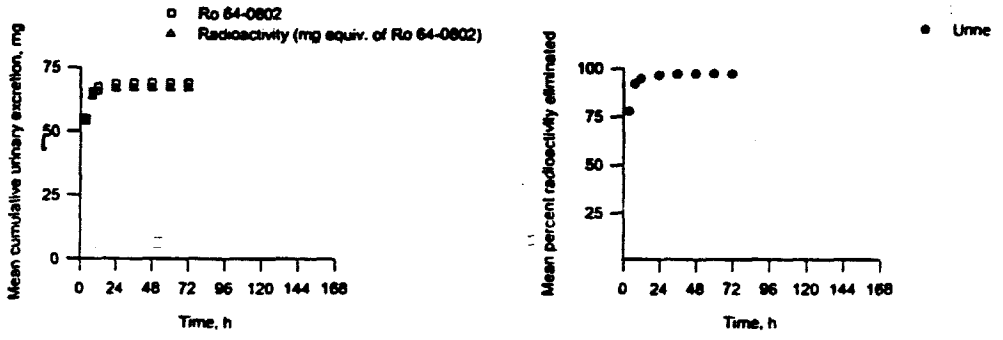


Figure 4

Selected urine and fecal samples were profiled to identify the various components present in these samples. In Treatment A, Ro 64-0796 and Ro 64-0802 were the only radiolabeled compounds in urine and feces. In Treatment B, Ro 64-0802 was the only radiolabeled compound in urine.

CONCLUSIONS: Results from this study indicate that approximately 75% to 85% of the orally administered Ro 64-0796 is absorbed. After oral administration of Ro 64-0796, plasma and urine data indicate that this compound is extensively converted to the active species, Ro 64-0802. Further, Ro 64-0796 and Ro 64-0802 were the only compounds identified in selected urine samples indicating lack of significant metabolism of Ro 64-0802. An average of 74% and 17% of the administered radioactivity (in the form of Ro 64-0796) was recovered in urine and feces, respectively.

Intravenously administered Ro 64-0802 was rapidly eliminated with a short half-life of 1 hour and was almost completely recovered in the urine. The steady-state volume of distribution was estimated to be 0.28 L/kg indicating distribution of Ro 64-0802 into extracellular fluids.

Multiple ascending oral dose study of the tolerability, safety and pharmacokinetics of the neuraminidase inhibitor Ro 64-0796 in healthy volunteers (Protocol NP15525) (Volume 89)

OBJECTIVE: To determine the pharmacokinetics, safety and tolerability of Ro 64-0796 and Ro 64-0802 after multiple administrations of Ro 64-0796 to healthy subjects.

SUBJECTS: 32 healthy *male* subjects (mean age: 34 years; mean weight: 78 kg) were enrolled in this study.

STUDY DESIGN: This study was conducted in a double-blind, placebo-controlled fashion. Subjects enrolled in this study were randomized to receive one of the following treatments.

Treatment A: 50 mg BID for 6 days followed by a single dose on Day 7 (n=6)
Treatment B: 100 mg BID for 6 days followed by a single dose on Day 7 (n=6)
Treatment C: 200 mg BID for 6 days followed by a single dose on Day 7 (n=6)
Treatment D: 500 mg BID for 6 days followed by a single dose on Day 7 (n=6)

Two subjects received placebo at each dose level. The first dose on Day 1 and the dose on Day 7 were administered after an overnight fast.

FORMULATIONS: Ro 64-0796 capsules (10 mg, /A03, batch number WEL02973 and 100 mg, /A02, batch number WEL029704) were used in this study.

SAMPLE COLLECTION: Blood samples were obtained at predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10 and 12 hours after drug administration on Day 1. In addition, two samples were obtained at 18 and 24 hours on Day 7. Trough samples were obtained before the morning dose on Days 3 and 5. Urine samples were collected during 0-4, 4-8 and 8-12 hours on Day 1 and during the above time intervals plus 12-24 on Day 7.

ANALYTICAL METHODOLOGY: See Analytical Methodology section (Section VI).

PHARMACOKINETIC DATA ANALYSIS: Pharmacokinetic parameters of Ro 64-0796 and Ro 64-0802 were estimated by non-compartment methods. The mean plasma concentration-time profiles on Day 1 are shown in Figure 1 and the mean pharmacokinetic parameters are presented in Table 1.

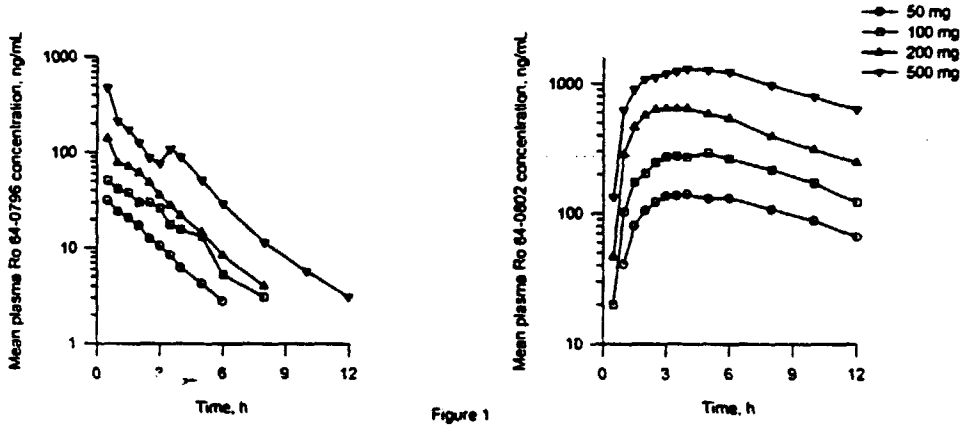


Figure 1

Table 1. Mean (%CV) Ro 64-0796 and Ro 64-0802 pharmacokinetic parameters on Day 1

Species	Ro 64-0796				Ro 64-0802			
Dose, mg	50	100	200	500	50	100	200	500
C_{max}, ng/mL	30.8	58.5	147	492	147	308	688	1363
	(17)	(27)	(35)	(52)	(20)	(14)	(33)	(25)
AUC_{0-12}, ng.h/mL	71.9	151	277	827	1206	2450	5207	14423
	(21)	(19)	(36)	(31)	(18)	(13)	(23)	(22)
Half-life, h	1.6	1.4	1.3	1.7	ND	ND	ND	ND
	(13)	(23)	(12)	(26)				

ND: Not determined due to lack of adequate data

Statistical analyses of dose normalized Ro 64-0796 C_{max} (p=0.13) and AUC_{0-12} (p=0.70) values do not indicate deviations from dose proportionality in the pharmacokinetic parameters over the dose range 50 to 500 mg. Similar analysis of Ro 64-0802 C_{max} (p=0.44) and AUC_{0-12} (p=0.72) also do not indicate deviation from dose proportionality. Average half-life values of Ro 64-0796 were not very different at various doses and ranged from 1.3 to 1.7 hours.

Trough plasma samples were obtained 12 hours after dosing on Day 1 and before the morning dose on Days 3, 5 and 7 (Figure 2). The mean Ro 64-0796 trough concentrations on Day 7 at the 200 mg and the 500 mg dose levels were statistically significantly lower when compared to the values observed on Day 3. The Applicant states that a reason for this is not known. Within each dose level, the trough concentrations of Ro 64-0802 were not significantly different on Days 3 – 7.

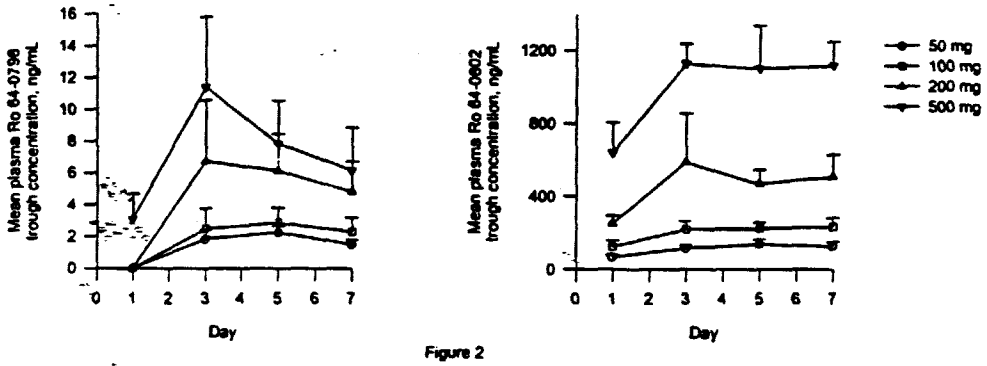


Figure 2

The mean plasma concentration-time profiles and urinary excretion profiles on Day 7 are shown in Figures 3 and 4, respectively, and the pharmacokinetic parameters are summarized in Table 2.

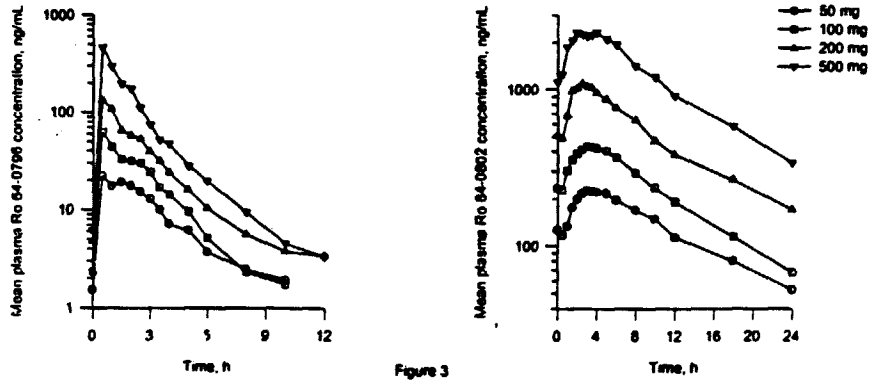


Figure 3

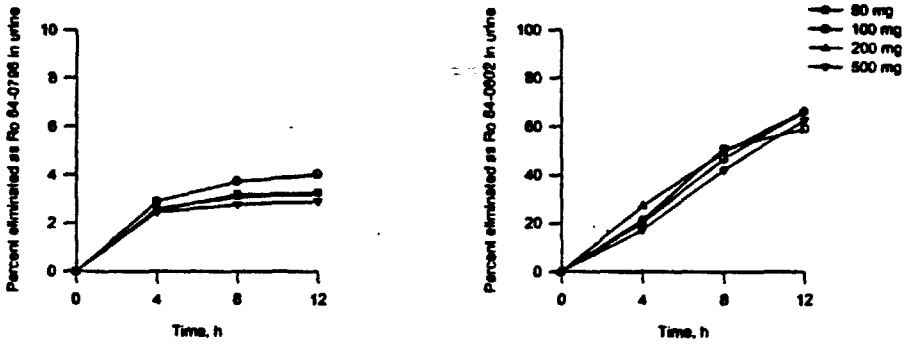


Figure 4

Table 2. Mean (%CV) Ro 64-0796 and Ro 64-0802 pharmacokinetic parameters on Day 7

Species	Ro 64-0796				Ro 64-0802			
Dose, mg	50	100	200	500	50	100	200	500
C_{max}, ng/mL	29	66	153	482	230	439	1132	2458
	(44)	(49)	(35)	(31)	(21)	(9)	(25)	(12)
AUC_{0-12}, ng.h/mL	78.8	156	314	813	2107	3845	8612	20317
	(16)	(22)	(28)	(23)	(18)	(15)	(15)	(13)
Half-life, h	2.4	2.0	2.7	2.1	9.7	7.5	8.7	7.6
	(34)	(49)	(53)	(22)	(17)	(11)	(18)	(13)
%UR (0-12h)	4.02	3.26	3.22	3.24	66.0	58.7	66.2	59.1
	(28)	(28)	(13)	(63)	(26)	(19)	(28)	(39)

Statistical analyses of dose normalized Ro 64-0796 C_{max} and AUC_{0-12} values and Ro 64-0802 C_{max} and AUC_{0-12} values do not indicate deviations from dose proportionality ($p > 0.1$) in the pharmacokinetic parameters over the dose range 50 to 500 mg. The percent of unchanged Ro 64-0796 and Ro 64-0802 eliminated in the urine over the dosing interval was comparable among the four dose levels. Half-life values estimated after the last dose were also comparable at the four dose levels. At steady-state, the mean ratio of Ro 64-0802 to Ro 64-0796 C_{max} ratios ranged from 6 to 9. Similarly, AUC_{0-12} ratios ranged from 25 to 29 indicating extensive conversion of Ro 64-0796 to Ro 64-0802.

Accumulation index of Ro 64-0796 and Ro 64-0802 upon administration of multiple doses of Ro 64-0796 was calculated by obtaining the ratio of Day 7 to Day 1 AUC_{0-12} values in individual subjects.

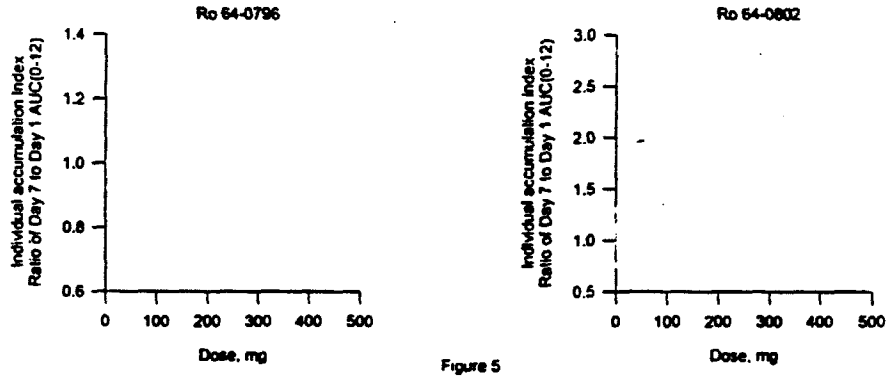


Figure 5

As shown in Figure 5, significant accumulation was not seen in the case of Ro 64-0796. However, mean accumulation indices ranging from 1.6 to 1.8 were noted in the case of Ro 64-0802.

SAFETY: The most prominent adverse events were incidence of nausea and vomiting at a dose of 500 mg BID. This adverse event was not noted at the lower doses or placebo administration. Four and two subjects (out of six) reported nausea and vomiting, respectively, at the 500 mg BID dose on Day 1. While three out of the four subjects did not report nausea on subsequent days, one subject reported nausea until Day 6. The Applicant speculates that administration of the drug under fed conditions on Days 2 – 6 might have helped in the cessation of nausea in these subjects.

CONCLUSIONS: The results of this study indicate dose proportional increase in the primary pharmacokinetic parameters of Ro 64-0796 and Ro 64-0802 over the dose range 50 – 500 mg BID. Urinary elimination of Ro 64-0796 and Ro 64-0802 was also independent of dose. In the context of the proposed recommended dose (75 mg BID), the dose range studied by the Applicant is acceptable. Consistent with a half-life value of approximately 9 hours estimated for Ro 64-0802, trough concentrations indicate that steady-state conditions were reached around 3 to 5 days of repeat dosing. Following administration of multiple doses of Ro 64-0796 for 7 days, 60 to 80% increase in AUC over the dosing interval was observed for Ro 64-0802.

Multiple ascending oral dose study of the tolerability, safety and pharmacokinetics of the neuraminidase inhibitor Ro 64-0796 in healthy elderly volunteers
(Protocol WP15647) (Volume 93)

OBJECTIVE: To determine the pharmacokinetics and safety of Ro 64-0796 and Ro 64-0802 after multiple dose administrations of Ro 64-0796 to healthy elderly subjects.

SUBJECTS: 24 healthy elderly subjects (mean age: 69 years; mean weight: 77 kg; male/female: 16/8) were enrolled in this study.

STUDY DESIGN: This study was conducted in a double-blind, placebo-controlled fashion. Subjects enrolled in this study were randomized to receive one of the following treatments.
Treatment A: 100 mg BID (Days 2 - 6) and single doses on Days 1 and 7 (n=6)
Treatment B: 200 mg BID (Days 2 - 6) and single doses on Days 1 and 7 (n=6)
Treatment C: 500 mg BID (Days 2 - 6) and single doses on Days 1 and 7 (n=6)

Two subjects received placebo at each "dose level". On Days 1 and 7, subjects were under fasting condition from midnight the night before dosing. Due to adverse events experienced at a dose of 200 mg BID, dose escalation to 500 mg BID did not occur. Instead subjects received 150 mg BID in Treatment C. The adverse events are discussed later in the review.

FORMULATIONS: Ro 64-0796 capsules (10 mg, /A03, batch number WEL069701 and 100 mg, /A02, batch number WEL049702) were used in this study.

SAMPLE COLLECTION: Blood samples were obtained at predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 18 and 24 hours after drug administration on Days 1 and 7. Trough samples were obtained before the morning dose on Days 3 and 5. Urine samples were collected during 0-4, 4-8, 8-12 and 12-24 hours on Days 1 and 7.

ANALYTICAL METHODOLOGY: See Analytical Methodology section (Section VI).

PHARMACOKINETIC DATA ANALYSIS: Pharmacokinetic parameters of Ro 64-0796 and Ro 64-0802 were estimated by non-compartment methods. The mean Cp-t profiles on Day 1 are shown in Figure 1 and the mean parameters are presented in Table 1.

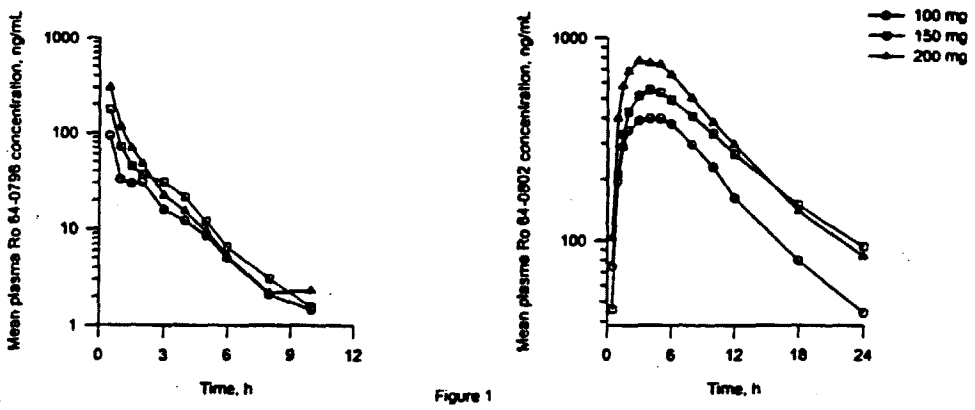


Figure 1

Table 1. Mean (%CV) Ro 64-0796 and Ro 64-0802 pharmacokinetic parameters on Day 1

Species	Ro 64-0796			Ro 64-0802		
Dose, mg	100	150	200	100	150	200
C_{max}, ng/mL	95.4	179	302	432	579	796
	(82)	(43)	(34)	(16)	(22)	(20)
AUC_{0-12}, ng.h/mL	149	253	341	3503	4731	6356
	(36)	(17)	(24)	(15)	(15)	(24)
Half-life, h	1.80	1.50	1.57	5.70	7.51	6.08
	(31)	(21)	(25)	(15)	(27)	(15)
%UR	2.85	3.24	3.47	62.6	64.0	57.2
	(25)	(33)	(16)	(20)	(6.5)	(23)

Statistical analyses performed by the Applicant did not reveal deviations from dose proportionality in Ro 64-0796 and Ro 64-0802 C_{max} and AUC. In healthy adult subjects (age: 18 – 55, Study WP15525), dose proportional increase in C_{max} and AUC_{12} was observed over a range of 50 to 500 mg BID.

Statistical analysis of Ro 64-0802 trough concentrations indicate increasing values at 3 and 5 days of dosing at the 150 and 200 mg BID dose levels. Unlike Study WP15525, subjects in this study started to receive multiple doses on Day 2. Therefore, increasing trough concentrations between Days 3 and Day 5 are not unexpected. Examination of mean C_{min} indicates that steady-state condition was achieved by Day 5.

The mean Cp-t profiles and urinary excretion profiles on Day 7 are shown in Figures 2 and 3, respectively and the pharmacokinetic parameters are summarized in Table 2.

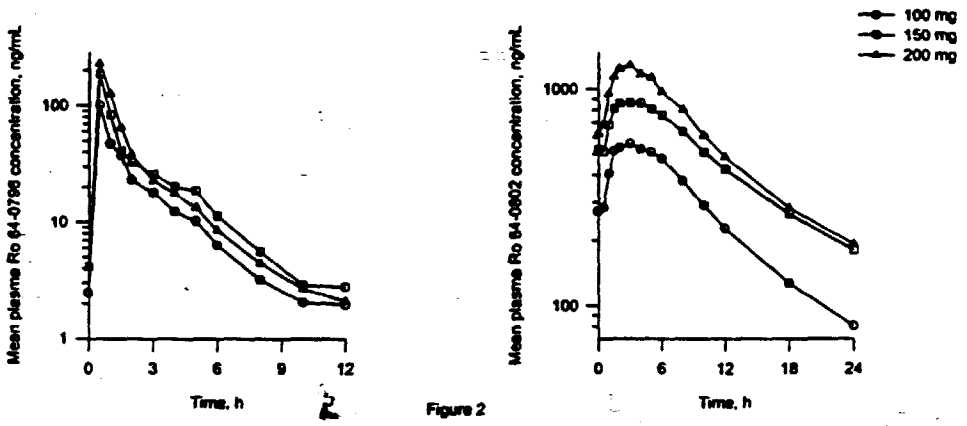


Figure 2

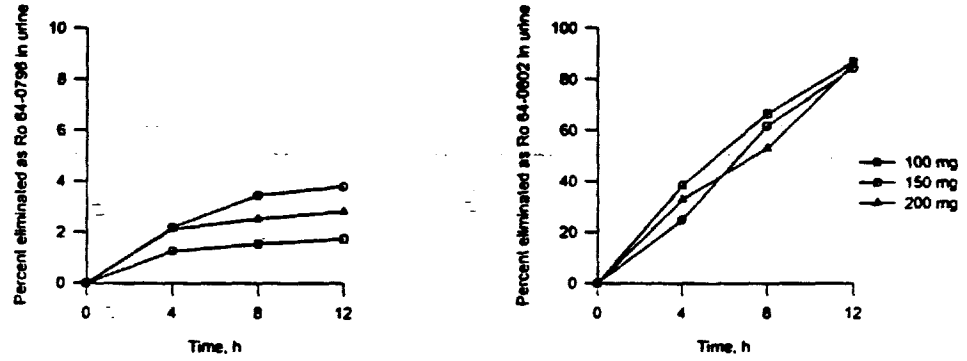


Figure 3

Table 2. Mean (%CV) Ro 64-0796 and Ro 64-0802 pharmacokinetic parameters on Day 7

Species	Ro 64-0796			Ro 64-0802		
Dose, mg	100	150	200	100	150	200
C_{max}, ng/mL	105	192	256	575	897	1293
	(59)	(36)	(17)	(14)	(14)	(11)
AUC_{0-12}, ng.h/mL	171	289	321	4943	8410	10809
	(19)	(24)	(12)	(20)	(14)	(13)
Half-life, h	2.37	2.55	2.62	6.76	8.28	7.32
	(15)	(16)	(22)	(14)	(19)	(11)
%UR (0-12h)	3.80	3.87	2.81	84.4	86.7	85.7
	(29)	(35)	(39)	(26)	(18)	(8)

n = 5 at 200 mg dose level; n=6 at other dose levels.

At steady-state, statistical analyses do not indicate deviation from dose proportionality in Ro 64-0796 and Ro 64-0802 C_{max} and AUC_{0-12}. The percent of drug eliminated as Ro 64-0802 was comparable across the three dose levels. This reviewer noted that the mean percent eliminated as Ro 64-0802 was higher in elderly subjects when compared to adult subjects (mean values ranged from 59 to 66% in Study WP15525). On Day 7, the mean ratio of Ro 64-0802 to Ro 64-0796 C_{max} ranged from 4.5 to 5.5 and mean ratios for AUC_{0-12} ratio ranged from 29 to 34 indicating extensive conversion of the prodrug to the active species in elderly subjects.

Accumulation index was calculated by obtaining the ratio of Day 7 to Day 1 AUC_{0-12} values for Ro 64-0796 and Ro 64-0802. At the three dose levels, the mean accumulation indices for Ro 64-0796 ranged from 1.0 to 1.2 indicating lack of significant accumulation. For Ro 64-0802, the mean accumulation indices ranged from 1.4 to 1.8.

Accumulation of Ro 64-0802 upon multiple dosing was, in general, similar in elderly subjects and adults (WP15525).

SAFETY: Changes were noted in the ECG of three subjects following administration of 200 mg BID. In one female subject, QTc prolongation was observed (baseline: 454 msec, Day 2, predose: 469 msec). T-wave flattening was also noted on Day 1 and Day 5 in this subject. Based on independent cardiological review, the Applicant states that the QT prolongation is "not definitely abnormal and is consistent with normal variation". The T-wave flattening observed in this subject and two other subjects, according to the Applicant, are abnormal but may occur with a variety of non-specific patho-physiological conditions. These adverse events were brought to the attention of the review team (7/6/99) and were also discussed with the Medical Officer separately (8/1/99). The Medical Officer concurs with the opinion of the Applicant and notes that such changes are not completely unexpected in the population enrolled in this study. The Medical Officer also noted that the QTc prolongation was close to the upper limit of normal.

ADULT SUBJECTS VERSUS GERIATRIC SUBJECTS:
The mean steady-state (Day 7) C_{max} and AUC values in elderly subjects and adult subjects (from WP15525) are shown in Table 3. This rather small data set indicates that Ro 64-0796 C_{max} is on an average 50% to 75% higher in elderly subjects when compared to adults. However, exposure to Ro 64-0796 was not substantially higher in elderly subjects. On the other hand, Ro 64-0802 C_{max} and AUC values were generally 25% higher in elderly subjects.

Table 3. Mean (%CV) and geometric mean ratio [90% CI] at the 100 and 200 mg dose levels on Day 7.

	100 mg BID			200 mg BID		
	Young (Y) (WP15525)	Elderly (E) (WP15647)	Geo. Mean ratio (E / Y) [90% CI]	Young (Y) (WP15525)	Elderly (E) (WP15647)	Geo. Mean ratio (E / Y) [90% CI]
Ro 64-0796						
C_{max}, ng/mL	66 (49)	105 (59)	1.50 [0.92 – 2.47]	153 (35)	256 (17)	1.74 [1.33 – 2.28]
AUC_{0-12}, ng.h/mL	156 (22)	171 (19)	1.10 [0.92 – 1.32]	314 (28)	321 (12)	1.05 [0.86 – 1.28]
CLr, L/h	20.9 (23)	22.8 (35)	1.06 [0.81 – 1.38]	21.4 (22)	17.4 (35)	0.78 [0.58 – 1.06]
Ro 64-0802						
C_{max}, ng/mL	439 (9)	575 (14)	1.30 [1.16 – 1.46]	1132 (25)	1293 (11)	1.17 [0.96 – 1.42]
AUC_{0-12}, ng.h/mL	3845 (15)	4943 (20)	1.28 [1.09 – 1.50]	8612 (15)	10809 (13)	1.26 [1.10 – 1.44]
CL_r, L/h	14.0 (18)	16.0 (34)	1.11 [0.86 – 1.43]	14.1 (25)	14.7 (18)	1.06 [1.85 – 1.31]

Confidence intervals were generated based on consultations with the statistician (Dr. Greg Soon)

According to the Applicant, doses of 75 and 150 mg BID were found to be equally safe and effective in large Phase 3 studies. It should be noted that at the proposed recommended dose of 75 mg BID, most elderly subjects may not exhibit exposures greater than those observed at 150 mg BID.

CONCLUSIONS: The pharmacokinetics of Ro 64-0796 and Ro 64-0802 are linear in elderly subjects in the dose range 100 to 200 mg BID. When compared to adult subjects, exposure to Ro 64-0802 was 25% higher in elderly subjects.

Changes in ECG were observed in three subjects at a dose of 200 mg BID. The Applicant considers these changes to be nonspecific (see above). A study titled "A double-blind, stratified, randomized, placebo-controlled study of Ro 64-0796 in the treatment of influenza in elderly adults (WV15876)" is in progress [redacted]. It is anticipated that this study would provide safety and tolerability data at the proposed recommended dose of 75 mg in approximately 250 elderly (age > 65 years) subjects with influenza.

An open-label bioequivalence and food effect study of the clinical trial and market formulations of Ro 64-0796 in healthy subjects (Protocol NP15729) (Volume 82)

BACKGROUND: The Applicant has used three different formulations of Ro 64-0796 in the drug development process. Under Protocol NP15729, the Applicant has evaluated the bioequivalency between the clinical trial formulation and the proposed market formulation. The two formulations are compositionally identical; the only difference is in the [redacted] used in the [redacted] procedure. In the manufacture of the proposed market formulation, [redacted] is accomplished by [redacted] whereas the Applicant has used [redacted] in the manufacture of the clinical trial formulation. Bioequivalency assessment between an early clinical trial formulation and proposed market formulation is the subject of Protocol NP15810.

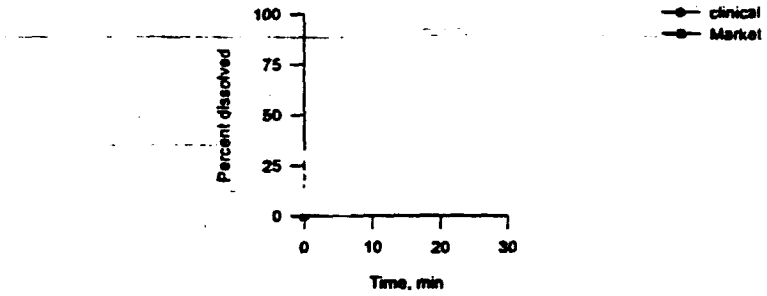
OBJECTIVES: (i) To assess the bioequivalence between formulations of Ro 64-0796 used in clinical trials and the proposed market formulation and (ii) To assess the effect of food on the pharmacokinetics of Ro 64-0796 administered as the proposed market formulation.

SUBJECTS: A total of 18 healthy subjects (9 male and 9 female, mean age: 26 years, mean weight: 64 kg) participated in this study.

STUDY DESIGN: This study was conducted in a three-way crossover fashion. Subjects received the following three treatments.
Treatment A: Single 150 mg dose of Ro 64-0796/V01 (clinical trial formulation) - fasted
Treatment B: Single 150 mg dose of Ro 64-0796/V14 (market formulation) - fasted
Treatment C: Single 150 mg dose of Ro 64-0796/V14 (market formulation) - fed

Subjects received the three treatments in one of the following six sequences: ABC, ACB, BAC, BCA, CAB and CBA. Treatment C was administered after consumption of a high-fat breakfast (2 fried eggs, 2 strips of bacon, 2 slices of toast, hash brown potatoes and whole milk). The washout period between the treatments was 7 to 10 days.

FORMULATIONS: Ro 64-0796/V01 (75 mg, batch number GMZ0067) and Ro 64-0796/V14 (75 mg, batch number GMZ0134/03) were used in this study. [redacted]



SAMPLE COLLECTION: Blood samples were collected at predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, 24, 36, 48 and 72 hours postdose. Complete urine output was collected during the time intervals 0-4, 4-8, 8-12, 12-24, 24-48 and 48-72 hours after drug administration.

PHARMACOKINETIC DATA ANALYSIS: Pharmacokinetic parameters were obtained by non-compartmental methods. Analysis of variance with factors including sequence, subjects within sequence, period and treatment was employed and log transformed C_{max} and AUC values were used in the analysis. The point estimates and 90% confidence intervals were obtained following analysis of variance.

Bioequivalency assessment

The mean plasma Ro 64-0796 and Ro 64-0802 concentration-time profiles following administration of the clinical trial formulation and the proposed market formulation under fasting conditions are shown in Figure 1. Individual values of C_{max} and AUC_∞ are shown in Figure 1b and the results of the statistical analyses are summarized in Table 1.

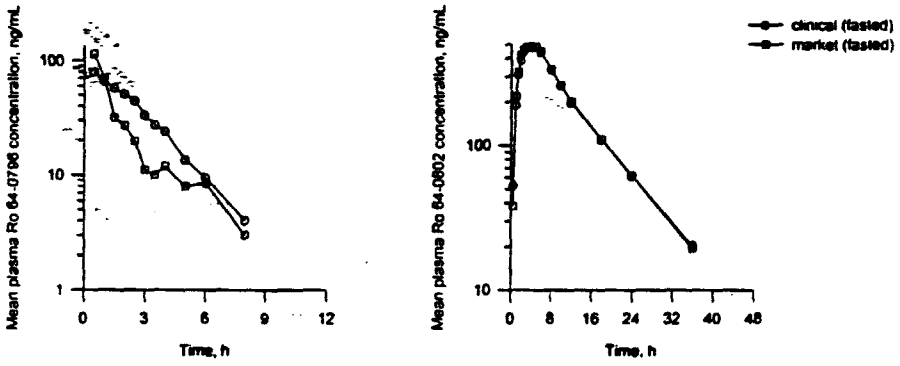


Figure 1

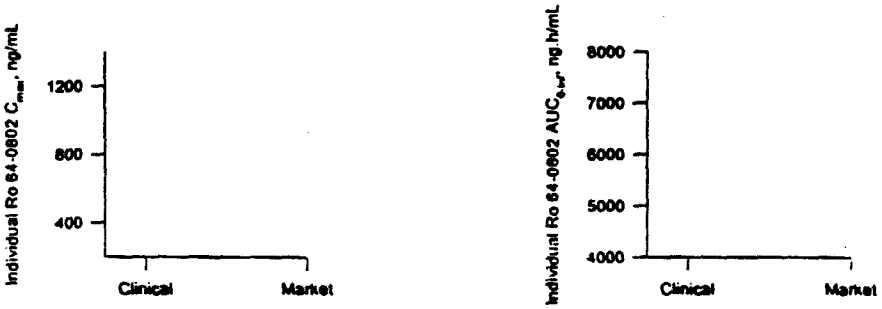


Figure 1b

Table 1. Results of statistical analysis

PK parameter of Ro 64-0802	Formulation	Arithmetic mean (%CV)	Geometric mean	% point estimate [90% CI]
C_{max}, ng/mL	Clinical trial	543 (45)	508	100
	Market	551 (37)	526	103.6 [97 – 111]
$AUC_{0-\infty}$, ng.h/mL	Clinical trial	6155 (16)	6083	100
	Market	6218 (12)	6176	101.5 [98 – 106]

Statistical analyses indicate that the proposed market formulation is bioequivalent to the clinical trial formulation. The 90% confidence intervals were well within [80 - 125] for C_{max} and AUC. As shown in the table on the next page, all other pharmacokinetic parameters [mean (%CV)] were virtually identical for the two formulations.

Ro 64-0802	Clinical trial formulation	Market formulation
t_{max}, h	4.58 (32)	4.37 (28)
Half-life, h	6.84 (21)	6.87 (20)
Renal clearance, L/h	13.8 (18)	13.4 (21)

Reviewer's remarks: The Sponsor's emphasis on Ro 64-0802 C_{max} and AUC for the assessment of bioequivalency was brought to the attention of the attendees of the 45-day pre-filing meeting. Following this meeting, a comment was sent to the Sponsor to provide results of statistical analysis for Ro 64-0796. In response, the Sponsor states that Ro 64-0796 is rapidly and extensively metabolized to the active species (Ro 64-0802) and, therefore, has performed bioequivalency assessments with respect to Ro 64-0802 only. However, the Sponsor has provided the following results for Ro 64-0796.

PK parameter Of Ro 64-0796	Formulation	Arithmetic mean (%CV)	% point estimate [90% CI]
C_{max}, ng/mL	Clinical trial	97.9 (42)	100
	Market	124 (51)	127.0 [105 – 154]
$AUC_{0-\infty}$, ng.h/mL	Clinical trial	233 (34)	100
	Market	244 (34)	107.0 [96 – 120]

The results indicate that the clinical trial and market formulations are not bioequivalent with respect to Ro 64-0796. The 90% confidence intervals for Ro 64-0796 C_{max} were outside [80 – 125]. However, doses much greater than the proposed recommended dose of 75 mg BID have been administered to a large number of subjects without a remarkable increase in the incidence of adverse events. (Safety data are available in about 450 subjects who were randomized to receive Ro 64-0796 at a dose of 150 mg BID for five days in Phase 3 clinical trials). Therefore, the 25% increase in mean Ro 64-0796 C_{max} when administered as the proposed market formulation is acceptable.

Food effect assessment

The mean plasma Ro 64-0796 and Ro 64-0802 concentration time profiles following administration of the market formulation under fasted and fed conditions are shown in Figure 2. Individual values of C_{max} and AUC_{∞} are shown in Figure 2b and the results of the statistical analyses are summarized in Table 2.

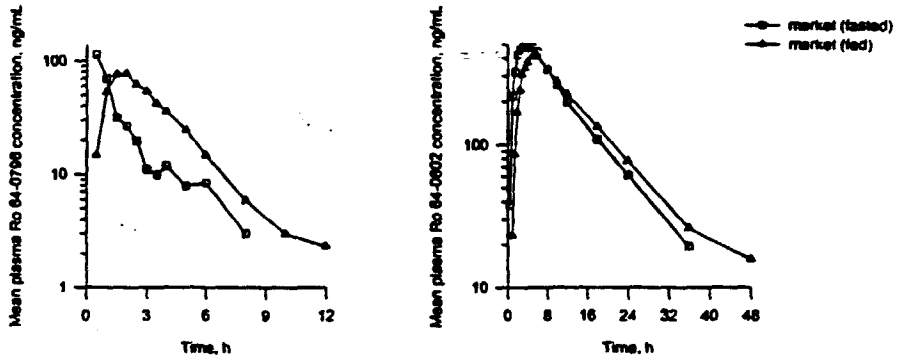


Figure 2

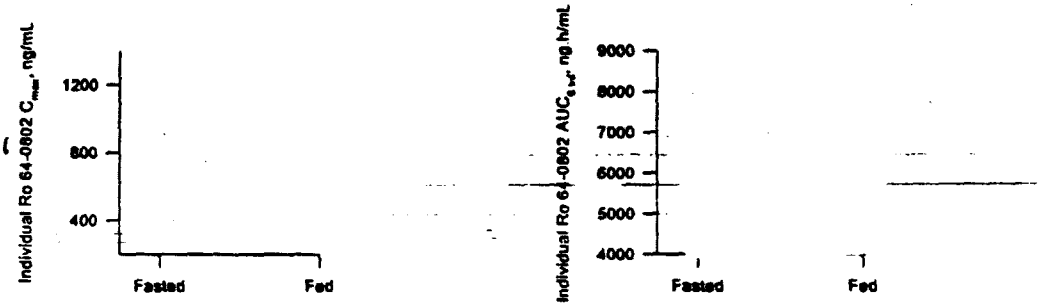


Figure 2b

Table 2. Results of statistical analysis

PK parameter of Ro 64-0802		Arithmetic mean (%CV)	Geometric mean	% point estimate [90% CI]
C_{max}, ng/mL	Market (Fasted)	551 (37)	526	100
	Market (Fed)	441 (32)	424	80.7 [76 – 86]
$AUC_{0-\infty}$, ng.h/mL	Market (Fasted)	6218 (12)	6176	100
	Market (Fed)	6069 (17)	5988	96.9 [93 – 101]

A 19% decrease in mean Ro 64-0802 C_{max} was observed when Ro 64-0796 was administered with food and this was associated with a minor (3%) decrease in Ro 64-0802 AUC. The mean Ro 64-0802 t_{max} values were 4.4 and 5.4 hours under fasted and fed conditions, respectively. The Applicant recommends that Ro 64-0796 can be taken with or without food. Since Ro 64-0796 was administered without regards to meals in clinical trials this is acceptable. As shown in the following table, when administered with food, Ro 64-0796 average C_{max} decreased by 13% and average AUC increased by 23%, respectively.

PK parameter of Ro 64-0796		Arithmetic mean (%CV)	% point estimate [90% CI]
C_{max}, ng/mL	Market (Fasted)	124 (51)	100
	Market (Fed)	101 (32)	86.9 [72 – 105]
$AUC_{0-\infty}$, ng.h/mL	Market (Fasted)	244 (34)	100
	Market (Fed)	287 (25)	123.1 [110 – 138]

ADDITIONAL OBSERVATION: A 33 year old female subject (53 kg) exhibited substantially higher Ro 64-0802 C_{max} when compared to other subjects (especially in Treatments A and B), however, Ro 64-0802 AUC value was not different in this subject (see Figure 1b). This subject also exhibited the least Ro 64-0796 C_{max} and AUC values suggesting

extremely rapid conversion of Ro 64-0796. The Applicant has not identified this event in the final study report and has not commented regarding this 'fast metabolizer'.

CONCLUSIONS: The conclusions of this study are:

(a) The clinical trial formulation and proposed market formulations of Ro 64-0796 were found to be bioequivalent based on C_{max} and AUC of Ro 64-0802.

(b) As evidenced by Ro 64-0802 concentrations, food decreased the rate of absorption but not the extent of absorption of Ro 64-0796. The average decrease in C_{max} was ~20% and may not be clinically significant.

An open-label, relative bioavailability study of the clinical trial and market formulations of Ro 64-0796 in healthy subjects (Protocol NP15810) (Volume 84)

BACKGROUND: The Applicant has employed three different formulations in the development of Ro 64-0796. Under Protocol NP15810, the Applicant has evaluated the bioequivalency between an early clinical trial formulation and the proposed market formulation. As part of this study, the Applicant has also evaluated the relative bioavailability of a [redacted] formulation of Ro 64-0796 with respect to the proposed market capsule formulation.

The early clinical trial formulation was manufactured in small batches by [redacted] This formulation has been used in single and multiple ascending dose studies and challenge studies. Manufacture of the proposed market formulation involves [redacted] which is accomplished by [redacted]

OBJECTIVES: (i) To assess the relative bioavailability of an early clinical trial formulation of Ro 64-0796 to that of the proposed market formulation and (ii) To assess the relative bioavailability of a liquid oral dosage formulation of Ro 64-0796 to that of the proposed market formulation.

SUBJECTS: A total of 18 healthy subjects (9 male and 9 female, mean age: 25 years, mean weight: 68 kg) participated in this study.

STUDY DESIGN: This study was conducted in a three-way crossover fashion. Subjects received the following three treatments.

Treatment A: Single 150 mg dose of Ro 64-0796/A03 and /A10 (clinical trial formulation) (1 x 100 mg capsule plus 5 x 10 mg capsule)

Treatment B: Single 150 mg dose of Ro 64-0796/V14 (market formulation) (2 x 75 mg capsule)

Treatment C: Single 150 mg dose of Ro 64-0796 (pediatric liquid formulation, 25 mL)

All three treatments were administered under fasting conditions. Subjects received the three treatments in one of the following six sequences: ABC, ACB, BAC, BCA, CAB and CBA. The washout period between the treatments was 7 to 10 days.

FORMULATIONS: Ro 64-0796 capsules (10 mg, /A03, batch number WEL089801 and 100 mg, /A10, batch number WEL089802), Ro 64-0796 capsules (75 mg, /V14, batch number GMZ0134/03) and Ro 64-0796 suspension formulation (150 mg/25 mL, /V06,

$AUC_{0-\infty}$, ng.h/mL	Market (Capsule)	6200 (22)	6050	100
	Liquid	5786 (22)	5666	93.7 [89 – 99]

An average of 18% decrease in mean Ro 64-0802 C_{max} was observed when the liquid formulation was administered and this was associated with a minor (3%) decrease in Ro 64-0802 AUC. The liquid formulation is not bioequivalent to the capsule formulation. The mean Ro 64-0802 t_{max} values were 4.3 and 5.1 hours after administration of the capsule and liquid formulations, respectively.

Statistical results for Ro 64-0796 are shown in the following table.

PK parameter of Ro 64-0802		Arithmetic mean (%CV)	% point estimate [90%CI]
C_{max}, ng/mL	Market (Capsule)	126 (40)	100
	Liquid	71.3 (50)	55.3 [43 – 71]
$AUC_{0-\infty}$, ng.h/mL	Market (Capsule)	280 (30)	100
	Liquid	223 (37)	78.0 [66 – 93]

The pharmacokinetic parameters of Ro 64-0796 suggest that absorption of Ro 64-0796 from the liquid formulation is lower.

CONCLUSIONS: The conclusions of this study are:

(a) The early clinical trial formulation and the proposed market formulation of Ro 64-0796 were found to be bioequivalent based on C_{max} and AUC of Ro 64-0802.

(b) The proposed market formulation (capsule) and the liquid formulation (intended for pediatric use) are not bioequivalent. It should be noted that the NDA under review, 21087, has been submitted for the capsule formulation and no regulatory decision is required for the liquid formulation at the present time.

Study of the safety and pharmacokinetics of the neuraminidase inhibitor Ro 64-0796 when administered concomitantly with paracetamol (acetaminophen) in healthy volunteers (Protocol WP15676) (Volume 100)

BACKGROUND: Acetaminophen was available for use as relief medication during Phase III studies and is a widely used over-the-counter drug. Although, there are no apparent mechanistic reasons for conducting a drug interaction study, the Applicant conducted this study to assess the pharmacokinetic interaction between acetaminophen and Ro 64-0796.

OBJECTIVE: To determine the effect of multiple doses of Ro 64-0796 on the single dose pharmacokinetics of acetaminophen.

SUBJECTS: 6 healthy male subjects (mean age: 40 years; mean weight: 77 kg) completed the study.

STUDY DESIGN: The subjects received the following treatments in a randomized crossover fashion.

Treatment A: Single oral dose of 500 mg of acetaminophen
Treatment B: Ro 64-0796 200 mg BID for five days followed by
a single dose of 200 mg of Ro 64-0796 plus 500 mg of acetaminophen.

The treatments were separated by a washout period of 4 days. Subjects received the two treatments in one of the following sequences: AB and BA. Serial blood samples were obtained after Treatment A and on the sixth day of Treatment B.

FORMULATIONS: Ro 64-0796 capsules (100 mg, /A02, batch number WEL049702) and acetaminophen tablets (500 mg) were used in this study.

SAMPLE COLLECTION: Blood samples were obtained at predose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18 and 24 hours after drug administration on pharmacokinetic assessment days. Urine samples were collected during 0-4, 4-8, 8-12 and 12-24 hours after drug administration.

ANALYTICAL METHODOLOGY: See Analytical Methodology section (Section VI).

PHARMACOKINETIC DATA ANALYSIS: Pharmacokinetic parameters of acetaminophen, Ro 64-0796 and Ro 64-0802 were estimated by non-compartment methods. The mean Cp-time profiles of acetaminophen are shown in Figure 1 and the pharmacokinetic parameters of acetaminophen are summarized in Table 1.

Table 1. Mean (%CV) acetaminophen pharmacokinetic parameters

PK parameter	Treatment A	Treatment B
C_{max}, µg/mL	7.16 (20)	6.51 (16)
AUC_{last}, µg.h/mL	22.1 (27)	19.3 (18)
$AUC_{0-\infty}$, µg.h/mL	23.2 (28)	20.2 (18)
% UR	1.86 (37)	1.77 (34)

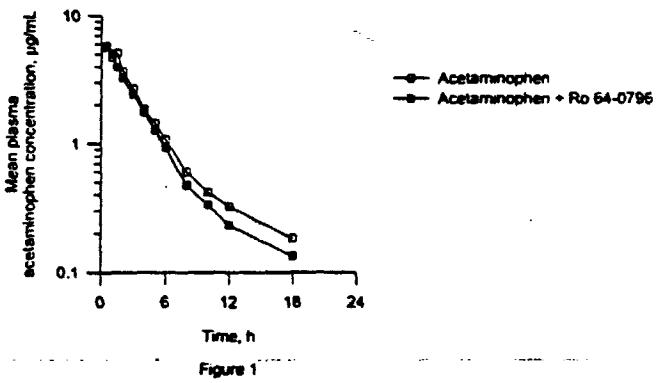
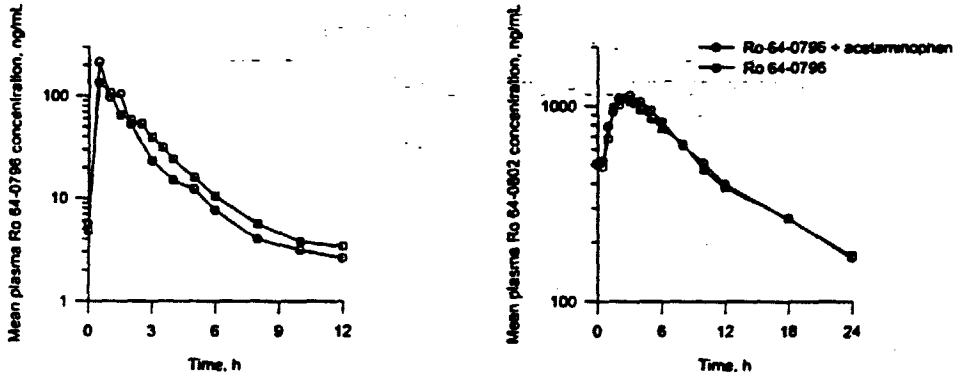


Figure 1

The pharmacokinetics of acetaminophen were not clinically significantly affected by concomitant administration of Ro 64-0796. The point estimates [90% CI] for log transformed C_{max} and AUC for Treatment B with respect to Treatment A were 0.92 [0.81 – 1.05] and 0.87 [0.77 – 1.02], respectively.

The mean plasma concentration - time profiles of Ro 64-0796 and Ro 64-0802 are shown in Figure 2 and the pharmacokinetic parameters of these species are summarized in Table 2. The Applicant has used historical pharmacokinetic data from

the multiple dose study NP15225 to compare the effect of acetaminophen on the pharmacokinetics of Ro 64-0796 and Ro 64-0802 in this study.



CROSS-STUDY COMPARISON

Figure 2

Table 2. Mean (%CV) Ro 64-0796 and Ro 64-0802 pharmacokinetic parameters

Species	Ro 64-0796		Ro 64-0802	
PK parameter	Treatment B	Historical data *	Treatment B	Historical data *
C_{max}, ng/mL	217 (46)	153 (35)	1142 (17)	1132 (25)
AUC_{0-12}, ng.h/mL	323 (38)	314 (28)	9098 (20)	8612 (15)
Half-life, h	2.44 (21)	2.71 (53)	8.4 (18)	8.7 (18)
% UR (0-12h)	5.2 (22)	3.2 (13)	105 (39)	66.2 (28)

* Historical data from Study NP15525

Cross-study comparison of pharmacokinetic data does not indicate a significant pharmacokinetic interaction. The mean C_{max} of Ro 64-0796 was increased by 38%, which may not be clinically significant. Percent of administered drug eliminated as Ro 64-0796 and Ro 64-0802 was higher when co-administered with acetaminophen. An explanation for this observation is not available. It was also noted that the total percent eliminated as Ro 64-0796 and Ro 64-0802 was significantly greater than 100% in some subjects.

CONCLUSIONS: The results of this small study suggest that Ro 64-0796 (at steady state) does not significantly effect the single dose pharmacokinetics of acetaminophen. This information will be presented in the package insert. Comparison to historical data indicates that a single dose of acetaminophen does not affect the disposition of Ro 64-0796.

An open-label study of the effect of cimetidine and probenecid on the pharmacokinetics of Ro 64-0796 in healthy subjects (Protocol WP15728) (Volume 102).

BACKGROUND: Upon oral administration, Ro 64-0796 is rapidly converted to Ro 64-0802. Less than 5% of the administered Ro 64-0796 is eliminated unchanged in the urine, whereas, approximately 75% is eliminated as Ro 64-0802. The renal clearance of Ro 64-0802 is substantially greater than the glomerular filtration rate, indicating active secretion in the renal tubules. The Applicant conducted this study to determine the active secretion pathway of Ro 64-0796 and Ro 64-0802. The model compounds used

in this study cimetidine (cationic pathway) and probenecid (anionic pathway) are appropriate for this type of study.

OBJECTIVE: To investigate the renal tubular secretion pathway of Ro 64-0796 and Ro 64-0802 by using two model compounds, cimetidine and probenecid.

SUBJECTS: 20 healthy male or female subjects (mean age: 35 years and mean weight: 69 kg) were enrolled in this study. Three subjects withdrew from the study due to adverse events. All withdrawals occurred during the probenecid treatment part of the study. The adverse events are discussed later in the review.

STUDY DESIGN: The subjects received the following three treatments in a randomized, 3-way crossover fashion.

Treatment A: Single oral dose of 150 mg of Ro 64-0796

Treatment B: Single oral dose of 150 mg of Ro 64-0796 plus cimetidine 400 mg every 6 hours. A total of 16 doses of cimetidine were administered beginning 23 hours before the dose of Ro 64-0796

Treatment C: Single oral dose of 150 mg of Ro 64-0796 plus probenecid 500 mg every 6 hours. A total of 16 doses of probenecid were administered beginning 23 hours before the dose of Ro 64-0796

The treatments were separated by a washout period of 8 to 14 days. Subjects received the three treatments in one of the following six sequences: ABC, ACB, BAC, BCA, CAB and CBA. Subjects consumed a standard breakfast 30 minutes prior to Ro 64-0796 dosing.

FORMULATIONS: Ro 64-0796 capsules (75 mg, /V01, batch number GMZ0082) and commercially available cimetidine and probenecid tablets were used in this study.

SAMPLE COLLECTION: Blood samples were obtained at predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 18, 24, 36, 48, 60 and 72 hours after Ro 64-0796 administration. Urine samples were collected during 0-4, 4-8, 8-12, 12-24, 24-48 and 48-72 hours after Ro 64-0796 administration. Plasma and urine samples were analyzed for Ro 64-0796 and Ro 64-0802 only.

PHARMACOKINETIC DATA ANALYSIS: Pharmacokinetic parameters of Ro 64-0796 and Ro 64-0802 were estimated by non-compartment methods. The mean plasma concentration - time profiles of Ro 64-0796 and Ro 64-0802 are shown in Figure 1.

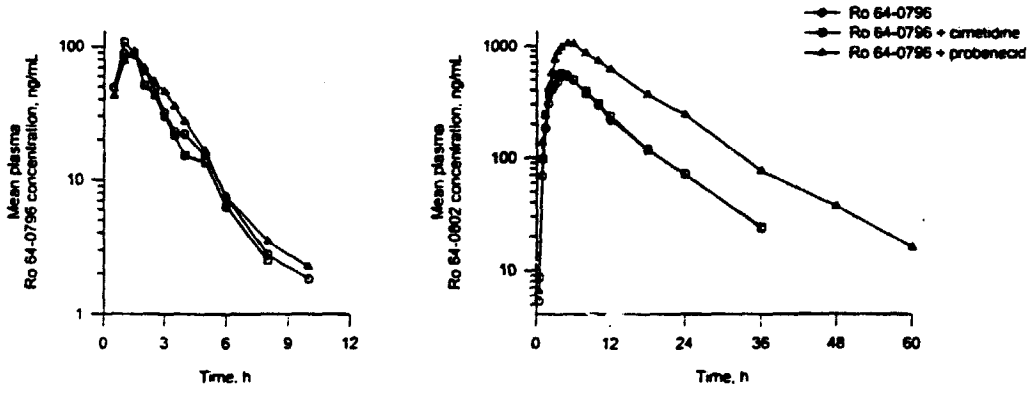


Figure 1

Effect on Ro 64-0796

The mean (%CV) pharmacokinetic parameters of Ro 64-0796, summarizing the effect of cimetidine and probenecid on Ro 64-0796, are shown in the following table.

PK parameter	Treatment		
	Ro 64-0796	Ro 64-0796 + Cimetidine	Ro 64-0796 + Probenecid
C_{max}, ng/mL	133 (45)	142 (44)	120 (32)
AUC_{last}, ng.h/mL	245 (21)	233 (34)	263 (33)
$AUC_{0-\infty}$, ng.h/mL	249 (21)	238 (33)	268 (33)
% UR	4.3 (23)	4.1 (31)	2.8 (31)
CLr, L/h	27.2 (28)	28.7 (40)	18.4 (48)

Coadministration of cimetidine or probenecid did not have a significant effect on the pharmacokinetics of Ro 64-0796. The point estimates [90% CI] for log transformed C_{max} and AUC for Treatment B with respect to Treatment A were 1.04 [0.81 – 1.34] and 0.93 [0.80 – 1.07], respectively. Renal clearance values were identical in Treatments A and B.

The point estimates [90% CI] for log transformed C_{max} and AUC for Treatment C with respect to Treatment A were 0.93 [0.72 – 1.20] and 1.04 [0.90 – 1.20], respectively. However, renal clearance of Ro 64-0796 was significantly reduced, by approximately 35%, by concomitant administration of probenecid. It should be noted that in spite of the 35% decrease, renal clearance was substantially greater than GFR.

Effect on Ro 64-0802

The mean (%CV) pharmacokinetic parameters of Ro 64-0802, summarizing the effect of cimetidine and probenecid on Ro 64-0802, are shown in the following table.

PK parameter	Treatment		
	Ro 64-0796	Ro 64-0796 + Cimetidine	Ro 64-0796 + Probenecid
C_{max}, ng/mL	587 (23)	599 (33)	1093 (30)
AUC_{last}, ng.h/mL	6420 (19)	6804 (28)	16169 (30)
$AUC_{0-\infty}$, ng.h/mL	6597 (19)	6992 (26)	16603 (31)
Half-life, h	7.2 (21)	7.7 (32)	8.9 (13)
% UR	71.5 (23)	69.6 (16)	78.0 (33)
CLr, L/h	15.7 (28)	15.0 (29)	7.5 (52)

Coadministration of cimetidine did not have a significant effect on the pharmacokinetics of Ro 64-0802. The point estimates [90% CI] for log transformed C_{max} and AUC for Treatment B with respect to Treatment A were 0.99 [0.91 – 1.09] and 1.04 [0.94 – 1.16], respectively. Renal clearance values were identical in Treatments A and B.

Coadministration of probenecid and Ro 64-0796 resulted in decreased clearance of Ro 64-0802. The point estimates [90% CI] for log transformed C_{max} and AUC for Treatment C with respect to Treatment A are 1.83 [1.66 – 2.0] and 2.45 [2.21 – 2.70], respectively. A stick plot depicting individual Ro 64-0802 C_{max} and AUC values following administration of Ro 64-0796 alone and following administration of Ro 64-0796 and probenecid are shown in Figure 2.

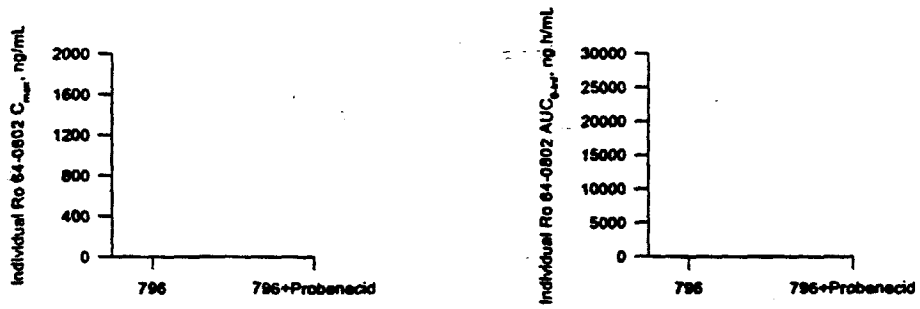


Figure 2

Renal clearance of Ro 64-0802 was reduced by 53% by concomitant administration of probenecid. In the presence of probenecid, renal clearance of Ro 64-0802 averaged 7.5 L/h, which is close to GFR. This suggests that the active tubular secretion of Ro 64-0802 was almost completely 'inhibited' by probenecid.

SAFETY: One subject withdrew due to mild eczema after receiving four doses of probenecid but before receiving Ro 64-0796. Another subject withdrew due to severe pelvic inflammatory disease after receiving all the 16 doses of probenecid and 73 hours after Ro 64-0796 administration. The investigator considered this event to be unrelated to treatment. These two withdrawals occurred during the first treatment period and these subjects were replaced. A third subjects withdrew during the third treatment period. This subject withdrew due to moderate rash after receiving 7 doses of probenecid and 10 hours after Ro 64-0796 administration. The investigator considered this event probably related probenecid administration.

CONCLUSIONS: Cimetidine, a known competitor for renal tubular secretion of cationic drugs, did not significantly alter the pharmacokinetics of Ro 64-0796 and Ro 64-0802. This indicates that renal active secretion of Ro 64-0796 and Ro 64-0802 does not involve the cationic transport process. Additionally, the Applicant points out that the pharmacokinetics Ro 64-0796 and Ro 64-0802 were not altered in the presence of cimetidine, which is a nonspecific inhibitor of cytochrome P450 enzymes.

On the other hand, coadministration of probenecid resulted in a substantial decrease in the renal clearance of both Ro 64-0796 and Ro 64-0802, indicating that renal tubular secretion of these compounds occur via the anionic pathway. This information will be presented in the package insert.

APPEARS THIS WAY
ON ORIGINAL

Multiple ascending oral dose study of the pharmacokinetics, tolerability, and safety of the neuraminidase inhibitor Ro 64-0796 in subjects with renal impairment
(Protocol WP15648) (Volume 96)

BACKGROUND: In other studies, the Applicant has demonstrated that orally administered Ro 64-0796 is extensively converted to Ro 64-0802, which is then mainly eliminated by the kidneys. The Applicant conducted this study to assess the impact of renal impairment on the pharmacokinetics and disposition of Ro 64-0796 and Ro 64-0802.

OBJECTIVE: To study the effect of renal impairment on the pharmacokinetics of Ro 64-0796 and Ro 64-0802 and the effect of multiple administrations of Ro 64-0796 on renal function.

SUBJECTS: 20 subjects participated in this study. Demographic information is provided in the following table.

	Group 1	Group 2	Group 3	Group 4
Mean age, years	41	45	42	24
No. of Male / Female	1 / 4	3 / 2	5 / 0	5 / 0
Mean weight, kg	60.5	75.1	87.0	78.6
Mean CLcr, mL/min	19.5	46.1	72.4	145
(range)	(12 - 27)	(42 - 53)	(62 - 81)	(114 - 197)

Subjects enrolled in Group 1 had creatinine clearance values between 10 and 30 mL/min but were not on dialysis.

STUDY DESIGN: Subjects with a wide range of creatinine clearance, as estimated by Cockcroft and Gault method, were enrolled in the study and received the following treatment. A single dose of 100 mg of Ro 64-0796 was administered on Day 1. On Days 2 thorough 5 subjects received Ro 64-0796 at a dose of 100 mg BID followed by a single 100 mg dose on Day 6.

On Day 1, all subjects received Ro 64-0796 after an overnight fast. Meal intake with respect to drug administration on Day 6 is not known. Renal function (GFR) was assessed on Days –1 and 6 by measuring elimination of diethylenetriamine pentaacetic acid (DTPA). The Applicant has not provided detailed information regarding this method.

FORMULATION: Ro 64-0796 capsules (100 mg, method /A02, batch number WEL 049702) were used in this study.

SAMPLE COLLECTION: Blood samples were obtained at predose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours after drug administration on Days 1 and 6. A trough blood sample was collected on Day 4. Urine samples were collected during the following intervals: 0-4, 4-8, 8-12, and 12-24 hours post-dose on these days.

ANALYTICAL METHODOLOGY: See Analytical Methodology section (Section VI).

PHARMACOKINETIC DATA ANALYSIS: Pharmacokinetic parameters were estimated by non-compartmental methods. The mean plasma concentration profiles for Ro 64-0796 and Ro 64-0802 on Day 7 are shown in Figure 1, the mean cumulative urinary excretion data are shown in Figure 2 and pharmacokinetic parameters are presented in Tables 1 and 2.

Graphical and numerical representation of summary data on Day 1 are presented in the Appendix to this review (page 43).

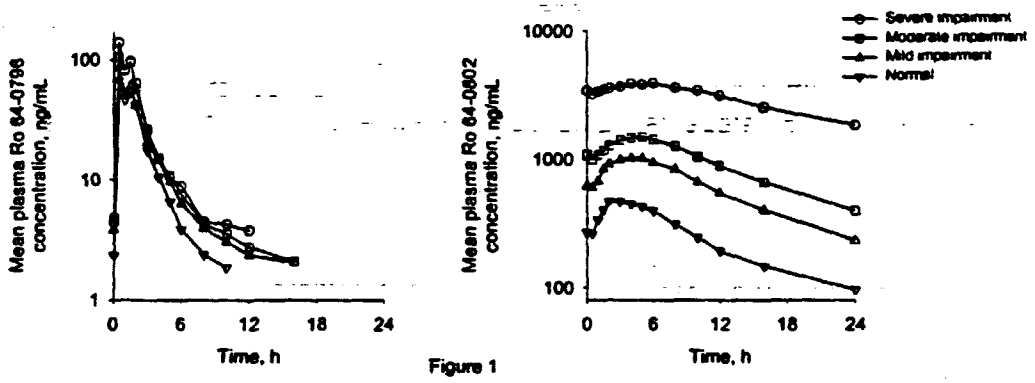


Figure 1

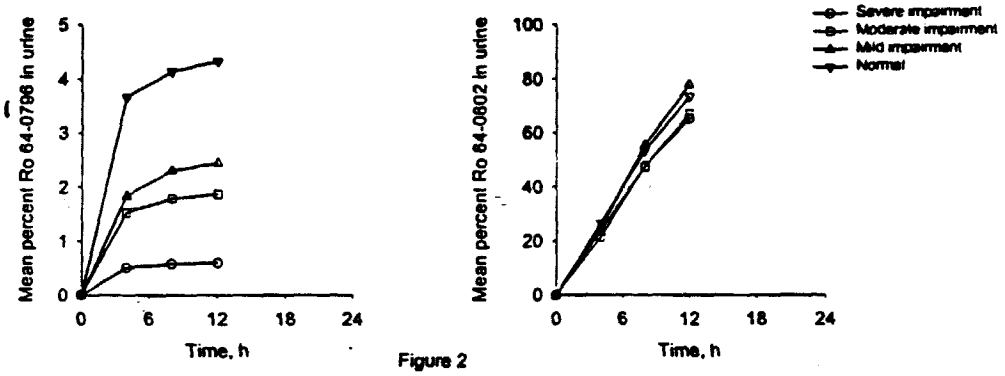


Figure 2

Table 2. Mean (%CV) pharmacokinetic parameters of Ro 64-0796 and Ro 64-0802 on Day 7

	Group 1 CL_{CR} < 30	Group 2 30 < CL_{CR} < 60	Group 3 60 < CL_{CR} < 90	Group 4 CL_{CR} > 90
Ro 64-0796				
C_{max}, ng/mL	159 (26)	135 (38)	97.4 (38)	80 (13)
AUC_{0-12}, ng.h/mL	286 (32)	271 (25)	202 (25)	164 (19)
CL_T/F, mL/min	6342 (33)	6395 (20)	8579 (20)	10427 (18)
CL_R/F, mL/min	36 (35)	113 (22)	202 (14)	501 (38)
Ro 64-0802				
C_{max}, ng/mL	4052 (37)	1514 (26)	1058 (17)	494 (16)
AUC_{0-12}, ng.h/mL	43086 (42)	15010 (28)	9931 (16)	4187 (15)
CL_T/F, mL/min	41 (45)	107 (26)	156 (16)	369 (15)
CL_R/F, mL/min	26 (36)	70 (16)	121 (16)	291 (16)
CL_{CR}, mL/min	19.5 (34)	46.1 (9)	72.4 (11)	145 (24)
Individual CL_{CR}	12, 13, 20, 20, 25	42, 44, 45, 46, 53,	62, 66, 74 79, 81	114, 122, 130, 160, 197

Renal impairment had a modest impact on the pharmacokinetics of Ro 64-0796. For Ro 64-0796 C_{max}, the ratio [90%CI] for Groups 1, 2 and 3 with respect to Group 4 was 1.99 [1.46 – 2.51], 1.69 [1.16 – 2.21] and 1.22 [0.69 – 1.74], respectively. For Ro 64-0796 AUC_{0-12}, the ratio [90%CI] for Groups 1, 2 and 3 with respect to Group 4 was 1.74 [1.31 – 2.18], 1.65 [1.22 – 2.09] and 1.23 [0.80 – 1.66], respectively. However, as expected, renal impairment had a profound impact on the pharmacokinetics of Ro 64-0802. For Ro 64-0802 C_{max}, the ratio [90%CI] for Groups 1, 2 and 3 with respect to Group 4 was 8.20 [6.42 – 9.97], 3.06 [1.30 – 4.83] and 2.14 [0.37 – 3.91], respectively. For Ro 64-

0802 AUC_{0-12}, the ratio [90%CI] for Groups 1, 2 and 3 with respect to Group 4 was 10.3 [7.83 – 12.75], 3.59 [1.13 – 6.04] and 2.37 [-0.08 – 4.82], respectively.

Based on individual Ro 64-0802 AUC_{12} on Day 6 and Day 1, the average accumulation index was calculated to be 3.3, 2.1, 1.8 and 1.7 in Groups 1, 2, 3 and 4, respectively. The relationship between Day 6 Ro 64-0796 C_{max} and AUC and creatinine clearance and Day 6 Ro 64-0802 C_{max} and AUC is shown in Figures 3 A and B, respectively.

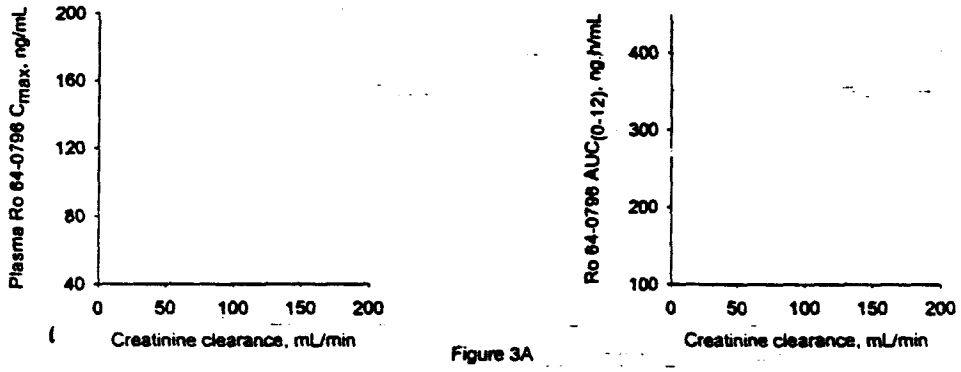


Figure 3A

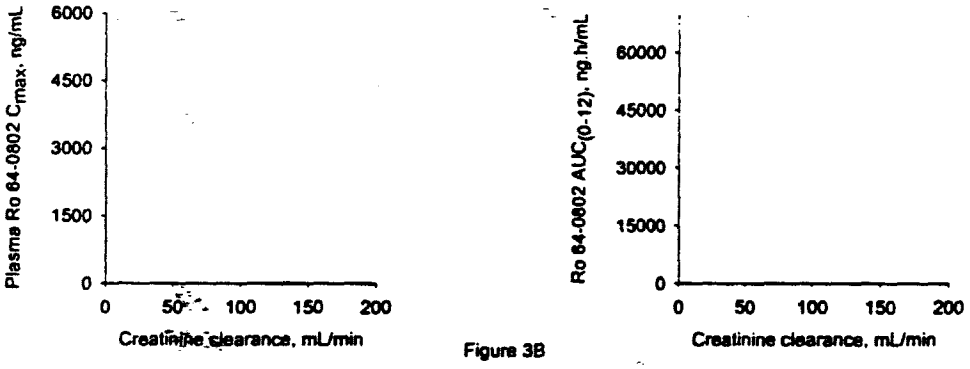


Figure 3B

The Applicant estimated glomerular filtration rate on Day –1 and Day 6 by measuring DTPA excretion. No marked changes in GFR were seen on Day 6 (see below), suggesting that administration of Ro 64-0796 for five days does not alter renal function.

	Group 1	Group 2	Group 3	Group 4
Day –1	15.1 (34)	39.0 (24)	56.4 (19)	132.1 (25)
Day 6	14.3 (29)	40.4 (18)	55.3 (12)	133.8 (15)

Due to lack of detailed information, it is not known if DTPA measurements on Day 6 had an impact on pharmacokinetic assessment of Ro 64-0796 and Ro 64-0802.

In the proposed package insert, the Applicant has recommended that patients with severe renal impairment (CLcr < 30 mL/min) should receive Ro 64-0796 75 mg QD for 5 days. No dose adjustments are recommended for patients with creatinine clearance greater than 30 mL/min. The rational for this dose reduction appears in the Human Pharmacokinetics and Biopharmaceutics summary (volume 75). In this section the Applicant states that the frequency of adverse events was examined as a function of creatinine clearance in Phase III studies in which patients with influenza were treated with Ro 64-0796 75 mg BID for 5 days. According to the Applicant, the incidence of

adverse events in patients with mild and moderate impairment was similar to patients with normal renal function. Further, in prophylaxis trials, 10 subjects with severe renal impairment (CLcr < 30 mL/min) received Ro 64-0796 75 mg QD for a period of *6 weeks*. In these patients, the incidence of adverse events was similar to that observed in subjects with mild and moderate renal impairment. The Applicant's claims have been brought to the attention of the Medical Officer.

The Applicant has also cited the multiple dose study (WP15525), in which a dose of 500 mg BID was administered for 7 days to six healthy male subjects and was found to be "generally well-tolerated". In this study, the mean steady-state AUC_{12} values for Ro 64-0796 and Ro 64-0802 were 813 ng.h/mL and 20317 ng.h/mL, respectively. It is anticipated that at the proposed dose of 75 mg BID, the AUC values in subjects with mild and moderate renal impairment (CLcr > 30 mL/min) would be less than the highest observed exposures in Study WP15525.

ADVERSE EVENTS: A subject with a history of epilepsy and mild renal impairment was enrolled in this study contrary to the exclusion criteria. On Day 3, this subject experienced grand mal convulsion (a severe event). The investigator documented that the event occurred due to emotional stress and has reported this event to be unrelated to the study drug. Another subject experienced a serious adverse event five days *after* the last dose. This subject with mild renal impairment with 25 years of Wolff-Parkinson-White syndrome, experienced mild chest pains for two days. An abnormal ECG was recorded and according to a cardiologist was found to be consistent with Wolff-Parkinson-White syndrome. This adverse event is considered by the investigator to be unrelated to the study drug.

CONCLUSIONS: The results of this study indicate the pharmacokinetics and disposition of Ro 64-0796 is dependent on the renal function. Renal impairment greatly affected the pharmacokinetics of the active species, Ro 64-0802. In subjects with severe renal impairment (CLcr ≤ 30 mL/min), the average total clearance and renal clearance value of Ro 64-0802 was approximately 10% of the average clearance value observed in subjects with normal renal function. According to the Applicant, the increased exposure to Ro 64-0802 was tolerated well by subjects with varying degrees of renal impairment. However, in order to achieve exposures that are comparable to subjects with normal function, the Applicant recommends a dose of 75 mg QD in subjects with creatinine clearance values of less than 30 mL/min. This is acceptable.

APPENDIX

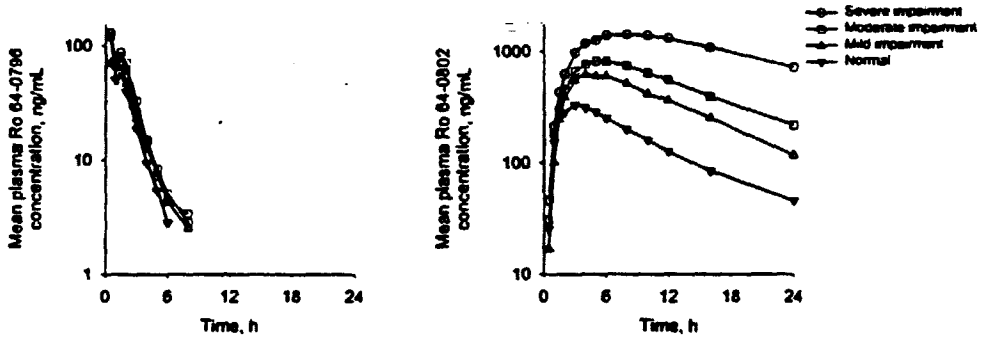
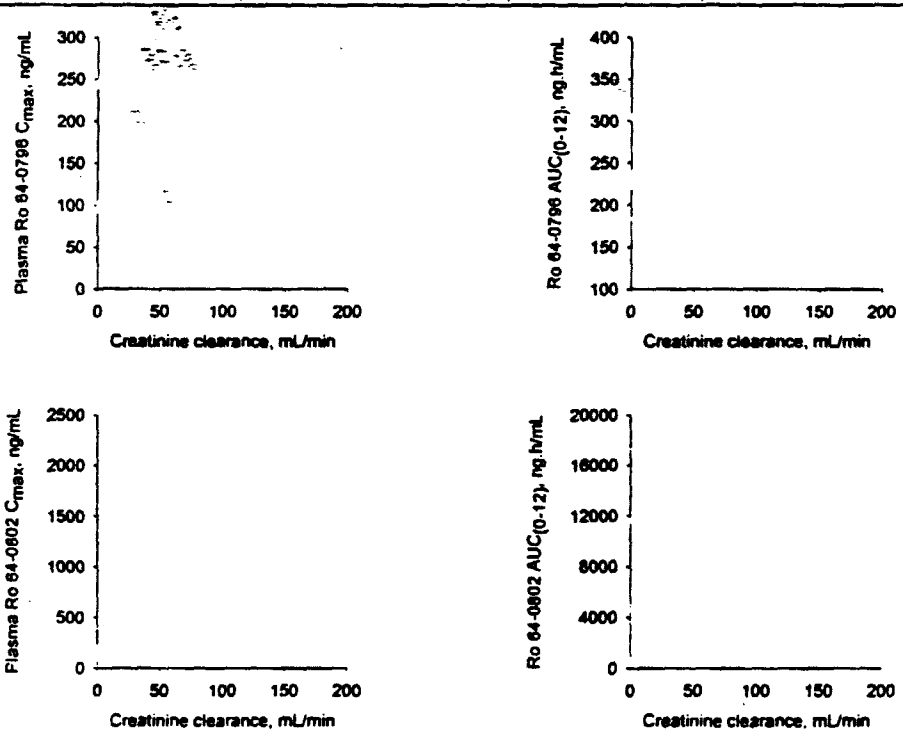


Table 1A. Mean (%CV) pharmacokinetic parameters of Ro 64-0796 and Ro 64-0802 on Day 1

	Group 1 CL_{CR} < 30	Group 2 30 < CL_{CR} < 60	Group 3 60 < CL_{CR} < 90	Group 4 CL_{CR} > 90
Ro 64-0796				
C_{max}, ng/mL	133 (58)	137 (60)	94.4 (45)	117 (35)
AUC_{0-12}, ng.h/mL	251 (33)	259 (21)	189 (33)	180 (19)
Half-life, h	2.31 (115)	1.56 (28)	1.89 (51)	1.20 (26)
CL_T/F, mL/min	7115 (43)	6573 (41)	9457 (38)	9332 (19)
CL_R/F, mL/min	48 (48)	133 (33)	219 (27)	474 (28)
Ro 64-0802				
C_{max}, ng/mL	1470 (26)	833 (26)	638 (8)	339 (39)
AUC_{0-12}, ng.h/mL	13170 (30)	7379 (27)	5373 (10)	2582 (28)
Half-life, h	13.9 (32)	9.9 (40)	7.3 (14)	8.4 (22)
CL_T/F, mL/min	42 (39)	105 (19)	166 (17)	380 (19)
CL_R/F, mL/min	31 (32)	79 (15)	109 (4)	297 (22)
CL_{CR}, mL/min	19.5 (34)	46.1 (9)	72.4 (11)	145 (24)
Individual CL_{CR}	12, 13, 20, 20, 25	42, 44, 45, 46, 53,	62, 66, 74 79, 81	114, 122, 130, 160, 197



A report on the pharmacokinetic results from Phase III studies for the neuraminidase inhibitor Ro 64-0796 (Protocols WV15670, WV15671 and WV15730) (Volume 115)

Three Phase III studies were conducted to determine the efficacy and safety of Ro 64-0796. The pharmacokinetic results from these studies are reviewed here.

SUBJECTS: Pharmacokinetics of Ro 64-0796 and Ro 64-0802 were determined in 44 patients enrolled in the three Phase III studies. The average age and weight of patients who provided pharmacokinetic data is 37 years and 76 kg, respectively.

STUDY DESIGN: The three Phase 3 studies were conducted in a double-blind, placebo-controlled fashion in patients with influenza-like illness. In studies WV15670 and WV15671, patients received placebo or Ro 64-0796 at a dose of either 75 mg BID or 150 mg BID for five days. In Study WV15730, Ro 64-0796 was administered at a dose of 75 mg BID for five days. Patients participating in the pharmacokinetic component received Ro 64-0796 one-hour prior to consuming breakfast on Day 5.

SAMPLE COLLECTION: Blood samples were obtained at predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10 and 12 hours after drug administration on Day 5. Urine samples were collected during 0-4, 4-8 and 8-12 hours after drug administration.

PHARMACOKINETIC DATA ANALYSIS: Pharmacokinetic parameters of Ro 64-0796 and Ro 64-0802 were estimated by non-compartment methods and are summarized in Table 1.

Table 1. Mean (%CV) pharmacokinetic parameters of Ro 64-0796 and Ro 64-0802 on Day 5

	Ro 64-0796		Ro 64-0802	
	75 mg BID	150 mg BID	75 mg BID	150 mg BID
N	24	20	24	20
C_{max}, ng/mL	84.7 (58)	141 (51)	398 (26)	772 (18)
AUC(0-12), ng.h/mL	148 (31)	266 (26)	3447 (30)	6518 (20)
Half-life, h	1.7 (31)	1.8 (23)	7.9 (36)	7.4 (39)
C_{12}, ng/mL	– *	– *	175 (33)	328 (36)
%UR	3.3 (30)	4.0 (34)	62.8 (39)	73.2 (25)
CLr (L/h)	17.5 (36)	23.5 (48)	13.2 (37)	15.8 (36)

* C_{12} – not reported due to a majority of subjects exhibiting concentration below the limit of quantitation.

Dose proportionality in the pharmacokinetics of Ro 64-0796 and Ro 64-0802 was assessed by performing analysis of variance on dose-normalized C_{max} and AUC values. These statistical analyses, performed by the Applicant, did not indicate a deviation from dose-proportionality at the two dose levels.

Steady-state pharmacokinetic data are not available at the above dose levels in healthy subjects. In study NP15525, six healthy *male* subjects receiving 50 and 100 mg of Ro 64-0796 twice daily, exhibited mean Ro 64-0802 AUC_{0-12} values of 2107 and 3845 ng.h/mL, respectively. The pharmacokinetic data obtained in Phase 3 trials suggest no major difference in the disposition of Ro 64-0796 in healthy subjects and patients.

CONCLUSION: In general, after oral administration of Ro 64-0796, exposure to the active species, Ro 64-0802, was not different in healthy subjects and in patients being treated for influenza like illness.

Exposure - response relationship

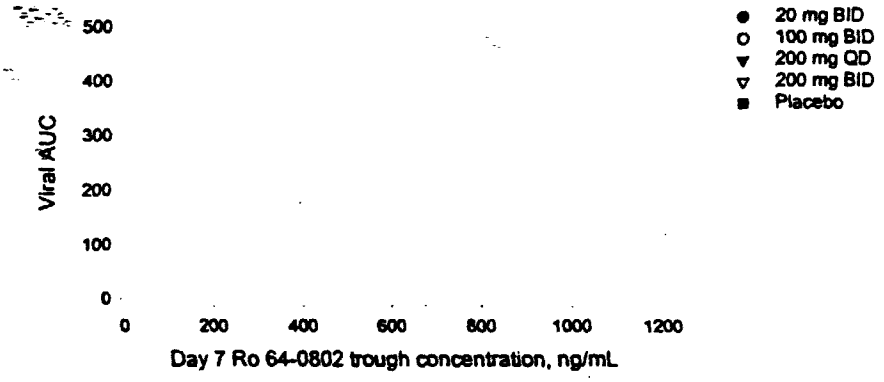
The Applicant has conducted two studies in subjects experimentally inoculated with human influenza virus (Type A or B). The main findings of these studies are summarized below.

Protocol GS 97-801: Safety, tolerability and activity of oral Ro 64-0796 in the treatment of subjects experimentally inoculated with human influenza virus.

In this double-blind, randomized study, 80 healthy male and female volunteers were experimentally inoculated with human influenza A/Texas/36/91 virus. Placebo or Ro 64-0796 at doses of 20 mg BID, 100 mg BID, 200 mg BID or 200 mg QD was administered for a period of five days starting 28 hours after inoculation. Trough concentrations of Ro 64-0796 were determined on Study Days 3, 4 and 7 (with respect to inoculation). Nasal wash for viral titer was collected twice daily on Days 2 and 3 and then once daily. The primary efficacy parameter for this study was area under the virus titer versus time curve (viral AUC). The viral AUC (units: log TCID50.hour/mL) at the various dose levels are tabulated below.

	Placebo	20 mg BID	100 mg BID	200 mg BID	200 mg QD	Pooled Ro 64-0796
N	16	16	16	16	16	64
Mean	175.2	98.3	57.8	91.8	116.3	91.0
%CV	85	122	100	107	110	112
Median	258.9	51.3	46.8	79.5	89.4	54.7

Day 7 trough concentrations were plotted against viral AUC to explore exposure-response relationship. As shown in the figure below, a relationship between C_{min} and viral AUC is not apparent.



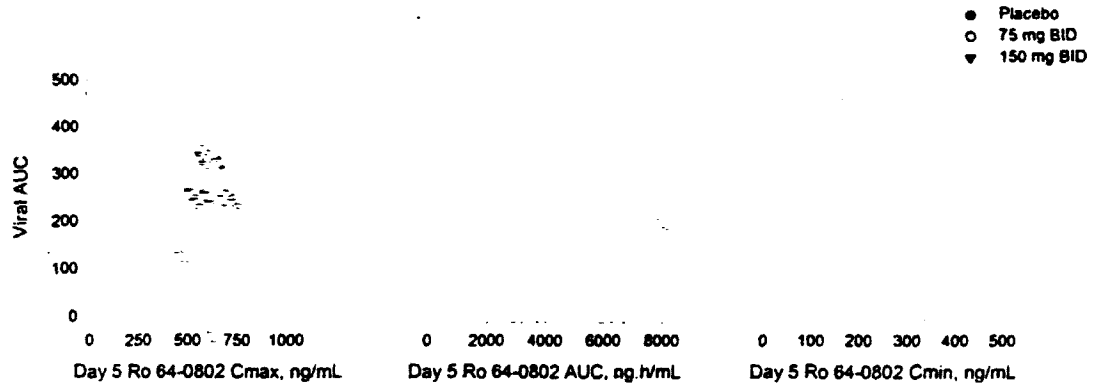
The results of this study indicate that at the doses studied, the mean and median value for viral AUC is similar across the dose groups in subjects experimentally inoculated with human influenza virus. It is not known if these results would be applicable in the event of naturally acquired influenza.

Protocol NP15717: Study of the pharmacodynamics and pharmacokinetics of the neuraminidase inhibitor Ro 64-0796 in the treatment of volunteers experimentally infected with human influenza B virus.

In this double-blind, randomized study, 60 healthy male and female volunteers were experimentally inoculated with attenuated influenza B/Yamagata/16/88 virus. Placebo or Ro 64-0796 at doses of 75 mg BID or 150 mg BID was administered for a period of five days starting 24 hours after inoculation. Blood samples were collected at predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10 and 12 hours after drug administration in Days 1 and 5. Nasal wash for viral titer was collected either once or twice daily for up to Day 7. The primary efficacy parameter for this study was area under the virus titer versus time curve (viral AUC). The viral AUC (units: log TCID50.hour/mL) at the two dose levels and placebo are tabulated below.

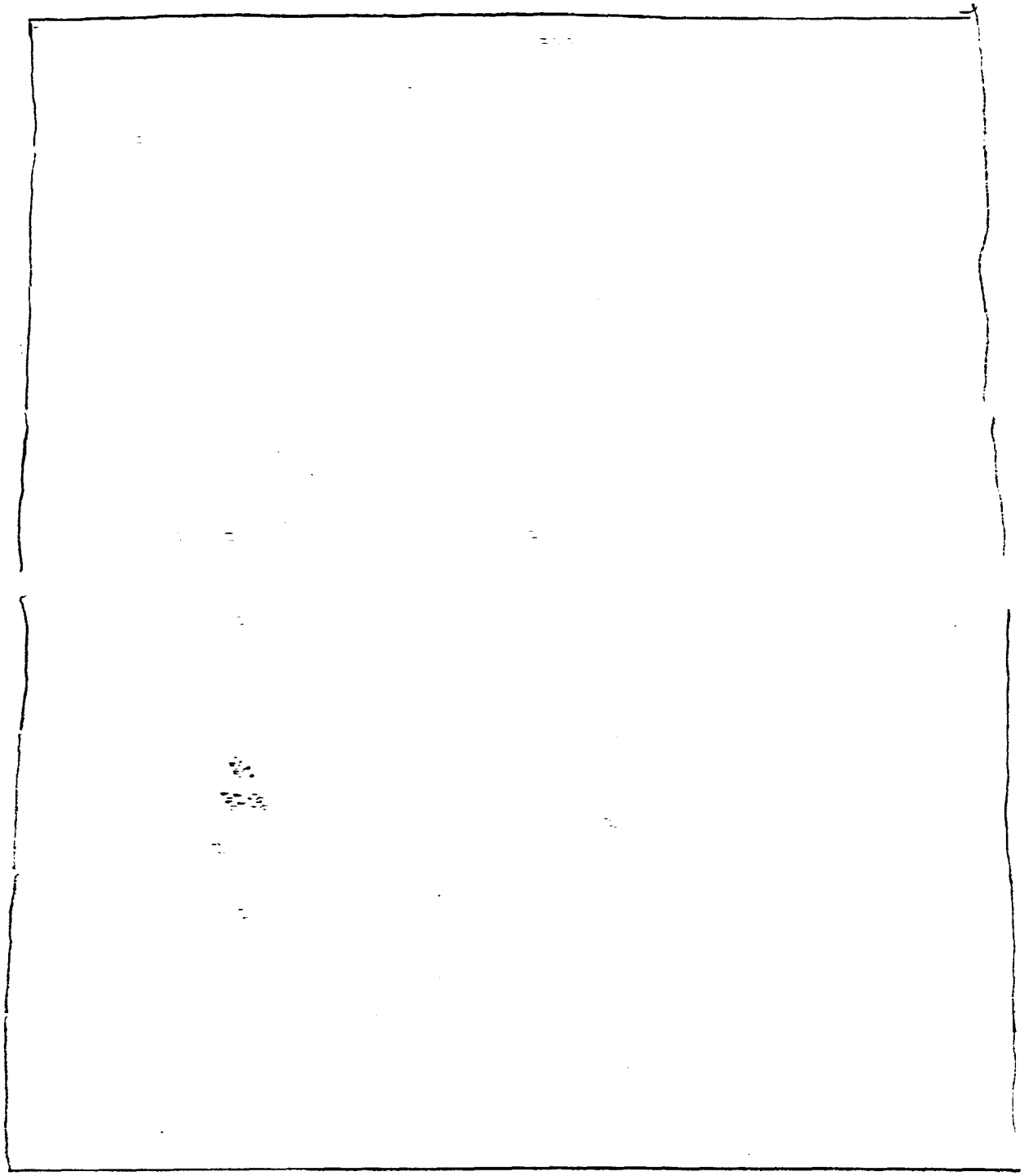
	Placebo	75 mg BID	150 mg QD	Pooled Ro 64-0796
N	16	15	15	30
Mean	182.2	79.7	125.3	102.5
%CV	133	159	150	155
Median	78.0	17.8	14.8	14.8

Day 5 C_{max}, AUC_{12} and C_{min} values were plotted against viral AUC to examine exposure-response relationships. As seen in the figure below, a clear relationship between the pharmacokinetic parameters and response is not apparent.



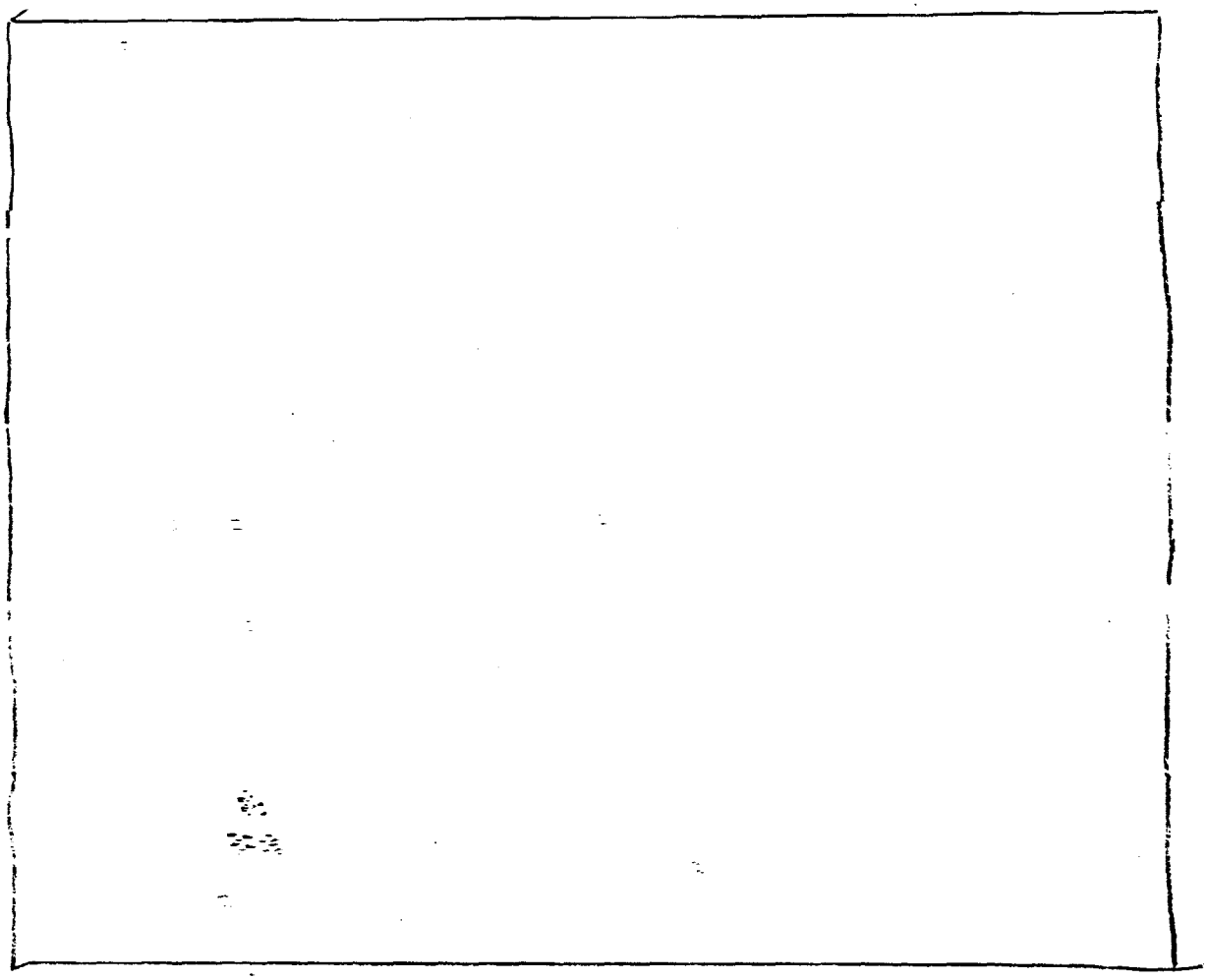
A relationship (that can be modeled) between exposure and response was not identified in studies GS 97-801 and NP15717. However, when compared to placebo, average viral AUC values were lower following administration of Ro 64-0796 in subjects experimentally inoculated with influenza A or B virus. The Applicant points out that it is possible that the doses of Ro 64-0796 investigated were at or near the plateau of the exposure-response relationship. It is also possible that plasma concentrations are not reflective of the drug concentrations at the site of action.

VI. ANALYTICAL METHODOLOGY



VII. DISSOLUTION

The dissolution profiles for [redacted] batch of the market formulation and [redacted] batches of clinical trial formulation are shown below.



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