CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21036

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

HFD-5 3C
Lynne

Clinical Pharmacology & Biopharmaceutics Review

JUN - 8 1999

NDA 21-036 (SN 000)	**Submission Dates:** 10/26/98, 3/3/99,
RELENZA (zanamivir for inhalation)	3/3/99, 6/2/99
Glaxo Wellcome, Inc.	**Draft Review:** 2/12/99
Type of Submission: New NDA,	**Final Review:** 06/08/99
NME	**Reviewer:** Brad Gillespie, PharmD

Background

Zanamivir has been shown to be a potent inhibitor of neuraminidase, the influenza virus surface enzyme. Neuraminidase is known to aid in the release of newly formed virus particles from infected cells and is thought to facilitate the infection of other cells. Thus, it is hypothesized that if the action of this enzyme can be inhibited, the spread of influenza can be blocked, attenuating the patient's course of illness. Glaxo Wellcome, the sponsor of this NDA, has evaluated the safety and efficacy of Zanamivir in three pivotal trials: NAIA3002 (North America), NAIB3001 (Australia, New Zealand and South Africa) and NAIB3002 (Europe). The sponsor was able to show a significant treatment effect in NAIB3002, an intermediate effect in NAIB3001 and no significant effect in NAIA3002. A reasonable explanation for these treatment differences is not apparent. A total of 15 clinical pharmacology and biopharmaceutics studies were submitted in this application using a combination of intravenous, oral, intranasal and inhaled routes of administration. With the exception of the oral absolute bioavailability study and the renal impairment trial, none of the studies using administration routes other than inhalation were evaluated. Also included in the above count of trials were two γ-scintigraphy deposition studies. It is critical to note that since zanamivir is presumed to act topically, pharmacokinetics are not expected to correlate well with clinical efficacy. Thus, it is unlikely that the collection of pharmacokinetic data would have contributed to the utility of the clinical efficacy trials. Pharmacokinetics may provide an indication of systemic exposure, helping to link available safety data.

RELENZA is proposed to be indicated for treatment of both influenza A and B in adults and adolescents at least 12 years of age. It is proposed to be administered to the respiratory tract by oral inhalation only, using the DISKHALER device provided. The recommended dose of RELENZA for treatment of influenza in patients $\geq$12 years of age is two inhalations (10 mg) twice daily for 5 days.

Synopsis The highlights of the pharmacokinetics and disposition of zanamivir are presented here. A more detailed review of each individual study begins on page 7.

Deposition

It appears that approximately 13-15% of the inhaled dose is deposited in the lung with the remainder deposited in the oropharynx and subsequently swallowed. For details, see the deposition discussion appearing at the end of this review.

Absorption

The pharmacokinetics of inhaled zanamivir were studied after a single 10 mg dose and after 6 days of administering a 10 mg dose at 0800, 1200, 1600 and 2000 (Study C94-009). It is critical to note that this is not the proposed dosing regimen of 10 mg every 12 hours. Subjects were administered single 10 mg doses in two separate phases of the trial. Single-dose results varied across the phases (e.g., $AUC_{0-\infty}$ of 655 ng·hr/mL and 242 ng·hr/mL reported in Phase 1 and Phase 2, respectively, after administration of a single 10 mg dose) and appropriate multiple-dose data were not obtained (e.g., 10 mg doses administered four times daily versus the proposed dose of 10 mg every 12 hours) so these studies are not necessarily reliable for assessing the bioavailability and pharmacokinetics of this product. For the purposes of determining safety multiples of animal exposure to this product, the prudent approach is to use the highest observed human concentrations (Phase 1, 10 mg single-dose). In this arm, a peak serum concentration of 95 ng/mL was documented. Total exposure ($AUC_{0-\infty}$) was 655 ng·hr/mL. The effect of food on zanamivir absorption was not evaluated.

Absolute Bioavailability

The absolute bioavailability of zanamivir when given as an inhalation has not been determined. Its absolute bioavailability after oral administration, which also represents the bioavailability of the portion of the inhaled dose that is swallowed, was investigated in Study NAIB1008. This study showed that the absolute bioavailability of a 50 mg oral dose is approximately 2%. Based on the premise that none of the systemic zanamivir is metabolized, and that it is eliminated nearly completely unchanged in the urine, the absolute bioavailability of inhaled zanamivir is approximately 11-19% based on urinary recovery in Study C94-009.

Distribution

Plasma protein binding of zanamivir over the range of 0.05 to 10 μg/mL and its association with red blood cells were less than 14%.

Metabolism and Elimination

The applicant has not completed any *in vitro* or *in vivo* trials designed to characterize the metabolism of zanamivir. Nevertheless, in the absolute bioavailability study, approximately 98% of the intravenously administered dose was excreted unchanged in the urine. This finding indicates that zanamivir undergoes little, if any, biotransformation *in vivo*. While elimination half lives ranged from 3-6 hours in inhalation studies, half lives of 2-3 hours were observed after intravenous dosing. This difference indicates that the elimination of zanamivir after inhalation may be absorption-rate limited.

Drug Interactions

The applicant has not conducted any pharmacokinetic/pharmacodynamic drug-drug interaction studies. They did complete a clinical trial demonstrating that the administration of zanamivir did not interfere with the immunity provided by influenza

vaccine. An in vitro drug-drug interaction trial suggested that zanamivir is unlikely to inhibit the metabolism of cytochrome P450 substrates.

Special Populations

The applicant conducted a pharmacokinetic trial in renally impaired patients which showed that the clearance of zanamivir is substantially decreased in this population compared to patients with normal renal function. In mild to moderately impaired patients, AUC nearly doubled, while in severely impaired patients, AUC increased by nearly a 7-fold margin. The elimination half-life was prolonged from 2.9 to 4.4 hours in mild to moderately impaired and to 15 hours in severely impaired patients. These findings were discussed with Dr. B. Styrt, the Medical Officer assigned to this submission, who concluded that, in light of available safety data, there is no need for a dosage adjustment.

Population Pharmacokinetics

The applicant conducted a NONMEM analysis on two Phase 1/2 trials and found no significant covariate interaction due to study type, demographic factors, formulation, infection status or concurrent medication usage.

Pharmacokinetic/Pharmacodynamic Correlation

No studies have been conducted.

Label

The proposed label begins on page 32 of this review. Preliminary labeling comments communicated to the sponsor in a 5/17/99 fax are identified by redline and strikeout. The sponsor has accepted most of these changes (see 6/2/99 submission), with a few exceptions described below. The companies position appears *italicized* and FDA interpretation of their intentions underlined. It is critical to note that these comments are preliminary, and should an approval action be taken, a more thorough review of the package labeling is indicated.

Recommendation

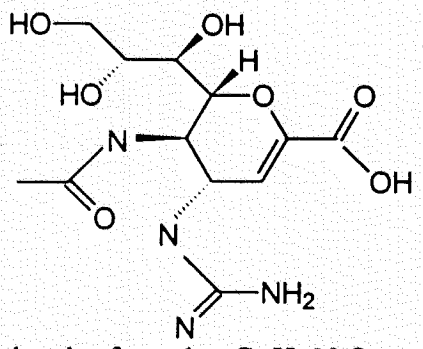
The human pharmacokinetics studies submitted under NDA 21-036 provide adequate information to describe the disposition of zanamivir when administered as a dry powder for inhalation. Nevertheless, should zanamivir be approved, the clinical pharmacology section of the label will need to be reviewed more comprehensively.

Clinical Pharmacology & Biopharmaceutics Briefing: 2/19/99. Drs. Lazor, Hunt, Sahajwalla, Collins, Huang, Uhl and Reynolds.

TABLE OF CONTENTS

I. Chemistry Overview

Chemical name: 5-(acetylamino)-4-[(aminoiminomethyl)-amino]-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enonic acid
Structure:



Molecular formula: $C_{12}H_{20}N_4O_7$
Molecular weight: 332.3
Solubility: 18 mg/mL in water

II. Formulation

Component	
zanamivir	
Lactose	

Zanamivir is blended with lactose and then sealed in the Rotadisk (double foil blister package). The drug is then dispensed as a dry powder using the Diskhaler device.

Studies C94-009 (pivotal bioavailability) NAIA2005 (population PK) and NAIA2006 (population PK), the only clinical pharmacology trials using an inhaled dose, all used the to be marketed formulation. The used in these studies was than that proposed While the According to the CMC reviewer assigned to this application, Dr. D. Boring, lot GFD 30105, the primary stability batch used in all three pivotal clinical trials . The only difference is the size of the blend In summary, the clinical formulation was probably representative of that proposed for marketing while that used in the bio-study was clearly different.

III. Indication (per label)

RELENZA is indicated for treatment of both influenza A and B in adults and adolescents at least 12 years of age.

IV. Dosage and Administration (per label)

RELENZA is for administration to the respiratory tract by oral inhalation only, using the DISKHALER device provided. The recommended dose of RELENZA for treatment of influenza in patients ≥12 years of age is two inhalations (10 mg) twice daily for 5 days.

A study to investigate the safety, tolerability and pharmacokinetics of single and multiple doses of GG167 dry powder administered by inhalation in man (Report No. GCP/95/031)

Study No. C94-009 **Volume** 1.18
Investigator Dr. V. Wanigasekara: Glaxo Clinical Pharmacology Unit; Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ
Clinical Dates 3/11/94 – 5/16/94
Analytical Facility Glaxo Research & Development Ltd., Greenford
Analytical Dates 4/5/94 – 6/9/94

Objectives To characterize the pharmacokinetics of GG167 administered by inhalation and to measure the antiviral activity in pharyngeal gargle samples.

Formulations GG167 was supplied to the study facility as a 4-blister 5/25 mg rotadisk containing a 5 mg GG167/25 mg lactose mixture in each blister (Batch numbers BN F93/191C and BN F94/016D for the single- and repeat-dose phases, respectively).

Study Design A total of 18 healthy, non-smoking adult males were included in this double-blind, randomized, two-phase (first phase: single ascending doses of GG167 and placebo to 6 subjects; second phase: multiple doses of GG167 and placebo to 12 subjects). Subjects 01-06 received single 5 mg and 10 mg doses of GG167 in a crossover fashion, with a washout period of at least 4 days separating the treatments. At the end of the single-dose phase, the safety and tolerability of GG167 at this dose level was ascertained prior to beginning the multiple-dose phase of the study (enrollment of Subjects 07-18). Subjects 07-18 received, by inhalation, 10 mg multiple doses of GG167 or placebo. GG167 or placebo was administered twice, separated by 12 hours, on Day 1 and four times daily (0800, 1200, 1600 and 2000) on Days 2-7 of each dosing period. A washout period of at least seven days separated the administration of GG167 and placebo. In the single-dose phase, and on Day 1 of the multiple-dose phase, all treatments were administered after an overnight fast. Subjects then remained fasting until after the 4 hour blood sample was obtained. On Days 2-7, breakfast was provided after the 0800 dose was administered. On Days 1-7, meals were provided at about 1200 and 1800. All meals were standardized. Subjects were confined throughout each study phase and abstained from the consumption of xanthine and ethanol containing foods and beverages.

Sampling
Day 1, Single-Dose Phase: Blood samples were obtained for serum GG167 determinations just prior to (zero hour), 0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6 and 8 hours after study drug administration. Urine was collected over the intervals 0-2, 2-4 and 4-8 hours after dosing.

Day 5 and 6, Multiple-Dose Phase: Trough samples were obtained prior to administering the 1600 dose.

Day 7, Multiple-Dose Phase: Blood samples were obtained for serum GG167 determinations just prior to (zero hour), 0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 3 and 4 hours after administration of the 1600 dose. Trough samples were also obtained prior to administration of the 0800 and 1200 dose. Urine was also collected over the periods of 0-2 and 2-4 hours following the 1600 dose. Subjects were further divided into 3 groups (4 subjects per group) for the purpose of collecting pharyngeal gargle samples. Samples were collected from all subjects prior to administering the 2000 dose on Day 7. Additional samples (one sample per subject) were then collected 1 hour (Group 1), 2 hours (Group 2) or 12 hours after dosing. Pharyngeal gargle samples were assayed for residual antiviral activity.

Assay methods were used for serum and urine determinations, respectively.

Data Analysis
Pharmacokinetic: C_{max}, T_{max}, AUC, $t_{1/2}$, Ae and CL_r
Statistical: All data were described using descriptive statistics

Results Of the original 18 subjects, 16 completed the study. Subjects 12 and 16 withdrew for non drug-related reasons. The median single-dose serum concentration versus time profiles from the first phase of the study are presented in Figure 1. Median single- and multiple-dose serum concentration versus time profiles from the second phase of the study are presented in Figures 2 and 3. Corresponding pharmacokinetic parameters from both phases are presented in Table 1.

Figure 1. Median Serum Levels of GG167 Following Inhalation of Single 5 and 10 mg Doses to Healthy Volunteers (Phase 1, n=6)

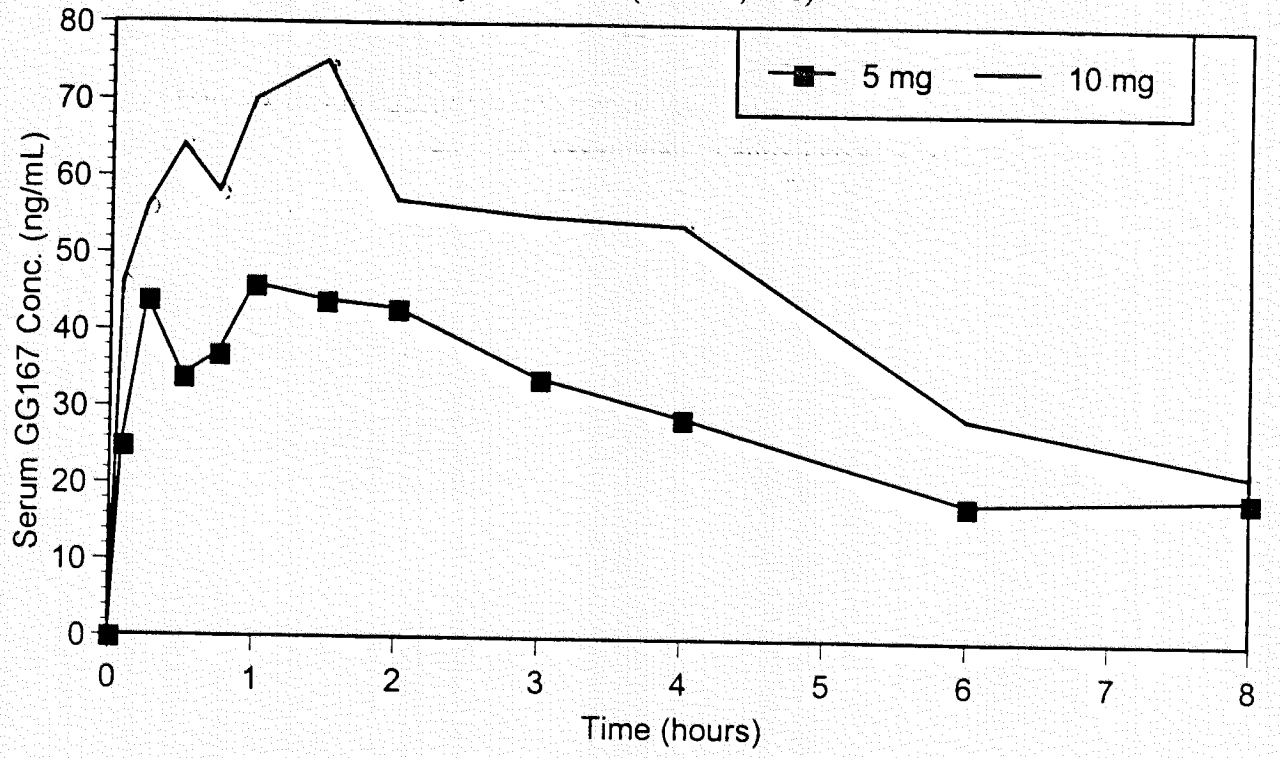


Figure 2. Median Serum Levels of GG167 Following Inhalation of a Single 10 mg Dose to Healthy Volunteers (Phase 2, n=10)

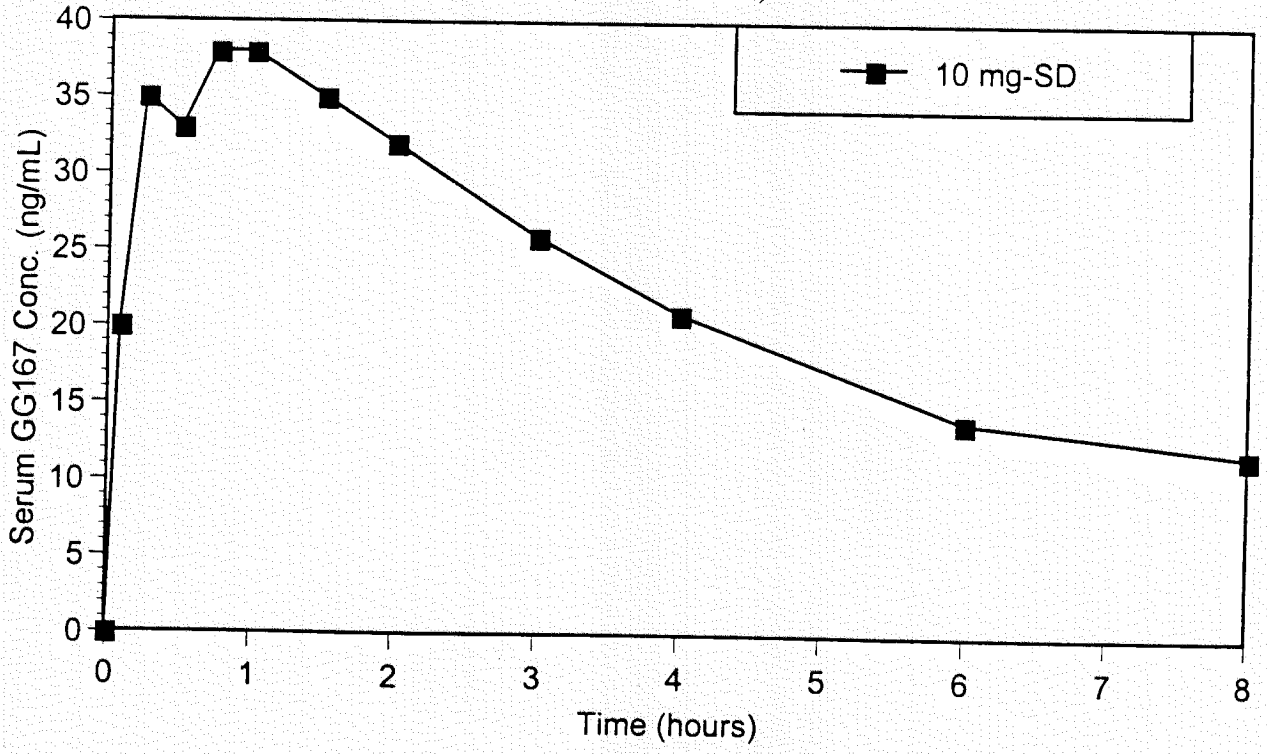


Figure 3. Median Serum Levels of GG167 Following Inhalation of Multiple 10 mg Doses for 7 Days to Healthy Volunteers (Phase 2, n=10)

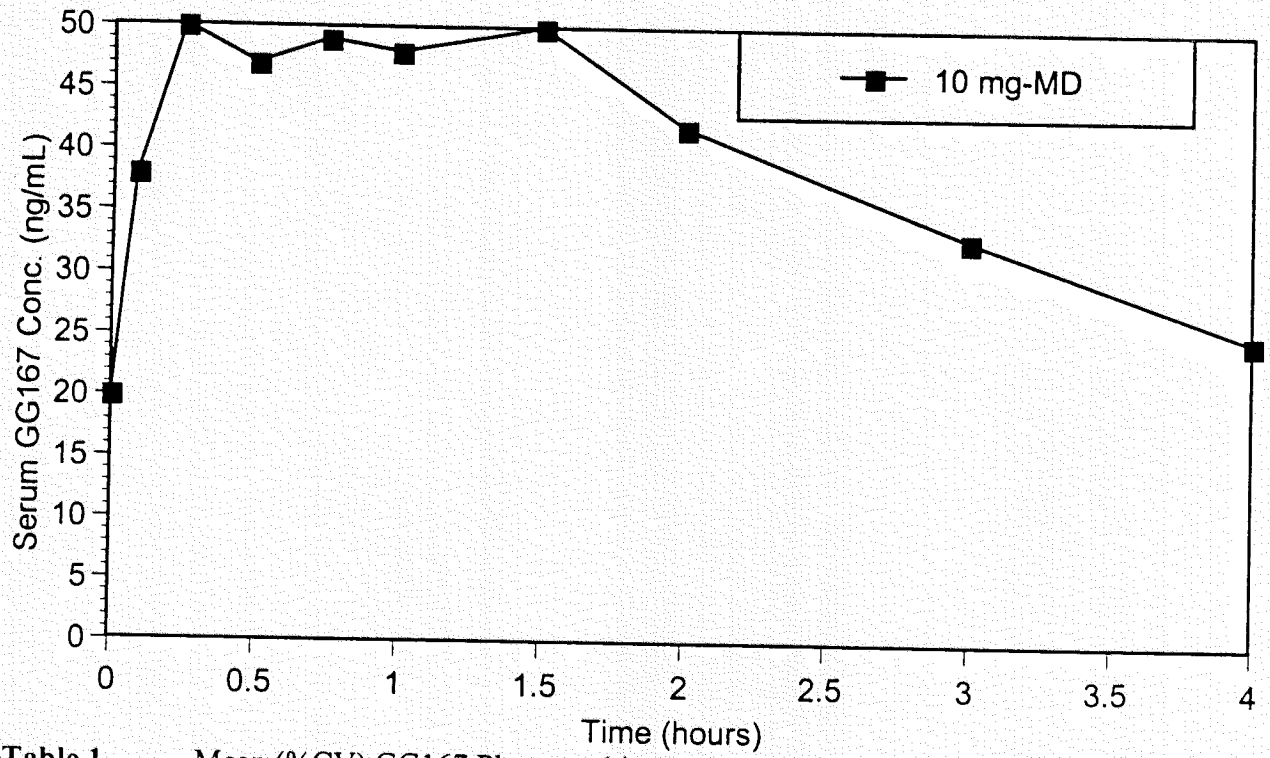


Table 1. Mean (%CV) GG167 Pharmacokinetic Parameters After Inhalation of Single- and Multiple-Doses of Zanamivir

	Phase 1		Phase 2	
Parameter (unit)	5 mg SD	10 mg SD	10 mg SD	10 mg MD
n	6	6	10	10
T_{max} (hours)[1]	1 (0.77-2)	1.25 (0.083-1.5)	0.75 (0.083-2)	0.75 (0.25-1)
C_{max} (ng/mL)	48 (17)	95 (36)	42 (36)	57 (37)
$t_{1/2}$ (hours)	5.32 (33)	4.59 (54)	4.01 (50)	---
$AUC_{0-\infty}$ (ng·hr/mL)	420 (36)	655 (56)	242 (23)	---
$AUC_{0-\tau}$ (ng·hr/mL)	---	---	---	165 (40)
A_e (mg)	0.61 (113)	1.83 (34)	1.10 (50)	1.88 (69)
% of Dose Excreted	12.1 (113)	18.3 (34)	11.0 (50)	18.8 (69)
CL_r (L/hr)	2.78 (114)	4.44 (27)	5.85 (34)	10.44 (32)

Discussion The pharmacokinetic parameters reported between the various dosing arms are inconsistent. Although the time to maximum serum concentration (T_{max}) and elimination half-lives are relatively uniform, the bioavailability parameters are not congruent. The sponsor attributes these differences to the variability inherent to inhaled drug products. This hypothesis is not supported by the variability estimates provided by

[1] *Median (range)*

the sponsor (10 mg: 27-69%). Alternative sources for these differences are not clear from the data submitted.

Comment

The multiple-dose segment of the study is not representative of the proposed dosing regimen for this product (dosed four times daily in this trial, proposed dose: every 12 hours). While this would presumably provide higher serum concentrations than that expected at the clinical dose, the inconsistencies observed in this study make predicting the actual differences impossible.

Conclusion Since this product is described as topically acting, bioavailability and pharmacokinetics are useful mainly as markers of systemic exposure and safety. Due to inconsistencies observed in this trial, data obtained are not necessarily reliable for describing the bioavailability of this product. Therefore, it seems reasonable to use the dosing arm with the highest observed serum concentrations (Phase 1, 10 mg single-dose) as the basis of this product's bioavailability and the calculation of animal safety multiples. These inconsistent data may also preclude the inclusion of descriptive pharmacokinetic data in the product label. In the case of this assumed topically-acting product, there is no reason to further characterize this product's multiple-dose pharmacokinetics at the recommended dose unless the sponsor wishes to include descriptive multiple-dose pharmacokinetic parameter estimates in the labeling or desires different animal safety multiples.

A study to investigate the pharmacokinetics of GG167 in subjects with impaired renal function

Study Nos. C94-051 and C95-014 **Volume** 1.10

[redacted]

Clinical Dates 1/23/95 – 7/25/95
Analytical Facility [redacted]
Analytical Dates 4/11/95 – 8/10/95

Note- Study C94-051 was originally set up to investigate the pharmacokinetics of GG167 in renally impaired subjects. Due to recruitment problems, a second center (with a similar protocol): C95-014 was designed to run concurrently. The results of these two studies were combined for analysis.

Objectives To evaluate the effect of renal impairment on the disposition of GG167.

Formulation
GG167 was supplied as an isotonic sterile solution (18 mg/mL) in glass ampules. On the day of study drug administration, the appropriate dose was further diluted in normal saline to provide a dose which was infused intravenously over a 20 minute period.

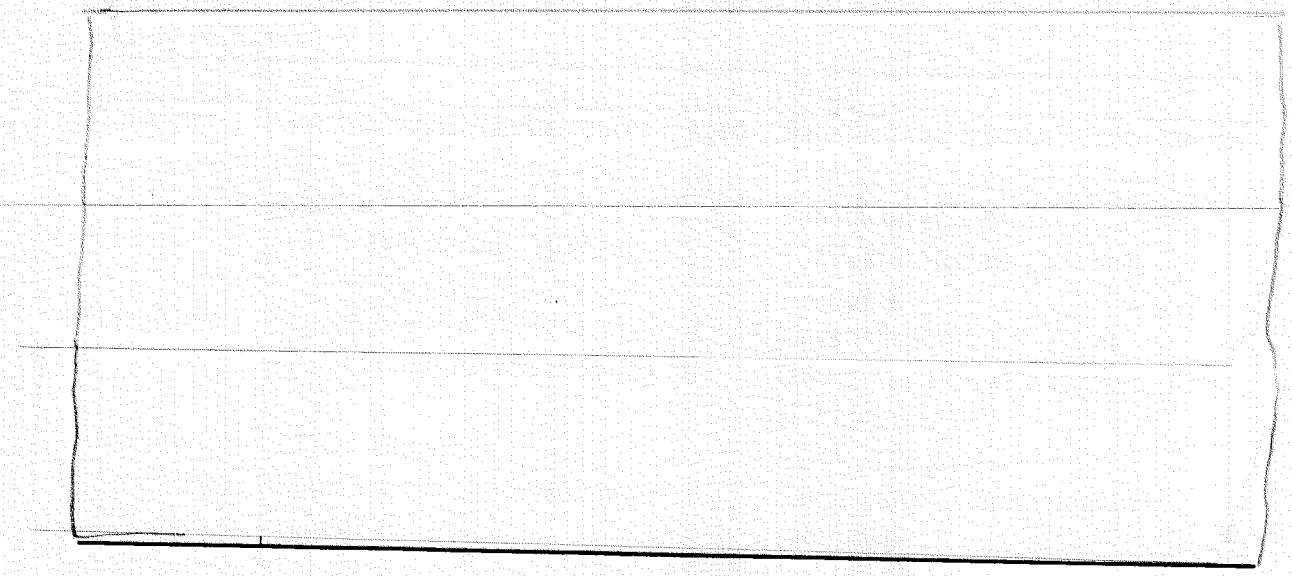
Study Design A total of 17 subjects (9 males, 8 females) were recruited and divided into three groups based on their creatinine clearance:

Group 1	normal renal function (creatinine clearance >70 mL/min) age, weight, height and gender matched to subjects in Group 2, below (n=7: 4 male, 3 female).
Group 2	mild-moderate renal impairment (creatinine clearance range: 25-70 mL/min) (n=5: 2 male, 3 female)
Group 3	severe renal impairment (creatinine clearance <25 mL/min) subjects NOT on dialysis (n=5: 3 male, 2 female)

Subjects enrolled in Group 1 were healthy adult males and females while subjects in Groups 2 and 3 were free from significant hepatic impairment. Patients in these groups using concurrent medications were admitted on a case by case basis. All subjects were admitted to the study facility the morning of the study. All subjects collected pre-dose urine samples and received a light breakfast at least 30 minutes prior to dosing. Subjects in Groups 1 and 2 received a 4 mg intravenous dose, while subjects assigned to Group 3 were administered a 2 mg dose. All doses were infused over a 20 minute time period. Volunteers fasted and remained ambulatory for 4 hours after study drug administration. At this time, regular, standardized meals were served. Subjects were confined throughout the study and abstained from the consumption of caffeine and alcohol containing foods and beverages. Smoking was prohibited during the study period.

Sampling
Blood samples were obtained for GG167 serum determinations just prior to (zero hour), 10, 20, 30 and 45 minutes and 1, 1.5, 2, 4, 6, 8 and 10 hours after study drug administration. Urine samples were collected over the following intervals: 0-2, 2-4 and 4-10 hours post-dose. In group 3, additional 12 hour blood and 10-12 hour urine samples were collected from the first two subjects. In the last three subjects in group 3, additional blood samples were also collected 24 hour hours after dosing and the final urine sample was collected over the 12-24 hour interval.

Assay [redacted] methods were used for serum and urine determinations, respectively.



Data Analysis
Pharmacokinetic: $C_{max.}$, T_{max}, AUC_{last}, $AUC_{0-\infty}$, $t_{1/2}$, Vd, and CL_r
Statistical: Descriptive statistics provided

Results All enrolled subjects completed the study. The median serum concentration versus time profiles for all subjects are presented in Figure 4. Pharmacokinetic parameters are presented in Table 2.

Figure 4. Median GG167 Serum Concentration Versus Time Profiles for Healthy and Renally Impaired Subjects After a 4 mg Intravenous Dose (Severely Impaired: 2 mg Dose)

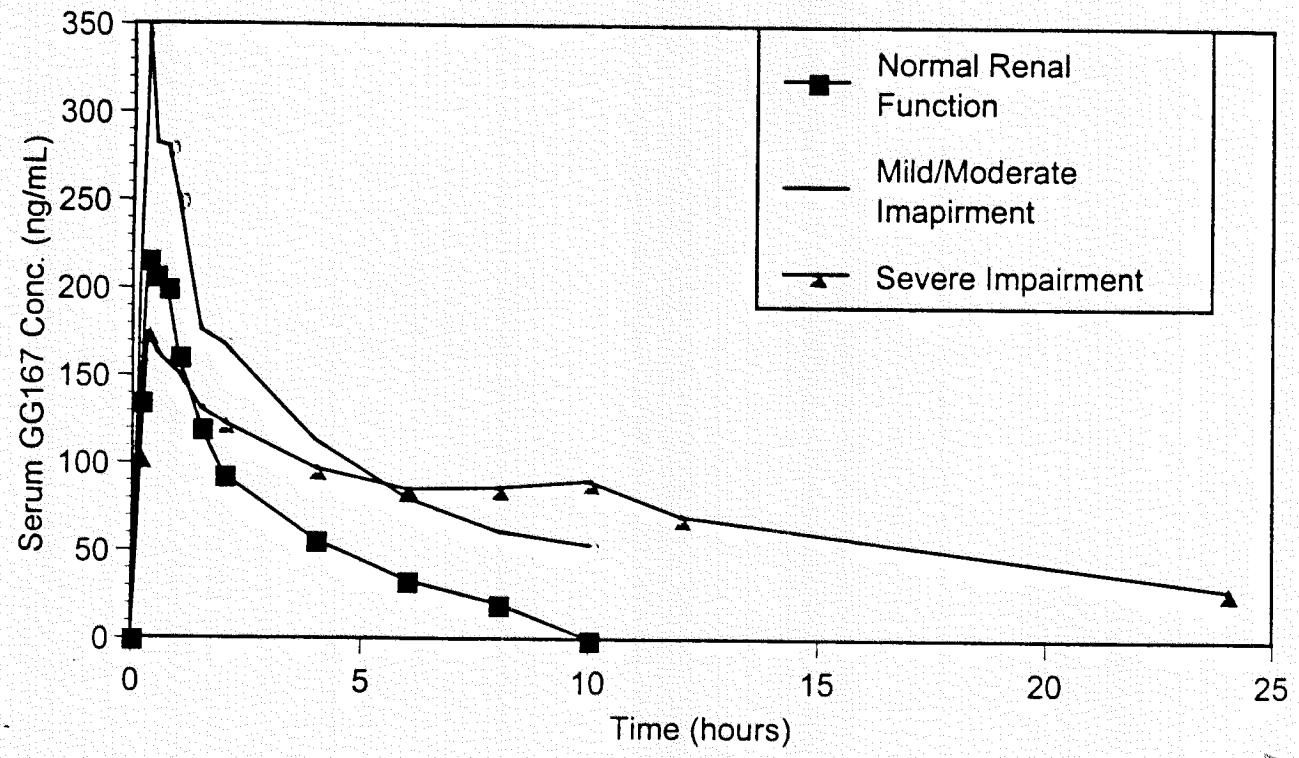


Table 2. Median GG167 Pharmacokinetic Parameters (%CV) after Intravenous Administration of A Single 4 mg Dose to Subjects With Varying Degrees of Renal Impairment (Severe Impairment: 2 mg dose)

	C_{max} (ng/mL)	T_{max}[2] (hours)	$t_{1/2}$ (hours)	AUC_{last} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	Vd (L)	CL (L/hour)	CL_r (L/hour)
Normal Subjects	272 (33)	0.36 (0.22-0.75)	2.9 (38)	653 (28)	762 (28)	22.9 (42)	5.6 (28)	5.2 (41)
Mild/Mod. Impaired	323 (22)	0.33 (0.17-0.50)	4.4 (21)	1203 (24)	1546 (22)	16.8 (24)	2.7 (19)	2.2 (43)
Severely Impaired	209 (33)	0.38 (0.35-0.50)	15.2 (46)	1679 (41)	2775 (40)	16.7 (39)	0.9 (45)	0.7 (55)

Conclusion This trial shows that renal impairment substantially decreases the clearance of GG167 (Zanamivir), increasing its elimination half-life and total exposure. As expected in a single-dose trial, there was no effect on C_{max} or T_{max}. $AUC_{0-\infty}$ approximately doubled in mild-to-moderately impaired subjects compared to normals, while in severely impaired subjects, exposure increased by 3.7 times. It is important to note that this population was administered a 2 mg dose (mild-to-moderately impaired

[2] *Median (range)*

and normal subjects received a 4 mg dose), thus, based on the assumption of linearity, this difference would be doubled to an approximate seven-fold increase. Although variability increased in the more renally impaired subjects, no subjects could be described as an "outlier." Based on these results, it is clear that renally impaired individuals receiving this product will experience substantial increases in systemic concentrations of GG167 with significant accumulation anticipated. These findings were discussed with Dr. B. Styrt, the Medical Officer assigned to this submission, who concluded that, in light of available safety data, there is no need for a dosage adjustment.