A study to evaluate the safety, tolerability and pharmacokinetics of GG167 administered intravenously and orally to healthy volunteers

Study Nos. NAIB1008 **Volume** 1.11

Clinical Dates 11/16/96 – 1/20/97

Analytical Dates 1/6/97 – 1/21/97

Objectives To evaluate the single-dose safety, tolerability, pharmacokinetics and absolute oral bioavailability of GG167.

Formulations

GG167 infusion solution (batch U96/325A)
GG167 powder for oral solution (batch GUAH 1206)

Study Design A total of 22 non-smoking subjects (10 males, 12 females) were recruited and divided into three groups. Subjects in Groups 1 (n=6) and 2 (n=7) received escalating doses of intravenous GG167 ranging from 50 to 600 mg and placebo over the course of three periods. Data from these subjects can be used to establish dose linearity. Group 3 volunteers (n=9) all received a 50 mg intravenous dose in Period I, and were then randomized to receive 500 mg oral doses both with and without glucose in Periods II and III. Data from these subjects can be used to establish the absolute bioavailability of oral zanamivir. A washout period of 4 days separated all treatments. All subjects were admitted to the study facility the evening prior to study drug administration and maintained an overnight fast. 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), 0.5, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10 and 24 hours after study drug administration (after start of infusion for intravenous arm). Urine samples were collected over the following intervals: 0-4, 4-8, 8-12, and 12-24 hours post-dose. Throat gargles and nasal washes were performed one hour after dosing (throat gargles performed prior to nasal washings).

Assay A method was used for serum determinations, while detection methods were used for urine, throat gargle and nasal washing determinations.

Data Analysis
Pharmacokinetic: C_{max}, T_{max}, AUC_{last}, $AUC_{0-\infty}$, $t_{1/2}$, F_{abs}, A_e, and Cl_{ur}. Actual amount of GG167 in throat gargle and nasal washings.
Statistical: Descriptive statistics provided.

Results Of the original 22 enrolled subjects, two were withdrawn due to non-drug-related abnormalities in telemetric monitoring. Only one of the subjects was replaced, yielding 21 evaluable subjects. Group 1 and 2 mean pharmacokinetic parameters are presented in Table 3. The median serum concentration versus time profiles for all subjects in Group 3 are presented in Figure 5. Pharmacokinetic parameters for subjects in Group 3 are presented in Table 4. Quantifiable concentrations of GG167 were observed in the nasal washings of 6 of the 9 volunteers after administration of the I.V. dose. No GG167 was detected in nasal washings after oral administration. GG167 was present in the throat gargles of all subjects after oral dosing and in 3 of 9 subjects after I.V. administration.

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Table 3. Mean (range) Pharmacokinetic Parameters After Administration of Intravenous Doses of GG167

	50 mg I.V.	*100 mg I.V.*	*200 mg I.V.*	*400 mg I.V.*	*600 mg I.V.*
n	13	4	8	4	4
C_{max}	3.49	6.85	14.5	27.1	41.5
(µg/mL)	(2.26-5.52)	(5.76-7.85)	(11.6-17.3)	(22.1-31.9)	(36.5-43.4)
$t_{1/2}$	1.90	1.85	1.81	1.95	1.79
(hour)	(1.57-2.41)	(1.71-1.99)	(1.57-2.06)	(1.82-2.14)	(1.64-1.95)
AUC_{last}	7.08	12.1	27.7	56.7	80.2
(µg·hr/mL)	(5.30-8.99)	(10.9-13.4)	(24.5-30.1)	(46.1-65.3)	(75.4-85.1)
$AUC_{0-\infty}$	7.28	12.3	28.0	56.7	80.6
(µg·hr/mL)	(5.47-9.16)	(11.1-13.8)	(24.9-30.1)	(46.1-65.3)	(76.0-85.2)
CL_{ur}	6.66	7.81	6.60	5.88	6.34
(L/hr)	(4.61-9.01)	(6.86-8.95)	(4.66-7.54)	(3.37-7.77)	(5.50-7.23)
A_e	47.5	95.7	184.1	322	509
(mg)	(42.3-52.5)	(89.1-105.0)	(134-210)	(220-418)	(468-550)

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Figure 5. Mean GG167 Serum Concentration Versus Time Profiles for Healthy Volunteers After Single 50 mg Intravenous and 500 mg Orally Administered Doses

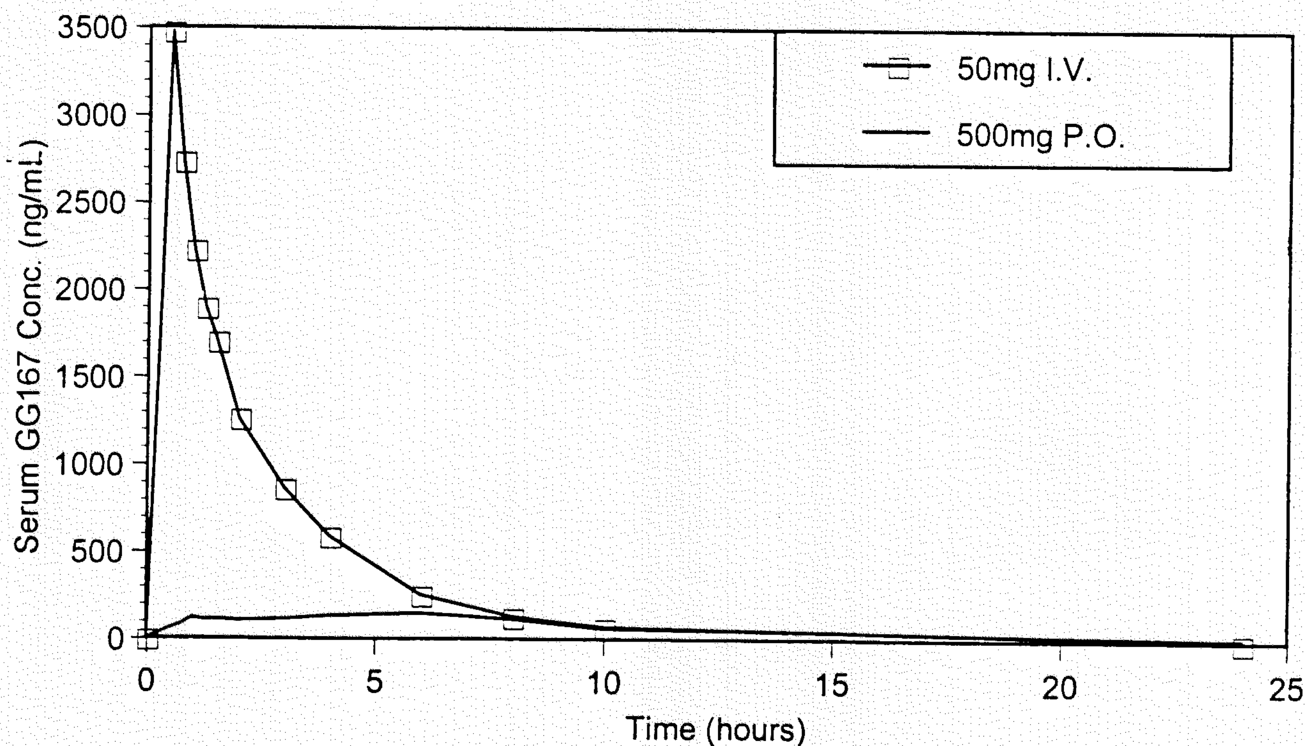

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Table 4. Mean GG167 Pharmacokinetic Parameters (%CV) After a Single 50mg I.V. and 500mg P.O. Dose to 9 Healthy Volunteers

	C_{max} (ng/mL)	T_{max}[3] (hours)	$t_{1/2}$ (hours)	AUC_{last} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	F_{abs}[4] (%)	A_e (μg)	CL_{ur} (L/hour)
50mg IV	3544 (30)	—	1.96 (14)	7152 (16)	7369 (16)	—	48739 (7)	6.81 (20)
500mg PO	158.6 (60)	4 (0.75-6)	4.89 (49)	1242 (40)	1364 (39)	2.0 (44)	7058 (42)	5.77 (31)

Comment

Variability in the 100-600 mg intravenous dosing groups was described only by its range (versus the standard deviation or coefficient of variance). For the purposes of establishing a rough dose proportionality, this description is adequate.

Conclusion Data obtained in this trial indicate that systemic GG167 (via intravenous administration) is nearly completely (97.5% of administered dose) eliminated unchanged in the urine. Dose linearity was shown over the intravenous dosing range of 50-600 mg. After oral administration, the absolute bioavailability was approximately 2%. Differences observed in elimination half-lives (P.O.: 4.89 hours, I.V.: 1.96 hours) suggest that the elimination of GG167 is absorption rate limited. Although GG167 was observed in nasal washings and throat gargles, relatively high variability prevented a quantitative assessment.

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[3] *Median (range)*

[4] Dose normalized P.O. $AUC_{0-\infty}$/I.V. $AUC_{0-\infty}$

Population pharmacokinetics of zanamivir (Protocols NAIA2005 and NAIA2006) (Including Combined Phases I+II Study Analysis)
Volume 1.28

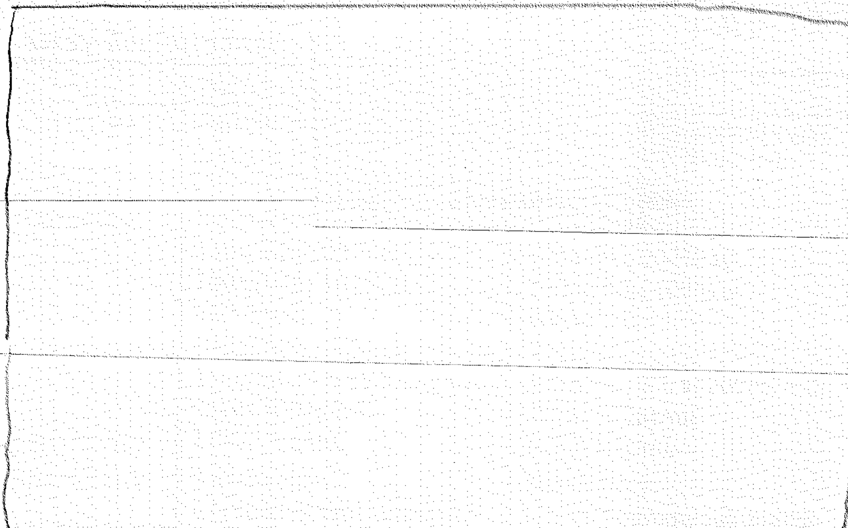
Objectives To evaluate the population pharmacokinetics of GG167 when inhaled, administered intranasally, or in combination.

Formulations

Dry powder: 5mg/blister (batch F94/086A and F94/087A)
Aqueous nasal spray: 16mg/mL (batch SPR F94/095A)

Study Design A total of 220 patients were enrolled in these two clinical safety and efficacy trials. Patients received GG167 for five consecutive days either intranasally (6.4 mg twice daily), by inhalation (10 mg twice daily) or in combination. Of these patients, population serum concentrations were collected from 75. Three samples were collected between 10-60 minutes, 1.5-3 hours and 4-8 hours after study drug administration. These samples were collected after either daily dose on any dosing day (1-5) during the treatment period. The exact time of sample collection as well as the time of the previous two doses were included in the analysis.

Assay A method was used for serum GG167 determinations



Data Analysis

Pharmacokinetic: Population analysis was conducted using non-linear mixed effects modeling (NONMEM) using a one compartment model with first order absorption (ADVAN2 TRANS2). Covariates such as the effects of study type, demographic factors, formulation, infection and concurrent medications were evaluated by adding them to the model and assessing their effect on its objective function.

Results Population parameter estimates are presented in Table 5. The implementation of additional covariates had no significant effect on the objective function of the model.

Table 5. Population Pharmacokinetic Parameter Estimates Obtained in Trials NAIA2005 and NAIA2006 Based on NONMEM Analysis (ADVAN2 TRANS2)

PK Model:

$V=\theta_1*EXP(\eta_1)$

$CL=\theta_2*EXP(\eta_2)$

$ka=\theta_3*EXP(\eta_3)$

Error model: $Y=F*EXP(\varepsilon_1)$

	V/F (L) θ_1	CL/F (L/hr) θ_2	ka (hr^{-1}) θ_3
Population Estimates (95% CI)	161 (126,196)	40.0 (35.7,44.3)	2.19 (1.52,2.86)
SE (θ)	17.7	2.19	0.342
ϖ_η (SE)	0.214 (0.081)	0.169 (0.046)	0.494 (0.176)
Residual Error σ^2_ε(SE)=0.818 (0.0190)			

Conclusion The estimates of oral clearance obtained in the inhaled pharmacokinetic study ranged from approximately12 to 60 L/hr compared to the value of 40 L/hr obtained in this analysis. Analysis of the population data obtained in these two clinical trials indicated that covariates such as study type, demographic factors, formulation, infection and concurrent medication usage had no significant effect on the pharmacokinetics of GG167.

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The effect of GR121167X on the cytochrome P450 metabolism of probe substrates *in vitro* in human liver microsomes

Document Code BDDR/96/0025 **Volume** 4 ( ) ( ) **Page** 339

Objective To evaluate the ability of GR121167 to inhibit the metabolism of various cytochrome P450 substrates in human liver microsomes.

Materials & Methods

- GR121167X (zanamivir): Glaxo Wellcome

Probe substrates

- Bufuralol, (S)-(+)-mephenytoin
- Chlorzoxazone, coumarin, 7-ethoxyresorufin, phenacetin, tolbutamide:
- Midazolam

Metabolites of probe substrates

- (±)-Hydroxybufuralol maleate, 6-hydroxychlorzoxazone, (±)-hydroxymephenytoin, 4-hydroxytolbutamide
- 7-hydroxycoumarin, resorufin
- N-acetyl-p-aminophenol
- 4-OH Midazolam

Inhibitors of probe substrates

- Diethyldithiocarbamate (CYP2E1), ketoconazole (CYP3A), quinidine (CYP2D6):
- Furafylline (CYP1A2), sulphaphenazole (CYP2C8/9/10)

Biological Material

Pooled liver microsomes from the obtained from male human donors (n=6). The microsomal protein content was 18.5 ± 3.22 mg/mL.

Incubations

Ethoxyresorufin Microsomal 7-ethoxyresorufin-O-deethylase (EROD) activity was estimated by assessing the metabolism of ethoxyresorufin to resorufin by Ethoxyresorufin (2.5 μM) was incubated with NADPH in the presence/absence of GR121167X (0.1, 1, 10, 100, 250 and 500 μM).

Coumarin Microsomal coumarin 7-hydroxylase activity was estimated by assessing the metabolism of coumarin to 7-hydroxycoumarin by CYP2A6. Coumarin (400 μM) was incubated with NADPH in the presence/absence of GR121167X (0.1, 1, 10, 100, 250 and 500 μM).

Phenacetin Microsomal phenacetin O-deethylase activity was estimated by assessing the metabolism of phenacetin to N-acetyl-p-aminophenol by CYP1A2. Phenacetin (4 μM)

was incubated with NADPH in the presence/absence of GR121167X (0.1, 1, 10, 100, 250 and 500 μM) or furafylline (10 μM), a specific inhibitor of this isoenzyme.

Tolbutamide Microsomal tolbutamide-4-hydroxylase activity was estimated by assessing the metabolism of tolbutamide to 4-hydroxytolbutamide by CYP2C8/9/10. Tolbutamide (500 μM) was incubated with NADPH in the presence/absence of GR121167X (0.1, 1, 10, 100, 250 and 500 μM) or sulphaphenazole (44 μM), a specific inhibitor of this isoenzyme.

S-Mephenytoin Microsomal S-mephenytoin-4-hydroxylase activity was estimated by assessing the metabolism of S-mephenytoin to 4-hydroxymephenytoin by CYP2C18/19. S-mephenytoin (100 μM) was incubated with NADPH in the presence/absence of GR121167X (0.1, 1, 10, 100, 250 and 500 μM).

Bufuralol Microsomal bufuralol 1-hydroxylase activity was estimated by assessing the metabolism of bufuralol to 1-hydroxy bufuralol by CYP2D6. Bufuralol (10 μM) was incubated with NADPH in the presence/absence of GR121167X (0.1, 1, 10, 100, 250 and 500 μM) or quinidine (25 μM), a specific inhibitor of this isoenzyme.

Chlorzoxazone Microsomal chlorzoxazone 6-hydroxylase activity was estimated by assessing the metabolism of chlorzoxazone to 6-hydroxychlorzoxazone by CYP2E1. Chlorzoxazone (500 μM) was incubated with NADPH in the presence/absence of GR121167X (0.1, 1, 10, 100, 250 and 500 μM).

Midazolam Microsomal midazolam 4-hydroxylase activity was estimated by assessing the metabolism of midazolam to 4-hydroxymidazolam by CYP3A4. Midazolam (60 μM) was incubated with NADPH in the presence/absence of GR121167X (0.1, 1, 10, 100, 250 and 500 μM) or ketoconazole (1 μM), a specific inhibitor of this isoenzyme.

All incubations were carried out in a [redacted] and were started with the addition of substrate. Reactions were quenched by the addition of [redacted] Incubation times ranged from [redacted]

Results At the concentrations tested, GR121167X had no inhibitory effect on the metabolism of any of the probe substrates.

Conclusion

Under the experimental conditions evaluated (concentrations ranging from 0.1 to 500 μM), GR121167X was shown to not inhibit the metabolism of probe substrates representing the major cytochrome P450 isoenzymes. Thus, it is unlikely that GR121167X has the potential to inhibit the metabolism of substrates relying on cytochrome P450 1A, 2A6, 2C8, 2C9, 2C10, 2C18, 2C19, 2D6, 2E1 or 3A.

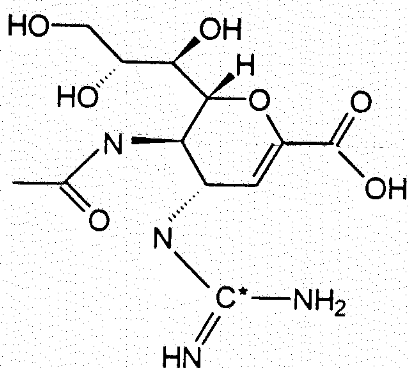
Investigation into the *in vitro* red blood cell and plasma protein binding of radiolabeled GR121167X in CRW rat, beagle dog and man

Protocol No. 92/DM/54 **Volume** 1.14
Pages 72 – 83

Objectives: To assess the extent of binding of GR121167X (zanamivir) to red blood cells and plasma proteins of rat, dog and man over the concentration range of 0.05-10 µg/mL

Materials:

Radiolabeled GR121167X: Batch C2479/11/5, specific activity 1.74 GBq/mmol



Pooled rat blood (n=10)
Pooled beagle blood (n=2)
Pooled human blood (n=3)
Sorensen's phosphate buffer

Plasma Protein Binding Experiment

Methods: Working solutions of radiolabeled GR121167X were combined with rat, beagle and human plasma to generate a series of solutions with nominal concentrations of 0.05, 0.5 and 10 µg/mL. Lengths of visking tubing were knotted and filled with solution to form sealed bags. The sealed bags were then inserted in glass-stoppered tubes containing Sorensen's buffer. Samples were then fixed on a Matching blank plasma sacs were also prepared. Both sacs were dialyzed for 20 hours, after which the plasma and buffer compartments were separated and assayed for radioactivity. The percentage of radiolabel bound to plasma protein (P) was calculated as follows:

$$P = \frac{(T - 0.948B)x100\%}{T}$$

where 0.948 is the ratio of plasma water content to buffer water constant.

Comments:

1. The molecular cut-off for the was not described.

2. It is unclear how the proper equilibration time was estimated. Normally, pre-study experiments are conducted to deduce the optimum equilibration time.
3. Since protein concentration determinations were not conducted inside the cells after equilibration, it is impossible to exclude the possibility of volume fluctuations.

Results: GR121167X was found to be bound between <1 and 14% to plasma proteins at concentration ranges of 0.05 to 10 μg/mL. Since the extent of binding is so low, it is not necessary for the sponsor to respond to the above comments.

Red Blood Cell Binding Experiment

Methods: Aliquots of freshly collected whole blood were dispensed into glass-stoppered tubes and working solution of GR121167X was added to give achieve concentrations of 0.05, 0.5 and 10 μg/mL. The tubes were then incubated in a [ ] After incubation, the hematocrit of each sample was determined prior to [ ] The resultant plasma was then analyzed for its radioactive content. The percentage of radiolabeled drug associated with the blood cell fraction (F) was calculated as follows:

$$F = [1 - \frac{Cp}{Cb}(1 - H)x100\%]$$

Where: Cp=concentration of radiolabel in whole blood
Cb=concentration of radiolabel in plasma
H=hematocrit

Results: GR121167X binding to erythrocytes was observed to be less than 10%.

Conclusions: Since GR121167X is only slightly protein bound, changes in serum protein concentration due to stress or various disease states would probably not result in clinically significant changes in its plasma protein binding. Binding of GR121167X to red blood cells was less than 10% and probably not clinically relevant.

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Pharmacoscintigraphic evaluation of lung deposition of GG167, inhaled from the Diskhaler and the [redacted] n healthy volunteers
Study No. NAIB1001 **Volume** 1.20

Clinical Dates: 11/12/96 - 12/12/96

Objectives To determine the sites of deposition of GG167 in the respiratory tract following inhalation via the Diskhaler

Note The was an alternative dry powder delivery system not selected for further development. Results obtained after administration via the Diskhaler system are of primary interest.

Formulations

- Diskhaler, Batch nos. U96/343A, U96/345A, U96/344A, U96/342A (labeled with ^{99m}Tc)
- , Batch nos. U96/322A, U96/333A, U96/334A (labeled with ^{99m}Tc)

Study Design A total of 14 healthy, non-smoking adult males and females were included in this open-label, block randomized, single-dose, 2-treatment, 2-period crossover study. After a 4 hour fast, subjects received a single, 10 mg dose of ^{99m}Tc-labeled study medication. Volunteers continued fasting and remained ambulatory for 2 hours after study drug administration. At this time, standardized meals were served. A washout interval of 4 weeks separated the dosing periods. Subjects were confined throughout each study phase and abstained from the consumption of xanthine containing foods and beverages.

Sampling
In Vitro: Deposition studies were conducted using a to validate the radiolabeling procedure. were calculated for:

1. Unlabeled drug
2. Labeled drug
3. The radiolabel

These tests were conducted on the formulations used after each day of dosing.
In Vivo: Immediately following dosing of the were recorded as described below:

1. Posterior view of the chest (approximately 1 minute post-dosing).
2. Anterior view of the chest (approximately 2 minutes post-dosing).
3. Right lateral view of the oropharynx (approximately 4 minutes post-dosing).
4. Anterior and posterior abdominal views if necessary, i.e., if activity had spread through the intestine, beyond the view in either of the chest images.
5. Device, blister

Blood samples were obtained for serum GG167 determinations just prior to (zero hour), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6 and 8 hours after study drug administration. Urine samples were collected over the following intervals: Pre-dose; 0-2, 2-4 and 4-8 hours post-dose.

Assay A method was used for serum and urine GG167 determinations.

Results A total of 11 subjects completed both phases of the study. In the Diskhaler arm (the treatment of interest) evaluable data were obtained from 13 volunteers. Scintigraphic deposition data are presented in Table 6. Additionally, approximately 9% of the administered radiolabel was recovered from the trachea, device mouthpeice and blister. The mean plasma concentration versus time profiles for the first 8 hours after dosing are presented in Figure 6. Pharmacokinetic parameters are presented in Table 7. The fine particle mass observed from each radiolabeled batch was similar to that of the unlabeled drug.

Table 6. *In Vivo* Deposition of ^{99m}Tc After Inhalation of Radiolabeled GG167 Using the Diskhaler System (% of Administered Dose)

	Peripheral Lung	*Intermediate Lung*	*Central Lung*	*Oropharynx*
Mean	3.9	4.2	5.1	77.6
Range	2.5-5.1	2.5-6.4	2.2-9.6	71.2-86.6
CV	26%	31	43	7

Figure 7. Mean Serum GG167 Concentration vs. Time Profile After Inhalation of a Single 10 mg Dose of ^{99m}Tc Radiolabeled GG167 Using the Diskhaler System

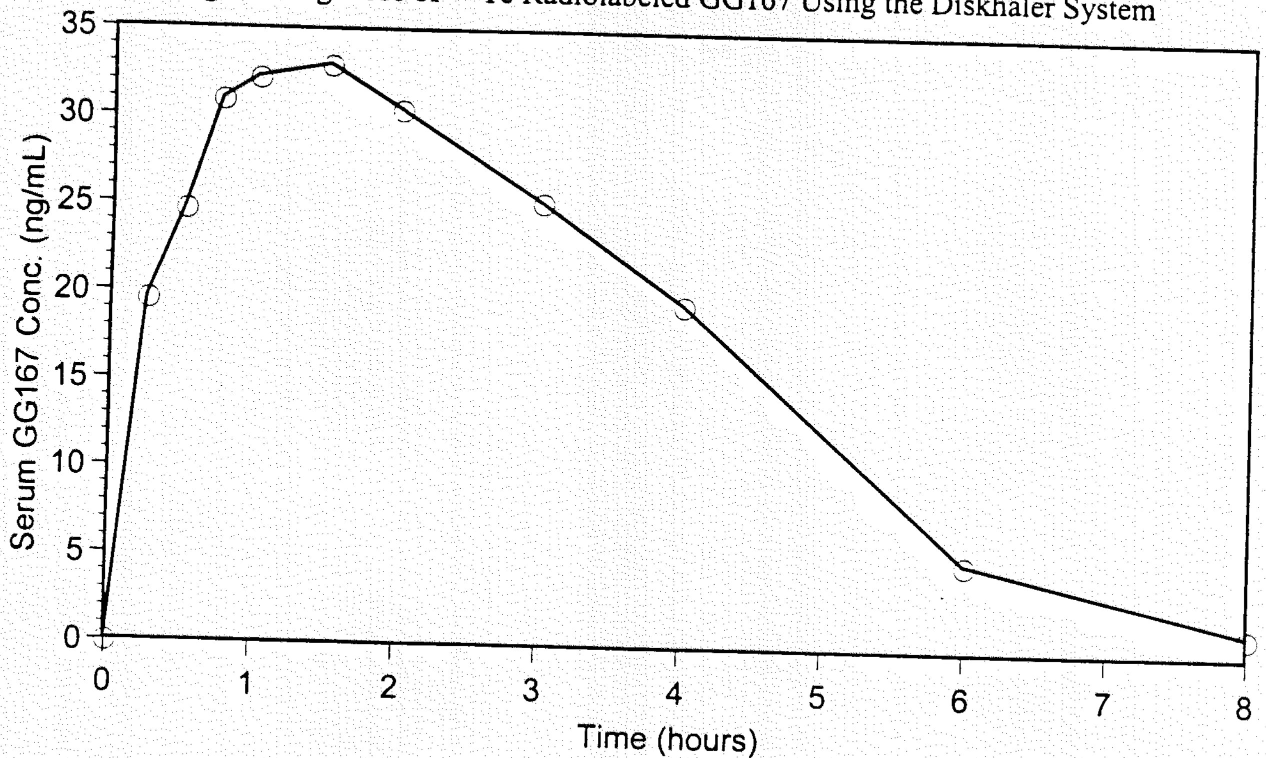

Table 7. Mean Pharmacokinetic Parameters After Inhalation of a Single 10 mg Dose of ^{99m}Tc-Labeled GG167 Using the Diskhaler System

	$AUC_{0-\infty}$	C_{max}	$t_{1/2}$	t_{max}[5]	A_e	CL_r
Unit	ng·hr/mL	ng/mL	hours	hours	µg	L/hr
Mean	199	32.2	3.40	1.5	301	2.67
CV	29%	38%	66%	0.8-2	36%	65%

Discussion is a novel and promising tool for use in the development of inhaled drug products. Nevertheless, the clinical relevance of results obtained using this methodology is currently unknown.

Conclusion Data obtained in this study suggest that when GG167 is inhaled as a dry powder using the Diskhaler system, approximately 13% of the total dose is deposited in the lung, while 78% was recovered in the oropharynx. Approximately 9% was recovered

[5] *Median (range)*

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on the trachea, the device or retained in the empty blister. Serum and urine pharmacokinetic data obtained appear similar to that observed in a previous inhalation study of unlabeled GG167 (C94-009) with the exception of urinary recovery, which was substantially lower in this study (3% vs. 15% of total dose). A reason for this discrepancy is unclear. These results should be interpreted in light of the warnings outlined in the discussion section, above.

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VI. Discussion of Deposition

Drug delivery via the inhalation route is normally quite inefficient, with the majority of the dosed drug deposited in the throat and subsequently swallowed, with a smaller fraction deposited in the lungs. Absorption can take place from either the lung or GI tract, depending on the drug's physiochemical properties. Activity can then take place either systemically, or locally, at the site of deposition. In the case of zanamivir, the sponsor has conducted a study designed to characterize the drug's deposition pattern after inhalation using the Diskhaler system. Although results obtained from this novel approach are interesting, the assay has not been adequately validated to ensure the reliability of these results. An alternative to this approach is to use what is known about the disposition of zanamivir *in vivo* to estimate the extent of deposition at various sites. This exercise is outlined below:

After inhalation of respirable substances, the largest fraction is most likely deposited in the oropharynx, while the balance reaches the lung. Substances reaching the lung are subject to four possible fates: it can remain in the lung (e.g., asbestos), it can be exhaled, it can be absorbed systemically or it can be carried out of the lung to the esophagus via the mucocilliary transport ladder and swallowed. Substances directly deposited in the oropharynx are generally swallowed and then either absorbed systemically or eliminated in the feces. Systemic drug is eliminated unchanged or after biotransformation, via urine, bile or exhalation. This is shown qualitatively in Figure A, below.

Figure A.

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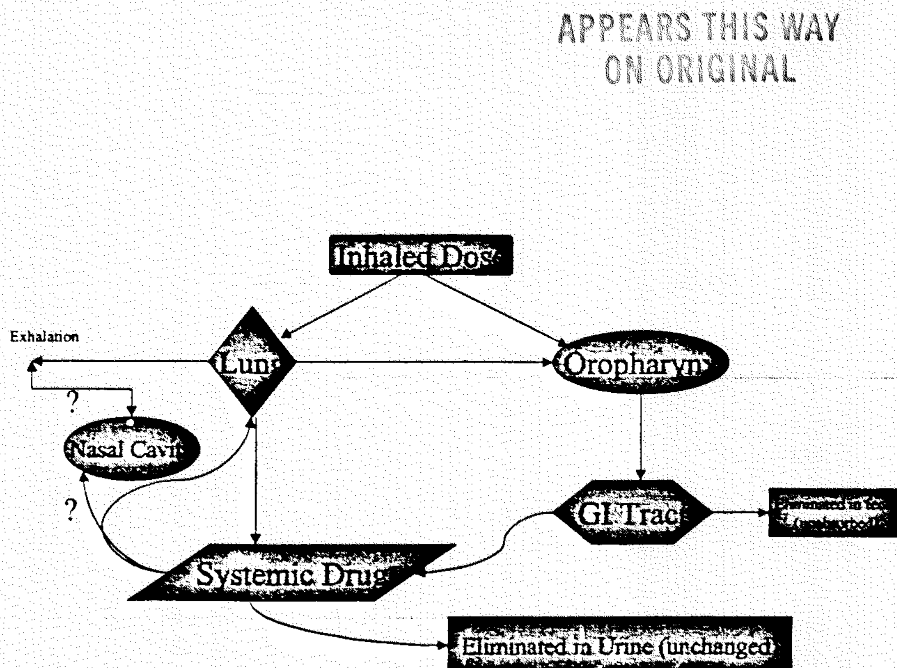

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By using a combination of known information and assumptions about the disposition of zanamivir, it is possible to quantitatively estimate the sites of zanamivir deposition.

Known Information	*Assumptions*
15% of inhaled drug is eliminated unchanged in the urine 91% of systemic drug is eliminated unchanged Oral bioavailability of zanamivir is 2%	Exhaled drug after inhalation is very small (≈0%) Lung absorption after deposition is very large (≈100%)

Since it is known that all of the drug deposited in the oropharynx is swallowed and that 2% of this drug is absorbed and we assume that all of the drug ultimately reaching the lung is absorbed, we can account for the source of all of the systemically available drug. Of this systemic drug, it is known that 91% of it is eliminated unchanged in the urine. From the inhalation study we know that 15% of the total dose is eliminated unchanged in the urine meaning that approximately 16.5% of the administered dose was available as systemic drug ($\frac{0.15}{0.91}$). By combining all these data, it follows that:

$$\textit{Systemic Drug} = \textit{Lung Deposition} + 0.02\,(\textit{Oroparynx Deposition}) = \frac{0.15}{0.91}$$

It is also apparent that since all of the delivered dose will be deposited in either the lung or the oropharynx:

$$\textit{Lung Deposition} + \textit{Oropharynx Deposition} = 1.0$$

The second equation can be substituted into the first, yielding the solution that 15% of the inhaled drug is deposited in the lung, while 85% is deposited in the oropharynx and swallowed. Since we assume that all of the drug deposited in the lung is absorbed while 2% of the swallowed dose is absorbed (1.7% of the total delivered dose), 16.7 of the total delivered dose is present systemically. These calculations are based on the assumption that all of the dose is inhaled with no residual drug remaining on the blister, device or trachea.

In the γ-scintigraphy study, pulmonary and oropharynx deposition of approximately 13% and 78%, respectively, were observed with about 9% of the total dose remaining on the blister, device or trachea.

Although neither of these methods are adequately validated to support a labeling claim, combined they provide evidence that approximately 13-15% of the inhaled dose is deposited in the lung with the remainder deposited in the oropharynx and subsequently swallowed.

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Concurrence: 6/8/99

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cc:

HFD-530	/NDA 21-036
	/MO/Styrt
	/CSO/Lynche
HFD-880	/Gillespie
	/TL/Reynolds
	/DPE III
HFD-340	/Viswanathan
CDR	/Barbara Murphy

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