CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-154

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	22154 Resubmission (Response to Complete Response Letter)
Submission Date:	2/27/2009
Brand Name:	TYZEKA®
Generic Name:	Telbivudine
Applicant:	Idenix Pharmaceuticals
Reviewer:	Jenny H. Zheng, Ph.D.,
Team Leader:	Kellie Reynolds, Pharm.D.
OCP Division:	DCP IV
OND Division:	DAVP

Issues Identified from Original Submission:

For patients with End Stage Renal Disease (ESRD), the proposed [redacted]

b(4)

b(4)

b(4)

b(4)

b(4)

3 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jenny H. Zheng
4/27/2009 04:54:50 PM
BIOPHARMACEUTICS

Kellie Reynolds
4/27/2009 04:59:25 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	22154 (original NDA for oral solution), 22011 (tablets), SE8-001
Submission Date:	12/21/2007
Brand Name:	TYZEKA®
Generic Name:	Telbivudine
Applicant:	Idenix Pharmaceuticals
Reviewer:	Jenny H. Zheng, Ph.D.,
Team Leader:	Kellie Reynolds, Pharm.D.
OCP Division:	DCP IV
OND Division:	DAVP

Table of Contents

I. Executive Summary

TYZEKA® 600 mg tablets were previously approved by the Agency for treatment of chronic hepatitis B in patients with evidence of viral replication and active liver inflammation in October 2006, based on one year safety and efficacy data. NDA 22011, SE8-001 comprises two year safety and efficacy data updates as well as a drug interaction study of telbivudine and tenofovir (TDF).

NDA 22154 is an original NDA for TYZEKA® (telbivudine, LdT) oral solution for the treatment of chronic hepatitis B in patients with evidence of viral replication and active liver inflammation. TYZEKA® oral solution is bioequivalent to the approved TYZEKA® tablets, and can be used as an alternative formulation to tablets. TYZEKA® oral solution can be used in patients with renal impairment who may require a dose reduction, without increase of dosing intervals. The current approved TYZEKA® regimens for patients with renal impairment are 1 tablet (600 mg) every 1 to 4 days depend on the severity of the renal impairment.

A. Recommendation

The newly proposed doses of TYZEKA® oral solution for patients with renal impairment in September 19th are acceptable except for doses proposed for patients with End Stage Renal Disease (ESRD) requiring dialysis. The dose recommendation for ESRD patients can not be made at this time due to the following deficiencies: b(4)

b(4)

The drug interaction data for telbivudine and tenofovir provided by the applicant are acceptable.

NDA 22154 for the oral solution will receive a Complete Response letter because of the above mentioned deficiencies as well as [redacted] In addition, the applicant is not able to provide MedGuide in a timely manner for the Agency to review. Therefore, NDA 22011, SE8-001 will require extended clock for review. b(4)

B. Phase IV Commitments

None.

C. Clinical Pharmacology Summary

These two applications contain dose recommendations for patients with renal impairment who use oral solution (based on simulation from previously submitted pharmacokinetic data) and drug interaction study of telbivudine and tenofovir (TDF). The following summarizes the results from these two studies.

Dose reduction in patients with renal impairment

The population pharmacokinetic model used for simulation was reviewed with the original NDA. The model was established based on a total of 382 subjects, 346 subjects were healthy volunteers (15 studies), including 36 subjects from renal impairment study (NV-02B-006), and 36 subjects were HBV-infected patients (1 Phase I/ IIa study). The population pharmacokinetic analysis showed that telbivudine clearance decreases as renal function decreases, and telbivudine bioavailabilty decreases as dose increases. Based on these relationships, a dosing interval adjustment is currently recommended for patients with reduced renal function taking telbivudine tablets. The applicant proposes to include dose reduction regimens of telbivudine solution for patients with reduced renal function.

The following table shows the approved dose regimens (tablets) as well as the proposed new regimens (oral solution).

Table 1 Dose Adjustment of Telbivudine in Patients with Renal Impairment

Creatinine Clearance (mL/min)	Proposed Oral Solution Dose	Approved Tablet Dose
≥ 50	600 mg every 24 hrs	600 mg every 24 hrs
30–49	400 mg every 24 hrs	1 tablet every 48 hrs
<30 (not requiring dialysis)	200 mg every 24 hrs	1 tablet every 72 hrs
ESRD	[redacted]	1 tablet every 96 hrs

b(4)

The population pharmacokinetic model was applied to the data from the renal impairment study (NV-02B-006) to simulate the different once daily dosing regimens. The applicant originally proposed 300 mg every 24 hours for patients with severe renal impairment (CLcr < 30 mL/min). [redacted] b(4)

[redacted] However, the applicant later realized that they mistakenly used [redacted] b(4)

[redacted] The applicant therefore submitted the results and the new dose proposal on September 19, 2008, in their CMC correspondence. Following summarizes the results from the new simulation.

Table 2 summarizes telbivudine $AUC_{0-\infty}$ observed in renal impairment study, obtained from estimates based on typical values from PPK, and obtained from individual estimates from PPK. The estimates based on typical values use the typical (population) values of PK parameters based on individual's body weight and race without considering inter-individual variability, and individual estimates from PPK incorporate inter-individual variability to fit the individual concentration-time profile. The data show that individual estimates from PPK are more similar to the observed data than the estimates based on the typical values. To determine the cause of the differences in the estimates, the Agency re-examined the original population PK model. Figure 1 shows that although the fitted line based on the model generally describes well the relationship of CLcr vs CL, it overestimates the telbivudine CL for subjects with CLcr less than 30 mL/min. Because most of the data under 30 mL/min were contributed from the renal impairment study, the observed data from the study are more reliable. In renal impairment study, 200-mg Phase III Clincal Study Formulation was used; 3 x 200 mg Phase III Clincal Study Formulation (tablet) are bioequivalent to the approved 600 mg tablet.

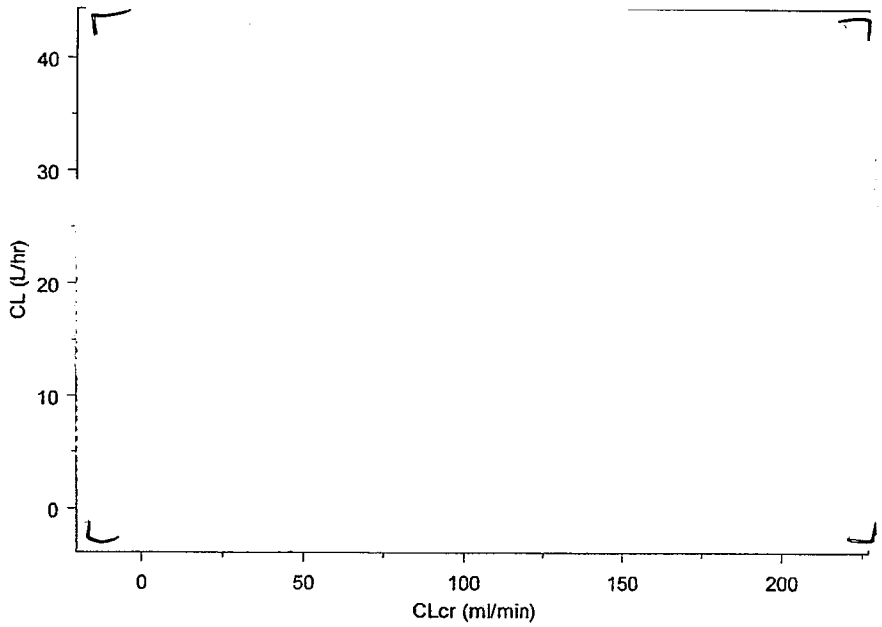
Table 2 Comparison of arithmetic mean AUC observed from renal impairment study with obtained from estimates based on typical values from PPK, and obtained from individual estimates from the PPK model

Degree of renal impairment	Dose used in renal impairment study (mg)	N	$AUC_{0-\infty}$ (h x mg/L)		
			Observed in renal impairment study	Estimates based on typical values from PPK	Individual estimates from PPK
Normal	600	8	28.5[a]	24.9	28.4
Mild	600	8	32.5	33.5	32.7
Moderate	400	8	36.0	32.7	37.4
Severe	200	6	32.5	30.2	37.9
ESRD	[redacted]				

b(4)

[a] n=7

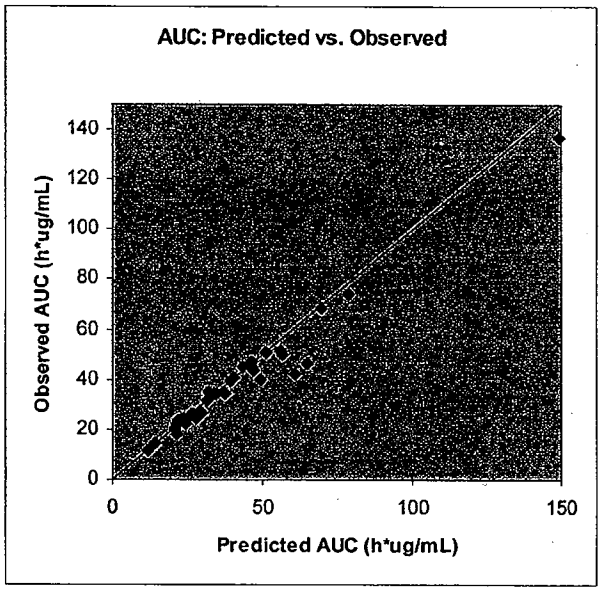
Figure 1 The Effect of CLcr on CL (the solid line is PPK model fit)



b(4)

As shown in Figure 2, the individual estimates of steady-state AUC from PPK well predict the observed AUC in the Study NV-02B-006.

Figure 2: Comparison of individual estimated AUC from PPK (predicted) vs observed AUC for 36 subjects in Study NV-02B-006



It needs to be mentioned that Study NV-02B-006 is a single dose study, the observed single dose Cmax may not represent the steady-state Cmax. Therefore, the individual estimates of steady-state Cmax from PPK will be used in combination with the observed $AUC_{0-\infty}$ from Study NV-02B-006, and the individual estimates of steady-state AUC from PPK, to determine the correct dose for renal impaired subjects.

b(4)

Therefore, geometric mean values from the study were used to scale exposures to different doses. The estimations assumed linear PK for doses at 200 mg or less because telbivudine bioavailability approached 1 for these doses. The results are shown in Table 3. The PK parameters that are within 35% of the values of the observed in subjects with normal renal function at 600 mg are highlighted, because similar efficacy and safety were observed for telbivudine in the 400-800 mg/d dosing range in the Phase I/IIa dose-finding trial [NV-02B-001].

Table 3: Observed or simulated (estimated) steady state (s.s) geometric mean of Cavg and Cmax by degree of renal impairment and daily dose level with percentage difference from subjects with normal renal function at 600 mg

Degree of renal impairment	Dose (mg)	N	Exposure (ug/mL)			% difference from normal 600 mg		
			Obs.[b] Cavg	Est. Cavg (s.s)	Est. Cmax (s.s)	Obs. Cavg	Est. Cavg	Est. Cmax
Normal	600	8	1.14	1.14	3.07	0	0	0
Mild	600	8	1.29	1.30	2.84	13.2	13.7	-7.4
Moderate	400	8	1.38	1.43	2.71	21.7	25.6	-11.7
Severe	200	6	1.26	1.45	2.09	11.2	27.0	-32.0
ESRD								
ESRD								
ESRD								

[a] post-dialysis; [b] obs. Cavg =$AUC_{0-\infty}$/24 hours;

b(4)

Conclusion:

- For subjects with mild, moderate or severe renal impairment, the proposed 600 mg, 400 mg, and 200 mg doses, respectively, result in observed Cavg and the individual estimates of Cavg and Cmax from PPK within 35% of the values of the observed in subjects with normal renal function at 600 mg. Therefore, the proposed doses for subjects with mild, moderate or severe renal impairment are acceptable.
-

b(4)

b(4)

Drug interaction study of telbivudine and tenofovir

Study NV-02B-028 was a Phase I, open-label, multiple-dose, parallel-group study to investigate the potential for a pharmacokinetic drug-drug interaction between telbivudine (LdT) and tenofovir disoproxil fumarate (TDF, Viread®) in 16 healthy subjects. The data indicated there was no clinically significant impact of TDF on LdT pharmacokinetics and no statistically significant impact of LdT on TDF pharmacokinetics following repeated once-daily administration.

II. Question Based Review

1. General Attributes

1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology review?

Telbivudine is currently approved as a 600 mg film-coated formulation. See the review of original NDA 22011 for the highlights of the chemistry and physical-chemical properties of the drug substance.

NDA 22154 is for telbivudine liquid oral dosage form, a 20 mg/mL solution. Thirty (30) mL provides the standard patient dose of 600 mg per day. Bioequivalence study (NV-02B-025), reviewed with the original NDA 22011, demonstrated that one 600 mg film-coated tablet is bioequivalent to 30 mL of the 20 mg/mL oral solution.

The following table shows the composition of telbivudine 20 mg/mL oral solution.

Table 1-1 Composition of telbivudine 20 mg/mL oral solution

Ingredient	Amount (mg/mL)	Function	Reference to standards
Telbivudine (LDT600)	20.0	Active ingredient	Novartis monograph
Citric acid anhydrous			Ph.Eur., USP/ NF
Benzoic acid			Ph.Eur., USP/ NF
Passion fruit flavor			Novartis monograph
Saccharin sodium			Ph.Eur., USP/ NF
Sodium hydroxide [1]			-
Water, purified/ Purified water			Ph.Eur., USP/ NF
			Ph.Eur., USP/ NF

b(4)

[1]

Note:

b(4)

1.2. What are the proposed dosage(s) and route(s) of administration?

The applicant proposes to include dose reduction regimens of telbivudine solution for patients with reduced renal function. The following table shows the approved dose regimens as well as the proposed new regimens.

Dose Adjustment of Telbivudine in Patients with Renal Impairment

Creatinine Clearance (mL/min)	Proposed Oral Solution Dose	Approved Tablet Dose
≥ 50	600 mg every 24 hrs	600 mg every 24 hrs
30–49	400 mg every 24 hrs	1 tablet every 48 hrs
<30 (not requiring dialysis)	200 mg every 24 hrs	1 tablet every 72 hrs
ESRD	[redacted]	1 tablet every 96 hrs

b(4)

The proposed doses are acceptable for subjects with mild (Creatinine Clearance (CLcr) ≥ 50 mL/min), moderate (CLcr: 30 -49 mL/min), and severe (CLcr: < 30 mL/min) renal impairment, but can't be determined for ESRD subjects, due to the insufficient data submitted by the applicant.

2. General Clinical Pharmacology

2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

A study in renal impaired subjects (Study NV-02B-006) was conducted and reviewed with the original NDA 22011. The dose reduction recommendations for patients with renal impairment are based on the simulation using the previously reviewed population pharmacokinetic model. No new study was conducted for renal impaired subjects in NDA 22154.

Telbivudine is currently approved based on 52-week data from a large Phase III international trial in subjects with chronic hepatitis B (NV-02B-007). NDA 22011, SE8-001, provides 2-year data from both the NV-02B-007 trial and from an independent, supportive Phase III trial conducted in China (NV-02B-015), which form the basis for the long term indication.

The 007 GLOBE study is a Phase III, randomized, double-blind, multinational study of telbivudine 600 mg PO once daily compared to lamivudine 100 mg once daily for a treatment period of 104 weeks in 1,367 nucleoside-naïve chronic hepatitis B HBeAg-positive and HBeAg-negative patients. NV-02B-015 is a Phase III, randomized, double-blind, study of telbivudine 600 mg PO once daily compared to lamivudine 100 mg once daily for a treatment period of 104 weeks in 332 nucleoside-naïve chronic hepatitis B HBeAg-positive and HBeAg-negative Chinese patients.

Week 104 efficacy analyses in NV-02B-007 and NV-02B-015 support the Week 52 results of the pivotal trial NV-02B-007, demonstrating durability of efficacy responses for telbivudine-treated subjects with continued treatment.

The safety profile of telbivudine in subjects with chronic hepatitis B that was established during 52 weeks treatment in study NV-02B-007 remained fairly consistent through 104

weeks of treatment in both NV-02B-007 and NV-02B-015. However, CK elevations were reported in a somewhat higher proportion of telbivudine recipients between 52 and 104 weeks than from baseline to week 52, and the median CK elevation was higher after week 52 than prior to that time.The safety profiles of telbivudine and lamivudine were generally comparable in these studies. New safety information from study CLDT600A2406 in which telbivudine 600 mg was compared to telbivudine 600 mg plus pegylated interferon-alfa-2a or pegylated interferon-alfa-2a alone has identified a risk of peripheral neuropathy in patients treated with telbivudine alone or in combination with pegylated interferon-alfa-2a. Preliminary data suggest that the risk and severity of peripheral neuropathy is increased with the telbivudine/pegylated interferon combination regimen in comparison to telbivudine alone.

3. Intrinsic Factors

3.1 What intrinsic factors influence exposure/response? What dosage regimen adjustments are recommended for each of these groups?

As shown in the review of original NDA 22011, the pharmacokinetics of telbivudine is not significantly affected by gender, race, hepatic impairment and disease state, but is affected by renal impairment. The population pharmacokinetic analysis showed that telbivudine clearance decreases as renal function decreases. Based on this relationship, a dosing interval adjustment is currently recommended for patients with reduced renal function taking telbivudine tablets. The applicant proposes to include dose reduction regimens of telbivudine solution for patients with reduced renal function. See Clinical Pharmacology Summary: Dose Reduction in Patients with Renal Impairment, for details.

4. Extrinsic Factors

4.1 What extrinsic factors influence exposure/response and what is the impact of any differences in exposure on response?

The only new study submitted in the current NDA submissions is the drug-drug interaction study between telbivudine and tenofovir. There is no clinically significant drug-drug interaction between telbivudine and tenofovir. No dose adjustment is needed when telbivudine is coadministered with tenofovir. See the individual study review for details.

5. General Biopharmaceutics

5.1 What is the relative bioavailability of the proposed oral solution to the approved tablet formulation?

Bioequivalence between the proposed oral solution and the approved tablet formulation has been demonstrated in Study NV-02B-025. The results were reviewed in the original NDA 22011.

6. Analytical Section

See the original NDA 22011 review.

III. Labeling Recommendation

The labeling negotiation is postponed until the applicant has provided the information required for the review.

IV. Individual Study Report Reviews

A SUMMARY OF SIMULATIONS PERFORMED FOR TELBIVUDINE DOSE REDUCTION IN PATIENTS WITH IMPAIRED RENAL FUNCTION

Background: The population pharmacokinetic model used for simulation was reviewed with the original NDA. The model was established based on a total of 382 subjects, 346 subjects were healthy volunteers (15 studies), including 36 subjects from renal impairment study (NV-02B-006), and 36 subjects were HBV-infected patients (1 Phase I/ IIa study). The population pharmacokinetic analysis showed that telbivudine clearance decreases as renal function decreases, and telbivudine bioavailabilty decreases as dose increases. Based on these relationships, a dosing interval adjustment is currently recommended for patients with reduced renal function taking telbivudine tablets. The applicant proposes to include dose reduction regimens of telbivudine solution for patients with reduced renal function.

Objectives: Use the same model that was previously used to simulate the dose adjustment for patients with reduced renal function to determine once daily doses that achieve concentrations similar to those observed for patients with normal renal function at recommended dose of 600 mg once daily.

Exposure Criterion for Dose Adjustment: Data from the phase I/IIa trial NV-02B-001 in HBV-infected patients showed that telbivudine exhibited an exposure- response relationship with ~3 log10 reduction in serum HBV DNA at week 4 at the 200 mg/day dose and near maximum antiviral effects (3.5-4.0 log10 reduction in viral load) achieved with telbivudine doses of 400-800 mg/day. Therefore, for patients with renal impairment requiring a daily dose adjustment, while the plasma exposure associated with the 200 mg/day dose can be regarded as an antiviral threshold for telbivudine, exposure resulting from the 400-800 mg/day doses should be targeted for optimal antiviral activity. This efficacious dose range (200-800 mg/day) encompasses the intended 600mg/day clinical dose of telbivudine (600±200 mg or 600 mg ± 33.3%), and supports the following exposure criterion for daily dose adjustment:

> Mean steady-state (SS) Cmaxss and AUCss of the adjusted dose must be within 35% of the exposure in healthy subjects with normal renal function receiving the 600 mg/day dose.

The criteria used for determination of dosing interval adjustment for renal impaired subjects were similar but less strict in Cmaxss. Mean steady-state (SS) Cmaxss for ESRD at approved 600 mg every 96 hours is estimated to be 56% higher than the value for subjects with normal renal function at approved 600 mg every 24 hours.

Model: As described in the review for original NDA22-011. A two-compartment model with first-order absorption and lag time best described the PK of telbivudine. CL was estimated as a function of creatinine clearance, V2 was proportional to body weight, and F1 was related to dose and race.

The population pharmacokinetic model was applied to the data from the renal impairment study (NV-02B-006) to simulate the different once daily dosing regimens. The applicant originally proposed [redacted] b(4)

[redacted] However, the applicant later realized that they mistakenly used [redacted] b(4)

[redacted] The applicant therefore submitted the results and the new dose proposal on September 19, 2008, in their CMC correspondence. Following summarizes the results from the new simulation.

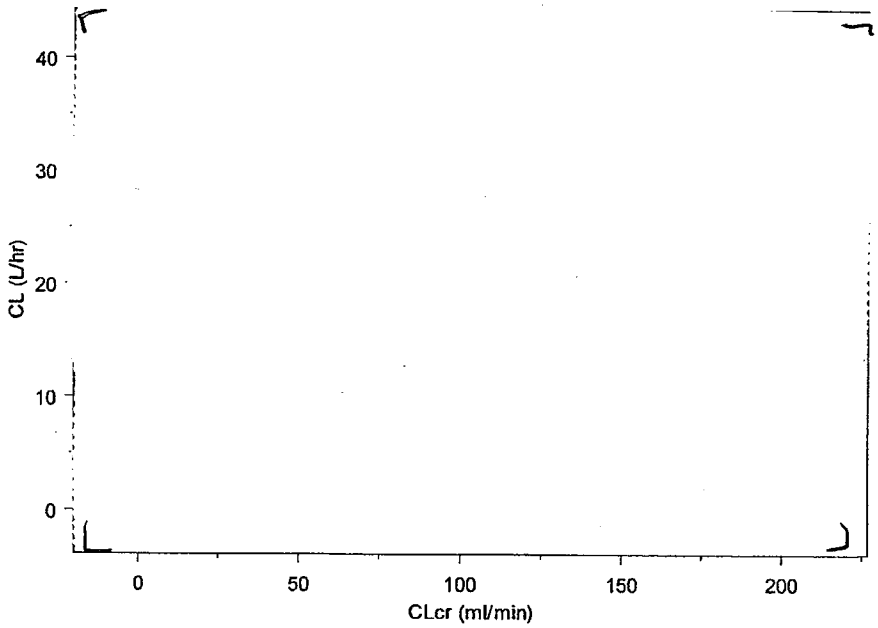
Results: Table 2 summarizes telbivudine $AUC_{0-\infty}$ observed in renal impairment study, obtained from estimates based on typical values from PPK, and obtained from individual estimates from PPK. The estimates based on typical values use the typical (population) values of PK parameters based on individual's body weight and race without considering inter-individual variability, and individual estimates from PPK incorporate inter-individual variability to fit the individual concentration-time profile. The data show that individual estimates from PPK are more similar to the observed data than the estimates based on the typical values. To determine the cause of the differences in the estimates, the Agency re-examined the original population PK model. Figure 1 shows that although the fitted line based on the model generally describes well the relationship of CLcr vs CL, it overestimates the telbivudine CL for subjects with CLcr less than 30 mL/min. Because most of the data under 30 mL/min were contributed from the renal impairment study, the observed data from the study are more reliable. In renal impairment study, 200-mg Phase III Clincal Study Formulation was used, 3 x 200 mg Phase III Clincal Study Formulation (tablet) are bioequivalent to the approved 600 mg tablet.

Table 2 Comparison of arithmetic mean AUC observed from renal impairment study with obtained from estimates based on typical values from PPK, and obtained from individual estimates from the PPK model

Degree of renal impairment	Dose used in renal impairment study (mg)	N	$AUC_{0-\infty}$ (h x mg/L) Observed in renal impairment study	Estimates based on typical values from PPK	Individual estimates from PPK
Normal	600	8	28.5[a]	24.9	28.4
Mild	600	8	32.5	33.5	32.7
Moderate	400	8	36.0	32.7	37.4
Severe	200	6	32.5	30.2	37.9
ESRD	[redacted]	6	[redacted]	[redacted]	[redacted] b(4)

[a] n=7

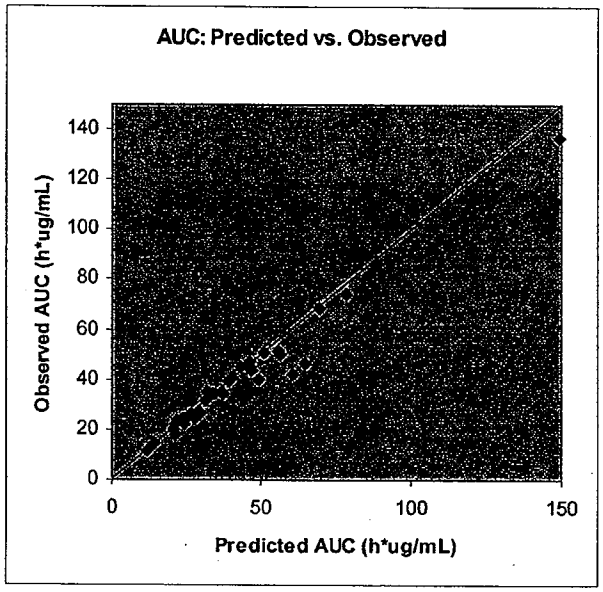
Figure 1 The Effect of CLcr on CL (the solid line is PPK model fit)



b(4)

As shown in Figure 2, the individual estimates of steady-state AUC from PPK well predict the observed AUC in the Study NV-02B-006.

Figure 2: Comparison of individual estimated AUC from PPK (predicted) vs observed AUC for 36 subjects in Study NV-02B-006



It needs to be mentioned that Study NV-02B-006 is a single dose study, the observed single dose Cmax may not represent the steady-state Cmax. Therefore, the individual estimates of steady-state Cmax from PPK will be used in combination with the observed $AUC_{0-\infty}$ from Study NV-02B-006, and the individual estimates of steady-state AUC from PPK, to determine the correct dose for renal impaired subjects.

b(4)

Therefore, geometric mean values from the study were used to scale exposures to different doses. The estimations assumed linear PK for doses at 200 mg or less because telbivudine bioavailability approached 1 for these doses. The results are shown in Table 3. The PK parameters that are within 35% of the values of the observed in subjects with normal renal function at 600 mg are highlighted, because similar efficacy and safety were observed for telbivudine in the 400-800 mg/d dosing range in the Phase I/IIa dose-finding trial [NV-02B-001].

Table 3: Observed or simulated (estimated) steady state geometric mean of Cavg and Cmax by degree of renal impairment and daily dose level with percentage difference from subjects with normal renal function at 600 mg

Degree of renal impairment	Dose (mg)	N	Exposure (ug/mL)			% difference from normal 600 mg		
			Obs.[b] Cavg	Est. Cavg (s.s)	Est. Cmax (s.s)	Obs. Cavg	Est. Cavg	Est. Cmax
Normal	600	8	1.14	1.14	3.07	0	0	0
Mild	600	8	1.29	1.30	2.84	13.2	13.7	-7.4
Moderate	400	8	1.38	1.43	2.71	21.7	25.6	-11.7
Severe	200	6	1.26	1.45	2.09	11.2	27.0	-32.0
ESRD								
ESRD								
ESRD								

b(4)

[a] post-dialysis; [b] obs. Cavg =AUC_{∞}/24 hours; [c]

Conclusion:

- For subjects with mild, moderate or severe renal impairment, the proposed 600 mg, 400 mg, and 200 mg doses, respectively, result in observed Cavg and the individual estimates of Cavg and Cmax from PPK within 35% of the values of the observed in subjects with normal renal function at 600 mg. Therefore, the proposed doses for subjects with mild, moderate or severe renal impairment are acceptable.
-

b(4)

A PHASE I, OPEN-LABEL, MULTIPLE-DOSE STUDY TO EVALUATE THE PHARMACOKINETIC INTERACTION BETWEEN TELBIVUDINE AND TENOFOVIR DISOPROXIL FUMARATE (VIREAD) IN HEALTHY SUBJECTS (Study NV-02B-028)

Objectives:

- To investigate the potential for a pharmacokinetic drug-drug interaction between telbivudine (LdT) and tenofovir disoproxil fumarate (TDF, Viread®) in healthy subjects.
- To evaluate the safety and tolerability of LdT in combination with TDF in healthy subjects.

Study Design: This was a Phase I, open-label, multiple-dose, parallel-group study. The overall study design is presented in the following table. Meal was not controlled in the study.

Overall study design

	Group 1	Group 2
LdT	Days 1 – 14: 1 daily dose of 600 mg for a total of 14 doses.	Days 8 – 14: 1 daily dose of 600 mg for a total of 7 doses.
TDF	Days 8 – 14: 1 daily dose of 300 mg for a total of 7 doses.	Days 1 – 14: 1 daily dose of 300 mg for a total of 14 doses.

Population: 16 healthy male and female subjects were enrolled in the study.

Formulation:

- Telbivudine (LdT) 600 mg tablets, manufactured by Novartis, Basel, Switzerland, Lot No.: X378KA, expiration date: 30 November 2006
- Tenofovir disoproxil fumarate (TDF, Viread®) 300 mg tablets, manufactured by Gilead Sciences, Inc., Lot No.: V0126A001, expiration date: September 2008

Pharmacokinetic Sampling: Blood samples were collected on Days 7 and 14 at predose (0 hour), 0.5, 1, 2, 3, 4, 8, 12, 16, 20, and 24 hours postdose.

Analytical Methodology: The following table summarizes the bioanalytical methods used to determine plasma concentrations of LdT and TDF. The performance of the sample analyses appears acceptable. All samples were analyzed during the period within which their analytes were stable.

Analyte	Methods	Linear Range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Deviation)	QC samples (ng/mL)	Stability
LdT	LC/MS/MS	10-5000 R^2 ≥0.9970	≤4.6	0.8 to 6.5	30, 200, 4000, and 8000	• Stable at -20°C for at least 965 days • Stable following 6 freeze/thaw cycles • Stable in human EDTA plasma at room temperature for at least 25 hours
TDF	LC/MS/MS	5 – 750 R^2 ≥ 0.9971	≤ 3.7	-2.6 to 1.7	15, 275, 575 and 1150	• Stable in human EDTA plasma at -20°C for at least 241 days. • Stable at room temp. for at least 24 hours • Stable following 6 freeze/thaw cycles

Results: Sixteen (16) subjects were included in the LdT and TDF PK analysis. The arithmetic means and standard deviation (SD) of the plasma LdT PK parameters for Group 1 are summarized in the following table:

Summary of the plasma LdT pharmacokinetic parameters

Pharmacokinetic parameters	Day 7		Day 14	
	Arithmetic mean	SD	Arithmetic mean	SD
Cmax (ng/mL)	4250	932	3710	695
Tmax (hr)#	3.00	2.00, 4.00	3.01	2.01, 4.01
Ctrough (ng/mL)	313	69.3	364	79.5
AUCss (ng*hr/mL)	33629.56	5330.683	31277	3481.9
CL/F (L/hr)	18.262	3.0543	19.393	2.1611

= Values for Tmax are reported as median instead of mean and range (min, max) instead of SD
Day 7 = 1 X 600 mg telbivudine tablet administered QD on Days 1 - 7
Day 14 = 1 X 300 mg Viread® (tenofovir disoproxil fumarate) tablet and 1 X 600 mg telbivudine tablet administered QD on Days 8 - 14

The arithmetic means and SD of the plasma TDF PK parameters for Group 2 are summarized in the following table:

Summary of the plasma TDF pharmacokinetic parameters

Pharmacokinetic parameters	Day 7		Day 14	
	Arithmetic mean	SD	Arithmetic mean	SD
Cmax (ng/mL)	515	155	499	147
Tmax (hr)#	0.500	0.500, 1.01	0.510	0.500, 1.01
Ctrough (ng/mL)	67.4	15.6	65.2	15.3
AUCss (ng*hr/mL)	3316.248	695.5858	3187.7	625.69

= Values for Tmax are reported as median instead of mean and range (min, max) instead of SD
Day 7 = 1 X 300 mg Viread® (tenofovir disoproxil fumarate) tablet administered QD on Days 1 - 7
Day 14 = 1 X 300 mg Viread® (tenofovir disoproxil fumarate) tablet and 1 X 600 mg telbivudine tablet administered QD on Days 8 - 14

The results of the statistical comparison for plasma LdT following administration of LdT in combination with TDF versus the administration of LdT alone (Group 1) are summarized in the following table:

Summary of statistical comparisons of plasma LdT PK: combination versus LdT alone

Pharmacokinetic parameters	- Least squares means -		90% CI	% Mean ratio
	Day 14	Day 7		
ln(Cmax)	8.202	8.333	(76.73 - 100.21)	87.69
ln(AUCss)	10.345	10.412	(84.44 - 103.68)	93.56

Least-squares means are on the log-scale, CI and mean ratio are on the original scale
Day 14 = 1 X 300 mg Viread® (tenofovir disoproxil fumarate) tablet and 1 X 600 mg telbivudine tablet administered QD on Days 8 - 14 (test)
Day 7 = 1 X 600 mg telbivudine tablet administered QD on Days 1 - 7 (reference)

The results of the statistical comparison for plasma TDF following administration of TDF in combination with LdT versus the administration of TDF alone (Group 2) are summarized in the following table:

Summary of statistical comparisons of plasma TDF PK: combination versus TDF alone

Pharmacokinetic parameters	- Least-squares means - Day 14	Day 7	90% CI	% Mean ratio
ln(Cmax)	6.173	6.203	(87.31 - 107.85)	97.04
ln(AUCss)	8.049	8.088	(87.38 - 105.95)	96.22

Least-squares means are on the log-scale. CI and mean ratio are on the original scale
Day 14 = 1 X 300 mg Viread (tenofovir disoproxil fumarate) tablet and 1 X 600 mg telbivudine tablet administered QD on Days 8 - 14 (test)
Day 7 = 1 X 300 mg Viread® (tenofovir disoproxil fumarate) tablet administered QD on Days 1 - 7 (reference)

Conclusion: There were no clinically significant impact of TDF on LdT pharmacokinetics and no statistically significant impact of LdT on TDF pharmacokinetics following repeated once-daily administration.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jenny H. Zheng
10/15/2008 11:35:24 AM
BIOPHARMACEUTICS

Kellie Reynolds
10/15/2008 12:43:45 PM
BIOPHARMACEUTICS