CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-154/S-029, S-030
20-155/S-021
20-156/S-022

CLINICAL PHARMACOLOGY BIOPHARMACEUTICS REVIEW

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-154 SE2-029, SCF-030 **Reviewer**: Robert O. Kumi, Ph.D.
DRUG: Didanosine or ddI (VIDEX®) **Submission Date**: 04/30/99
Formulation: Chewable/ Dispersible Buffered Tablets (200 mg) **Draft Review**: 08/10/99; 12/01/99
Applicant: Bristol-Myers Squibb Company

I. Background

A. Clinical Studies

The applicant wishes to introduce a new 200 mg strength tablet (SCF-030) to support once a day (QD) 400 mg dosing. The three clinical studies supporting QD dosing of VIDEX® (SE2-029) have been reviewed by the Medical Officer, Russell Fleischer (DAVDP), and the study results suggest that QD dosing is as effective as BID dosing. The following efficacy studies were conducted:

Study AI454-143	**400 mg ddI QD** 2 x 200 mg + ddI placebo QD + 40 mg d4T BID	vs.	**200 mg ddI BID** 2 x 100 mg + 40 mg d4T BID
Study AI454-146	**400 mg ddI QD** 2 x 150 mg and 1 x 100 mg + 40 mg d4T BID	vs.	**200 mg ddI BID** 2 x 100 mg + 40 mg d4T BID
Study AI454-148	**400 mg ddI QD** 2 x 200 mg + 40 mg d4T BID + 750 mg NLF TID	vs.	300 mg ZDV BID + 150 mg 3TC BID + 750 mg NLF TID

Abbreviations used for study drugs are, ddI- didanosine (Videx), d4T- stavudine (Zerit), 3TC- lamivudine (Epivir) and NLF- nelfinavir mesylate (Viracept).

B. Submitted Studies

This review summarizes the findings of studies submitted to NDA 20-154 SCF-030 for **didanosine or ddI (VIDEX®) 200 mg tablets**. Six studies were submitted to the Human Pharmacokinetics and Bioavailability Section of this NDA supplement, but only **study AI454-145** will be reviewed in detail. NDA 20-154 SLR-023 and NDA 20-154, which included the other five study reports have been previously reviewed by the Division of Pharmaceutical Evaluation III. **Key findings** from these previously reviewed studies include the following:

- **Studies AI454-001-001, AI454-022-001, and AI454-002-001: Dose linear** increases in ddI C_{max} and AUC occur in patients over the dose ranges of 7.0-20.4 mg ddI/kg, 0.8-10.2 mg ddI/kg, and 125-375 mg ddI, respectively following repeated oral administration. **Reviewer**: I. Bernstein (8/29/91) NDA 20-154, 20-155 and 20-156.
- Study **AI454-128**: Patients with moderate renal impairment (Creatinine CL: 30-59 mL/min) have average ddI C_{max} and AUC_{∞} values that are approximately two fold greater than the average C_{max} and AUC_{∞} for patients with normal renal function following a single 200 mg ddI oral dose.
  Reviewers: P. Rajagopalan and B. Davit (2/4/97)

C. Safety and Tolerability of VIDEX® Tablets

Adult patients are required to take at least two tablets at each dose to provide adequate buffering to prevent degradation of ddI by gastric acid. In general, administration of ddI as 2 buffered tablets does not result in any severe adverse events. Post-marketing safety surveillance reports suggest that patients receiving a 400 mg ddI daily dose via 4 tablets (4x100 mg tablets) have a higher incidence of gastrointestinal (GI) side effects than patients receiving the same dose via 3 tablets (2x150 mg and 1x100 mg tablets). The sponsor attributes the increase in GI irritation or decreased tolerability to the increased buffer amount.

II. INTRODUCTION TO STUDY

A. Tablet Strengths and Proposed Labeling Changes

VIDEX® (tablets and buffered powder) is an approved drug for the treatment of HIV-1, in combination with other antiretroviral agents. Tablet strengths currently available contain 25, 50, 100 and 150 mg of didanosine (ddI). In adults, the dosage regimen for VIDEX® depends on the patient weight as illustrated in tables I and II.

Current Insert: Table I.

Patient Weight (kg)	VIDEX® Tablets	VIDEX® Powder
≥ 60	200 mg BID	250 mg BID
< 60	125 mg BID	167 mg BID

Proposed Revisions to Insert: Table II.

Patient Weight (kg)	VIDEX® Tablets	VIDEX® Powder
≥ 60	400 mg QD or 200 mg BID	250 mg BID
< 60	250 mg QD or 125 mg BID	167 mg BID

For renally impaired patients, the proposed dosing changes affect patients with creatinine clearance ≥ 60 mL/min (normal renal function) and creatinine clearance between 30 and 59 mL/min (moderate renal impairment). A summarized version (relevant portions) of the current and proposed dosing in patients with renal impairment is presented in Table III.

Table III. Currently Approved and Proposed Dosing of VIDEX® in Renal Impairment

Patient Weight (kg)	Creatinine CL (mL/min)	Label Version	Tablet (mg)
≥ 60 kg	≥ 60	current	200 BID
		proposed	400 QD or 200 BID
	30-59	current	100 BID
		proposed	200 QD or 100 BID
< 60 kg	≥ 60	current	125 BID
		proposed	250 QD or 125 BID
	30-59	current	75 BID
		proposed	150 QD or 75 BID

B. Comparison of New 200 mg Formulation to VIDEX® (100 mg)

Table IV : Composition of bulk granulation and Chewable/Dispersible Buffered Tablets

Ingredients (Function)	Amount per Tablet (mg) VIDEX®	New Formulation
Didanosine		
Calcium Carbonate		
Magnesium Hydroxide		
Aspartame		
Sorbitol		
Microcrystalline Cellulose		
Polyplasdone		
Mandarin Orange		
Magnesium Stearate		
Total Tablet Weight		

*total amount of sorbitol may vary depending on amount of ddI required for activity
** total amount of magnesium stearate can be adjusted up to tablet for compaction and tableting
NC non-compendial; USP United States Pharmacopoeia; NF National Formulary

III. STUDY REVIEW Protocol No. AI454-145 (Study Report 910067148)
Investigator

Title: "Assessment of the Dose Proportionality of Didanosine, Administered as the 2.1 G Chewable Tablet to Healthy Subjects (AI454-145)"

Objective: To demonstrate dose proportional increases in didanosine C_{max} and AUC values over the dose range of 50 to 400 mg following administration of the chewable tablet formulations of didanosine

Subjects: Twenty-four (24) healthy volunteers were enrolled, screened, randomized into four treatment sequences, and dosed; however two subjects dropped out of the study for "personal reasons". These two subjects were replaced with two new volunteers. Inclusion criteria included, age 18-50 years, weight ≥ 60 kg and within 15% of ideal body weight, and child bearing females had negative serum pregnancy test. No concomitant therapy was allowed.

Demographic Factors:

- Gender 9 females, 15 males
- Age 17-48 years, Mean (SD) 32 (10) years
- Race 3 Black, 21 White
- Weight Mean (SD) 75.7(10.5) kg, Range 60.3-104.8 kg

Dietary Compliance: Subjects fasted from 10 hours before dosing (food and beverages). Food was not allowed until 4 hours after dosing but water was allowed in this 4-hour period *ad libitum*.

Study Design: An open label, single center, single dose, randomized four-way crossover study design was employed to assess the dose proportionality of orally administered ddI in healthy volunteers. The washout period between treatments was 3 days.

Analytical Methodology: ddI concentration in plasma samples was determined by a validated radio-immunoassay method and ddI concentration in urine samples was determined by a validated HPLC method with UV detection. Assay performance was acceptable for both methods.

Formulations: The VIDEX® Buffered Tablets (Chewable/Dispersible) used in the study are:

- 25 mg (NDC No. 0087-6650-01) Batch No. MAO02
- 50 mg (NDC No. 0087-6651-01) Batch No. MDO01
- 100 mg (NDC No. 0087-6652-01) Batch No. MDO07
- 200 mg (Product Identification 40900A200-138-0) Batch No. 8MEH130

Dosing Regimen: Following an overnight fast, subjects received ddI treatments as follows:

1. **Treatment A** ddI 50 mg, 2 x 25-mg strength tablets
2. **Treatment B** ddI 100 mg, 2 x 50-mg strength tablets
3. **Treatment C** ddI 200 mg, 2 x 100-mg strength tablets
4. **Treatment D** ddI 400 mg, 2 x 200-mg strength tablets

Tablets for a given treatment were chewed thoroughly, together, or in rapid succession to give desired dose of ddI. Each dose was given with 240 mL room temperature tap water.

Sample Collection

Blood Samples were collected at 0 (predose), 15, 30, 45 and 60 minutes, and 1.5, 2, 3, 4, 5, 6, 8 and 12 hours post-dose.

Urine Samples were collected predose and over the intervals 0-4, 4-8, and 8-12 hours post-dose.

Pharmacokinetic Analysis

Pharmacokinetic parameters were calculated using noncompartmental methods.

Statistical Analysis: ANOVA was used in the preliminary analyses, using treatment sequence, subject within sequence, treatment (dose), period and first order treatment carryover as factors. If carryover sequence effects were insignificant or absent, ANOVA was repeated excluding carryover in the model. Log-transformed and dose normalized values of AUC_∞ and C_{max} were analyzed by a 90% confidence interval approach to determine the differences, if any, between 50, 100 and 400 mg doses and the 200 mg dose. The 200 mg dose was chosen as the reference because 200 mg BID is the current recommended starting dose for the treatment of HIV-infected individuals with weight ≥ 60 kg. Didanosine AUC_∞ and C_{max} were considered to be dose proportional over the given dose range, if all three confidence intervals for the test-to-reference ratios of the dose normalized means were between 80 and 125 %. ANOVA was performed on untransformed values of T_{max}, $t_{1/2}$, CL_R, and UR (percent excreted in urine).

Study Results

A. Pharmacokinetics

Pharmacokinetic parameters for the various doses are summarized in Table V and the confidence intervals for dose normalized AUC and C_{max} are presented in Table VI. Pharmacokinetic parameters obtained in this study are comparable to those obtained in previous studies at similar doses.

Sequence and carryover effects were not significant for all the variables analyzed; however, period effects were statistically significant for AUC_∞, C_{max}, and $t_{1/2}$. Mean T_{max}, MRT, $t_{1/2}$, UR, and CL_R were similar among treatment groups, suggesting that these parameters are dose independent. Thus, ddI pharmacokinetics over the studied dose range are linear.

Table V: Mean^ ± SD Pharmacokinetic Parameters of ddI

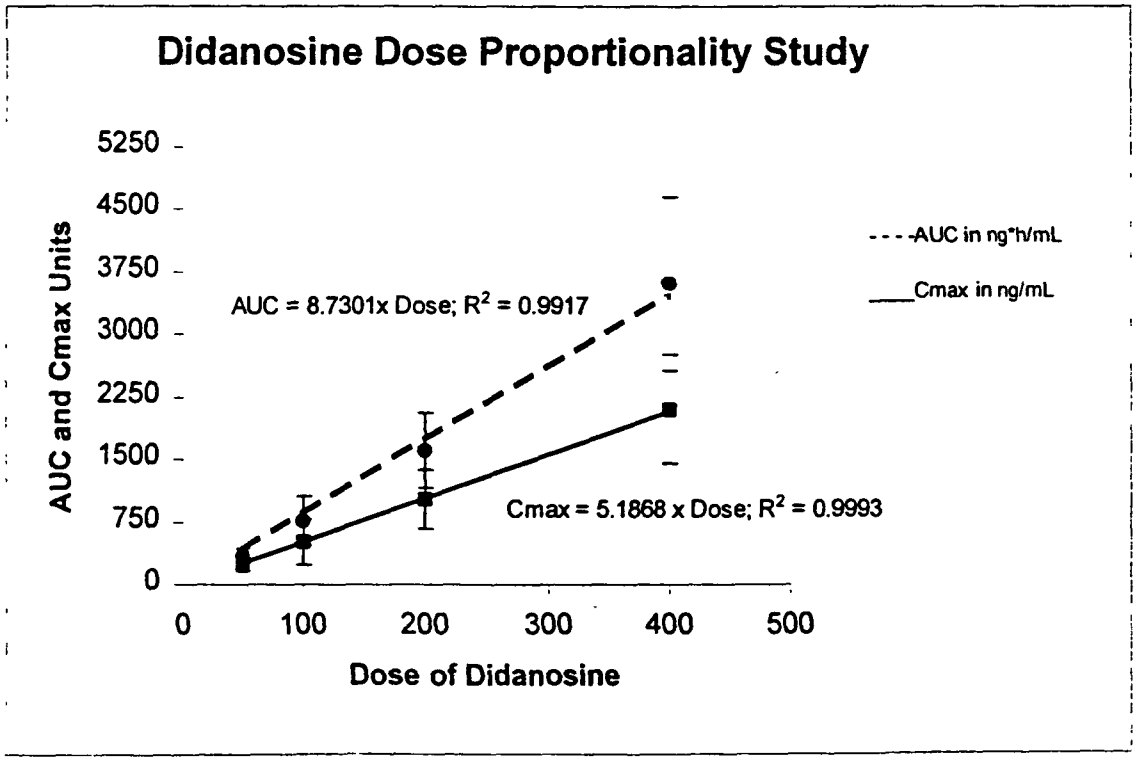
Parameter	Didanosine Dose (mg)				
	50	100	200	400	200 (renal imp)
$AUC_{0-\infty}$ (ng·h/mL)	349 ± 88	765 ± 296	1602 ± 452	3602 ± 1036	3616 ± 1212
C_{max} (ng/mL)	236 ± 80	508 ± 265	1014 ± 347	2092 ± 657	1728 ± 526
T_{max}* (h)	0.50	0.50	0.50	0.75	0.75
Half-life (h)	1.37 ± 0.31	1.31 ± 0.19	1.33 ± 0.17	1.47 ± 0.31	1.75 ± 0.43
CL_R (mL/min)	329 ± 87	380 ± 161	336 ± 89^	348 ± 79^	100 ± 44.1
UR (%)	13.2 ± 2.9	16.5 ± 7.9	15.5 ± 3.8	18.0 ± 3.9	11.5 ± 3.5

* median value; range of values was 0.25-1.00 h; ^ n=23, for all remaining values n=24.
renal imp- patients with renal impairment (Creatinine Clearance 33-57 mL/min) received 200 mg dose. Renal impairment data were obtained from review of NDA 20-154 SLR-023 and are included in the table because labeling changes for these patients are proposed by the sponsor (See Discussion)

Table VI: Ninety Percent (90 %) Confidence Intervals (CI) of Dose Normalized AUC and C_{max} Geometric Means Ratios Relative to 200 mg Dose

Pharmacokinetic Parameter	Contrast by Dose (mg)	Point Estimate	90 % CI Limits	
			Lower	Upper
C_{max} (ng/mL)	50 vs. 200	0.922	0.809	1.050
	100 vs. 200	0.959	0.842	1.093
	400 vs. 200	1.040	0.913	1.184
AUC_∞ (ng·h/mL)	50 vs. 200	0.877	0.802	0.960
	100 vs. 200	0.930	0.850	1.018
	400 vs. 200	1.123	1.027	1.229

Figure 1: Plot of Didanosine AUC and C_{max} against Didanosine Dose



Discussion

Over the dose range of 50-400 mg, ddI AUC_∞ and C_{max} increased dose proportionally following single oral doses of chewable tablet formulation and dose normalized exposures following administration of the new 200 mg strength tablet were similar to those following administration of the marketed formulations. It should be noted that the design of the study and results obtained from the study preclude establishment of bioequivalence of the new 200 mg formulation to the previous formulation (s). In this study, the new formulation was not tested against a reference formulation (s) at the same dose level, which is required in typical bioequivalence studies. A possible reason why the sponsor did not conduct a traditional bioequivalence study is the GI irritation observed upon administration of four 100 mg tablets (see I.C. Safety and Tolerability).

The T_{max}, MRT, $t_{1/2}$, UR, and CL_R were independent of dose, suggesting that ddI exhibits linear kinetics over the dose range of 50-400 mg. Dose linearity of ddI in this dose range has been observed in previously conducted studies.

Labeling changes for patients with moderate renal impairment were proposed by the sponsor are relevant to the current discussion. It should be noted that the applicant included a study report from a previously conducted study in patients with renal impairment, but does not link the data from these renal impairment studies to the current findings or proposed labeling changes (not annotated in the label). The average ddI C_{max} and AUC_∞ values obtained in patients with moderate renal impairment (1728 ng/mL and 3,616 ng h/mL, respectively) following a 200 mg dose are comparable to those obtained in subjects with normal renal function (2092 ng/mL and 3,602 ng h/mL, respectively) following a single 400 mg dose (Table V). The similarity in ddI exposure following administration of 200 mg ddI to moderately renally impaired patients and 400 mg ddI to healthy subjects supports the proposed labeling change for patients with moderate renal impairment.

B. Dissolution Studies

Dissolution studies for testing of all VIDEX® tablets have the following conditions:

- USP2 paddle apparatus, 75 rpm, 900 mL water at 37°C
- Q = [redacted] in [redacted] minutes

Table summarizes the dissolution data for the three 200-mg tablet batches using the approved dissolution methodology. These dissolution data are presented in the stability section of the report. All three batches meet the dissolution specifications.

Table V: Dissolution of 200 mg Tablets in Water

	Mean Percent of Label Dissolved for Individual Tablets		
Lot Number	8MEH132	8MEH131	8MEH130
Time (minutes)			
[redacted]	94.5	94.1	95.8
	97.7	97.9	98.4
	98.6	99.1	99.3
	98.9	99.5	98.7

IV. CONCLUSIONS

1. The dose normalized exposures (AUC and C_{max}) observed following administration of the 50 mg (2 x 25 mg tablets), 100 mg (2 x 50 mg tablets), and 400 mg (2 x 200 mg) doses were similar to those observed following the 200 mg (2 x 100 mg tablets) dose, suggesting that the new 200 mg tablet provides exposure comparable to that of the marketed tablet strengths.

2. Over the dose range of 50-400 mg, ddI AUC and C_{max} increase in a dose proportional manner after single oral doses of the chewable tablet formulation. These findings confirm previous study results.

3. The proposed dissolution conditions and specifications for the 200-mg formulation are as follows:

- Method: USP 2, paddle apparatus at 75 rpm in 900 mL water at 37°C
- Specification: Q =

The method and specification for the new 200 mg tablets are acceptable.

4. Patients with moderate renal impairment may be dosed at the proposed dose of 200 mg QD, because ddI exposure following administration of 200 mg ddI to these patients is similar to that obtained following administration of 400 mg ddI to patients with normal renal function.

V. LABELING

The applicant proposed changes to the label to account for the new tablet strength and for once daily dosing in patients with normal renal function and patients with moderate renal impairment. These labeling changes were discussed with the applicant and the final version of the label is included in the appendix.

VI. RECOMMENDATION AND COMMENTS

The pharmacokinetic information provided in 20-154 SCF-030 by the applicant demonstrates dose proportionality in the dose range of 50 mg – 400 mg ddI. The similarity between dose normalized exposure data for the 400 mg dose obtained via 2 x 200 mg tablets and the marketed tablet strengths provides indirect evidence that the new 200 mg strength tablet is "bioequivalent" to the marketed formulations. The clinical evidence submitted with the NDA (SE2-029) indicates that the 200 mg strength tablet may be used for QD dosing. The new 200 mg strength tablet is not indicated for use in the BID regimen as inadequate buffering is achieved with a single tablet. Approval of this 200 mg strength tablet was contingent upon approval of the QD regimen (SE2-029) by the Clinical Division (DAVDP); otherwise the tablet would have no indication for its use.

/S/ 12/02/99

Robert O. Kumi, Ph.D.
Reviewer, Pharmacokinetics
Division of Pharmaceutical Evaluation III

APPEARS THIS WAY
ON ORIGINAL

Concurrence: /S/ 12/2/99

Kellie Schoolar Reynolds, Pharm.D.
Pharmacokinetics Team Leader
Antiviral Drug Products Section

cc:

HFD-530	/NDA20-154 /MO/Fleischer /PM/Sillivan
HFD-880	/Kumi, R. /TL/Reynolds
HFD-340	/Viswanathan

APPEARS THIS WAY
ON ORIGINAL