CENTER FOR DRUG EVALUATION AND RESEARCH

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MEDICAL REVIEW

Medical Review
(Supplemental NDA)

Date Submitted: June 30, 1998
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Applicant: Bristol Myers-Squibb Company
5 Research Parkway
Wallingford, CT 06492

Drug: Generic didanosine (ddI)
Trade Videx®

Dosage forms: Chewable/dispersible tablets and buffered powder for oral solution

Proposed indication: Treatment of HIV infection in combination with other approved antiretroviral agents

Related NDAs:
20-155 Videx® Buffered powder for oral solution
20-156 Videx® Pediatric powder for oral solution
20-363 Crixivan® (indinavir), Merck
20-412 Zerit® (stavudine), Bristol-Myers Squibb
20-636 Viramune® (nevirapine), Boehringer Ingelheim
20-705 Rescriptor™ (delavirdine mesylate), Pharmacia & Upjohn

1.0 Resume

The applicant has submitted the results from five clinical studies to support the use of didanosine (ddI) in combination with other antiretroviral agents: the AIDS Clinical Trials Group (ACTG) studies 241 and 261, [redacted] study 1046, and Bristol-Myers Squibb (BMS) studies AI455-053 and BMS01-002 (START 2). This supplement was submitted in response to a request by the Division of Antiviral Drug Products that the applicant submit an application to support amendment of ddI labeling to include safety and efficacy data from studies that included ddI as a component of combination regimens for the treatment of HIV infection.

ACTG 241 demonstrated that the addition of nevirapine (NVP) to ddI+zidovudine (ZDV) resulted in a small but greater mean increase in CD4 cells and suppression of HIV RNA over the 48-week treatment period compared to treatment with ZDV+ddI. A durable antiviral response was not documented in either treatment arm, thus precluding conclusions about the efficacy of ddI in these combinations. Grade 3 and 4 abnormal hepatic, pancreatic, and hematologic values were reported with similar frequency between the two treatment groups.

ACTG 261 demonstrated that, after six-months of treatment, the combination of delavirdine (DLV)+ddI+ZDV resulted in higher CD4 cell counts and lower HIV RNA level than treatment with DLV+ZDV, the only arm not containing ddI. However, this trial was not designed or powered to determine if the addition of ddI was the factor resulting in the improved efficacy of the triple combination regimen. Rash, hematologic and liver function test abnormalities were the most commonly reported adverse events in this trial and they were reported with similar frequency across the four treatment arms.

BMS 053 demonstrated that zalcitabine (d4T) and ZDV when combined with ddI resulted in similar antiviral and immunologic activity after six months of treatment. Since ddI was in both treatment regimens, it was also not possible to assess ddI's specific contribution to efficacy. Peripheral neuropathy occurred twice as frequently in patients treated with d4T+ddI. Elevated liver function tests were reported by many patients, but with similar frequency between treatment groups.

Study [redacted] 046 demonstrated that the combination of NVP+ddI+ZDV produced greater reductions in HIV RNA and increases in CD4 cell counts than NVP+ZDV or ZDV+ddI after six months of treatment. In this study, as in study ACTG 261, above, the triple combination arm resulted in better immunologic and antiviral activity than the arm that did not contain ddI (NVP+ZDV). Because of the small number of patients available at weeks 60-76, it was not possible to assess the durability of these responses. Peripheral neuropathy was reported infrequently, one patient in each treatment group. Abnormal liver function tests, GI symptoms (nausea, vomiting, diarrhea), and rash occurred frequently but were reported with similar frequency between the three treatment groups.

Study START 2 demonstrated that treatment with d4T+ddI+indinavir (IDV) or ZDV+lamivudine (3TC)+IDV resulted in similar immunologic and virologic responses through 48 weeks of treatment. Because of the multiple substitutions between the two treatment arms, it was not possible to assign the contribution of ddI to the outcomes of this trial. Significantly more clinically relevant LFT abnormalities were observed in patients treated with a backbone of d4T+ddI. The occurrence of peripheral neuropathy and the death due to pancreatitis in the d4T+ddI arm supports retaining these adverse events in the ddI label.

None of the trials were designed to specifically determine the contribution of ddI to efficacy. However, the data demonstrate that combinations of antiretroviral agents that included ddI produced reasonable antiviral and immunologic effects. Therefore, the data submitted in this supplement support the use of ddI in combination with other approved antiretroviral agents for the treatment of HIV-1 infection. Information related to liver-related toxicities, including elevated LFTs, fatty infiltrates and lactic acidosis, peripheral neuropathy, and fatal pancreatitis reported in patients treated with combinations including ddI should be included in the safety sections of the label.

2.0 Summary of Clinical Section

The applicant submitted the results of five clinical trials: ACTG 241, ACTG 261, BMS START 2, BMS AI455-053, and — 1046.

Table 1. Overview of clinical studies

Study Title	Study Description
ACTG 241	48-week study comparing open-label ddI+zidovudine (ZDV) with blinded nevirapine (NVP) to open-label ddI+ZDV with matching NVP placebo in antiretroviral-experienced patients (>6 months of ZDV, ddI or ddC) with CD4 counts $\leq$350 cells/mm^3.
ACTG 261	48-week study comparing delavirdine (DLV)+ddI+ZDV, ZDV+DLV, DLV+ddI, and ZDV+ddI in antiretroviral-naïve patients (<6 months of ZDV or ddI) with CD4 counts 100-500 cells/mm^3.
BMS START 2	48-week open-label study comparing d4T+ddI+(indinavir) IDV to ZDV+3TC+IDV in antiretroviral-naïve patients ($\leq$4 weeks of ZDV) with CD4 counts 200-700 cells/mm^3 and HIV RNA $\geq$10,000 copies/mL.
BMS 053	24-48 week study comparing ddI+d4T and ddI+ZDV in antiretroviral-naïve patients with CD4 counts $\leq$500 cells/mm^3.
— 1046	52-week study comparing NVP+ddI+ZDV, ZDV+ddI, and ZDV+NVP in antiretroviral-naïve patients with CD4 counts 200-600 cells/mm^3.

Three studies, ACTG 241, ACTG 261 and — 1046, were not conducted by the applicant. During pre-submission discussions FDA specifically requested that the applicant prepare a review of these three studies in order to define the contribution of ddI to the effectiveness and safety of the various combination regimens. However, the

applicant did not perform any additional analyses on these studies, and submitted the Executive Summaries and/or Final Study Reports prepared by the ACTG and —. Studies BMS 053 and START 2 were conducted by the applicant, and full study reports, CRFs, efficacy and safety data were submitted.

3.0 Study ACTG 241

A Comparative Study of Zidovudine, Didanosine, and Double-Blinded Nevirapine versus a Combination of Zidovudine and Didanosine.

3.1 Design

ACTG 241 was a phase 2, randomized multi-center, trial that compared the safety, anti-HIV activity, and efficacy of nevirapine (NVP)+didanosine (ddI) + zidovudine (ZDV) versus ddI+ZDV. Patients were randomized to NVP or matching placebo and all received open-label ddI and ZDV. The treatment duration was 48 weeks.

Eligible subjects had received more than six months of prior nucleoside therapy and had CD4 cell counts $\leq 350/mm^3$. The objectives were to compare the immunologic, virologic and clinical activity (time to HIV progression or death), and safety of the treatment regimens.

The study was sponsored and conducted by the ACTG . Results from this study were previously submitted by — to support accelerated approval of NVP. At that time a detailed review of this study was conducted by DAVDP reviewers (see Medical Officer and Statistical reviews of NDA 20-636 dated September 9, 1996). The current submission includes the ACTG's Executive Summary of the study.

3.2 Patient Population and Disposition

A total of 400 patients were enrolled in the study. At baseline, patients were primarily Caucasian (74%), and male (80%), with a median age of 38 years. At baseline, the median CD4 cell count was $150/mm^3$; the median HIV RNA was 5.94 log_{10} copies/mL, and the median duration of previous antiretroviral therapy was 25 months.

3.3 Results: Efficacy

At weeks 40-48, the mean change from baseline in CD4 cell counts was +6 cells/mm^3 in the NVP+ddI+ZDV arm compared to -16 cells/mm^3 in the ddI+ZDV arm. Analysis stratified by CD4 cell counts demonstrated a treatment effect that was most evident among patients with 51-200 CD4 cells at baseline; the reason for this result was not clear.

Sixty-one patients (15%) experienced HIV disease progression or died during the 48-week study, 34 in the NVP+ddI+ZDV arm and 27 in the ZDV+ddI arm. The reasons for disease progression and death were similar across the treatment arms and generally reflected complications associated with advanced HIV disease.

At 48 weeks, treatment with NVP+ddI+ZDV resulted in a mean change from baseline in HIV RNA of -0.14 $\log_{10}$ copies/mL compared to +0.11 $\log_{10}$ copies/mL with ddI+ZDV.

Comment: The efficacy analyses suggested that there was a minimal additive benefit when NVP was added to the double-nucleoside combination. Since neither arm demonstrated a durable antiviral effect, this study contributes little to support the use of ddI in combination.

3.4 Results: Safety

A total of 16 deaths were reported during the study period: eight in each arm; these were primarily due to complications of advanced HIV infection.

The ACTG only described adverse events that were reported as Grade 3 (severe) and Grade 4 (potentially life-threatening). Rash was the most commonly reported adverse event in patients who received the triple combination. More patients treated with NVP+ddI+ZDV reported Grade 3 (serious) and Grade 4 (life-threatening) rashes, some of which resulted in Stevens-Johnson syndrome.

Grade 3 and 4 abnormal hepatic, pancreatic, and hematologic values were reported with similar frequency between the two treatment groups.

4.0 Study ACTG 261

A Phase II Double-Blind Study of Delavirdine Mesylate (DLV) in Combination with Zidovudine (ZDV) and/or Didanosine (ddI) Versus ZDV and ddI Combination Therapy.

This study was sponsored and conducted by the ACTG . Results from this study were previously submitted by — to support accelerated approval of DLV. At that time a detailed review of this study was conducted by DAVDP reviewers (see Medical Officer review of NDA 20-705 dated March 31, 1997). The current submission includes the ACTG's Executive Summary and Final Analysis report of the study.

4.1 Design

ACTG 261 was a Phase 2, randomized, multi-center, double-blind study that compared the combination of DLV+ZDV+ddI to DLV+ZDV, DLV+ddI, and ZDV+ddI over a 48 week treatment period. The objectives of the study were to obtain anti-HIV activity data and to compare the safety of the four treatment arms. Eligible subjects had baseline CD4

counts between 100-500 cells/mm^3, and had received ≤6 months of monotherapy with ddI or ZDV, but not both.

The primary outcome measures were short-term (within 12 weeks) and long-term (mean of week 40 and 48 measurements) changes in CD4 cell counts and long-term changes in HIV RNA levels. Changes in HIV RNA were measured in a viologic sub-study of 250 subjects using an assay with a reported lower limit of detection of 200 copies/mL.

4.2 Patient Population and Disposition

A total of 544 HIV-infected patients were enrolled in the study. Study participants were primarily male (82%), Caucasian (56%), with a median 35 years of age, with a median CD4 cell count of 295 cells/mm^3. A subset of 247 patients included in a virologic sub-study had median baseline plasma HIV RNA levels of 4.45 $\log_{10}$ copies/mL.

Comment: The study arms were well balanced at baseline with regard to demographic and disease characteristics. The baseline characteristics of patients in the virologic sub-study were consistent with those of the overall study population.

4.3 Results: Efficacy

The analysis of CD4 cell counts at week 12 demonstrated mean changes from baseline of 49, 17, 33 and 48 cells/mm^3 in the DLV+ZDV+ddI, DLV+ZDV, DLV+ddI, and ZDV+ddI arms, respectively. At 40-48 weeks, the mean change in CD4 cell counts was higher in the DLV+ZDV+ddI group (+65 cells/mm^3) compared with DLV+ddI (+26 cells/mm^3), ZDV+ddI (+44 cells/mm^3) and DLV+ZDV (-20 cells/mm^3).

The analysis of change in viral HIV RNA at weeks 40-48 was based on 149 of the 247 patients in the virologic sub-study. The results demonstrated mean reductions of -0.73 $\log_{10}$ copies/mL from baseline in the DLV+ZDV+ddI arm, -0.40 $\log_{10}$ copies/mL in the DLV+ZDV arm, -0.62 $\log_{10}$ copies/mL in the DLV+ddI arm and –0.52 $\log_{10}$ copies/mL in the ZDV+ddI arm.

Comment: The addition of ddI to ZDV+DLV appeared to contribute to improved changes in HIV RNA and CD4 cell counts.

4.4 Results: Safety

There were four deaths reported in this study; none appeared directly attributable to ddI. Only Grade 3 and 4 events of clinical interest were reported by the ACTG (GI system, neurologic system, skin, aches/pains, fatigue, weight loss, and chills/sweats). There were no differences in the frequency or severity of events between regimens that contained or did not contain ddI.

Rash, hematologic and hepatic function abnormalities were the most commonly reported events in this trial, and were reported with similar frequency between the four treatment arms.

5.0 Study BMS AI455-053

A Randomized Double Blind Study of Virologic, Clinical and Safety Effects of a Combination of d4T and ddI Versus Combination of ZDV and ddI in Treatment Naïve HIV-Infected Subjects.

This study was conducted by the applicant, and a full study report, including virologic, immunologic and safety data, and Case Report Forms (CRFs) for patients who died and who experienced Serious Adverse Events were submitted.

5.1 Design

This was a Phase 3, multi-center, randomized 48-week study of open-label ddI in combination with blinded D4T or ZDV. Subjects received ddI with either D4T, ZDV or matching D4T or ZDV placebo. Subjects were to receive study treatment for at least six months but no longer than 12 months.

Eligible subjects were antiretroviral treatment naïve, with CD4 cell counts $\leq$500 cells/mm^3. The study was conducted in Europe between October 15, 1996 and September 22, 1997.

The objective of the study was to compare d4T to ZDV+ddI in treatment naïve HIV-infected patients. The primary outcome measure was the averaged difference of HIV RNA using the [redacted] over the first 24 weeks of therapy. The proportion of patients with undetectable plasma HIV RNA (<500 copies/mL) at each time point was assessed. Improvements in CD4 cell counts were assessed as a secondary endpoint.

Comment: This study utilized an unapproved branched DNA signal amplification assay with a reported lower limit of detection of 500 copies/mL. The assay could not be reliably quantified at levels below 1,200 copies/mL. The units measured by this assay most likely do not represent actual viral particles on an absolute scale and, therefore, do not correlate with other HIV RNA/PCR assays.

5.2 Patient Demographics and Disposition

A total of 137 subjects were randomized, 66 to d4T+ddI and 67 to ZDV+ddI. Subjects were primarily male (70%), with a mean age of 35 years, mean baseline CD4 cell count of 300 cells/mm^3, and a mean baseline HIV RNA of 4.55 $\log_{10}$ copies/mL.

Eighty-three percent of d4T+ddI-treated patients and 86% of ZDV+ddI-treated patients completed 24 weeks of study treatment. There were more discontinuations from the d4T+ddI arm than the ZDV+ddI arm (35% versus 24%). The higher number of discontinuations among patients treated with d4T + ddI were due to more adverse events, disease progression, or withdrawal of consent.

5.3 Results: Efficacy

At week 24, there was no differences in the time-averaged difference between treatment arms, thus the two treatments were considered comparable.

At week 24, the median change in plasma HIV RNA levels was -1.5 $\log_{10}$ copies/mL in the d4T+ddI arm and -1.6 $\log_{10}$ copies/mL in the ZDV+ddI arm. The proportion of patients with HIV RNA $\leq$1,200 copies/mL was 76% of d4T+ddI-treated patients and 66% of ZDV+ddI-treated patients; the difference was not statistically significant.

The median change in CD4 cell counts was also similar between the treatment groups at week 24; median increases of 115 cells/mm^3 and 116 cells/mm^3 in the d4T+ddI and ZDV+ddI arms, respectively.

Comment: At week 24, both treatments resulted in similar reductions from baseline in plasma HIV RNA and increases in CD4 cell counts. No conclusions about long-term changes in viral load could be made because of the small numbers of patients at weeks 36 and 48. Based on what is known about treatment responses to monotherapy, it is likely that ddI contributed to virologic and immunologic benefit in both arms.

5.4 Results: Safety

5.4.1 Deaths and Serious Adverse Events

Two patients died during the study, one on each treatment arm. The deaths were due to a heroin overdose and a suspected gastric lymphoma.

Nine patients reported serious adverse events; five and four in the d4T+ddI and ZDV+ddI arms, respectively. The events did not appear to HIV-related or related to study medications.

5.4.2 Adverse Events Leading to Discontinuation of Study Medication

Twelve patients, seven in the d4T+ddI arm and five in the ZDV+ddI arm, discontinued study treatment due to an adverse event.

In the d4T+ddI arm, the events included gastrointestinal complaints (abdominal pain, nausea, vomiting, and/or diarrhea) (n= 2), peripheral neuropathy (n= 4), and increased SGOT/SGPT (n= 1). Gastrointestinal complaints (n=3) and increased SGOT/SGPT (n=2) accounted for the events in the ZDV+ddI arm.

Of note, one patient (d4T+ddI) discontinued study medication when hospitalized for abdominal pain, nausea, vomiting and dyspepsia. The reason cited in the CRF for discontinuation was non-compliance. At the time of study medication discontinuation the patient also had signs and symptoms of moderate peripheral neuropathy that was being treated with Elavil.

Another patient in the d4T+ddI arm (04-012) also reported peripheral neuropathy that was confirmed by EMG. The CRF, however, listed the reason for study medication discontinuation as disease progression.

Comment: The cited reasons for study medication discontinuation in patients treated with d4T+ddI were not consistent with their clinical situations. Peripheral neuropathy led to study medication discontinuation only in patients from the d4T+ddI arm suggesting that when these two drugs are used together patients may be at increased risk for this toxicity.

5.4.3 Clinical and Laboratory Adverse Events

Seventeen patients treated with d4T+ddI experienced peripheral neuropathic symptoms, including numbness, tingling and pain in the arms and/or legs, compared to nine treated with ZDV+ddI. Gastrointestinal complaints, such as nausea, vomiting and abdominal pain were reported more frequently by patients in the ZDV+ddI arm.

Similar numbers of patients in the two treatment arms had elevations in liver function tests and lipase levels; however, more patients in the ZDV+ddI arm experienced Grade 3-4 elevations of these enzymes.

6.0 Study [redacted] 1046

A Randomized, Placebo-Controlled, Double-Blinded Multinational Trial Comparing the Immunologic and Virologic Effects of Nevirapine, Didanosine, and Zidovudine Combinations for the Treatment of Antiretroviral Naïve HIV-1 Infected Patients with 200-600 CD4 T-Cells and No AIDS Defining Disease.

6.1 Design

This was a 52-week randomized, placebo-controlled, double-blind multinational trial comparing the immunologic and virologic efficacy of NVP+ddI+ZDV compared to ZDV+ddI and NVP+ZDV for the treatment of antiretroviral naïve HIV-1 infected patients who had 200-600 CD4 cells/mm^3 at entry, and without AIDS-defining disease. This trial was conducted in Canada, the Netherlands, Italy and Australia between July 1994 and July 1996.

The primary outcome measures were changes from baseline in plasma HIV RNA levels and CD4 cell counts over the 52-week trial period.

— 1046 was conducted and analyzed by ——————————————
——). Study results were previously submitted b — o support both accelerated and traditional approval of NVP. The current applicant submitted the Final Clinical Trial Report as prepared by — The original data sets were retained by — and were not submitted with this supplement.

6.2 Patient Demographics and Disposition

A total of 153 patients were enrolled. Study participants were primarily male (92%), Caucasian (94%), and were a mean age of 37 years. Patients in the NVP+ddI+ZDV arm had a median CD4 cell count of 340 cells/mm^3 and HIV RNA of 4.47 log_{10} copies/mL, compared to 380 cells/mm^3 and 4.24 log_{10} copies/mL and 395 cells/mm^3 and 4.52 log_{10} copies/mL in the ddI+ZDV and NVP+ZDV arms, respectively. All patients were antiretroviral naïve at baseline.

Comment: There were small differences between the treatment groups in baseline HIV RNA and CD4 cell counts. Otherwise, the demographic characteristics were well balanced.

Ninety-nine patients (66%) completed the 52-week study period. The reasons for failure to complete the study were similar across the treatment arms.

6.3 Results: Efficacy

At weeks 60-76 (treatment ended at week 52, but patients were followed until the last randomized patient completed 52 weeks of therapy), the mean change in CD4 cell counts were 147 cells, -23 cells, and 38 cells in the NVP+ddI+ZDV, NVP+ZDV, and ZDV+ddI arms, respectively.

The mean change in HIV RNA at weeks 60-76 was -1.43 logs in the NVP+ddI+ZDV arm, compared with -0.13 logs in the NVP+ZDV arm and -0.72 logs in the ZDV+ddI arm.

An analysis of the proportion of patients below a detection limit of 400 copies/mL at weeks 60-76 using the Roche Amplicor Monitor assay demonstrated that 75% (27/36) in the NVP+ddI+ZDV arm, 46% (18/39) in the ZDV+ddI arm, and 0% (0/28) in the NVP+ZDV arm had reached that goal.

Comment: The addition of ddI to NVP+ZDV appeared to result in greater increases in CD4 cell counts and decreases in HIV RNA compared to NVP+ZDV alone; however, the study was not designed or powered to determine the contribution of ddI to overall efficacy.

6.4 Results: Safety

6.4.1 Deaths and Serious Adverse Events

Three deaths were reported during the study, one in each treatment group. The causes of death were euthanasia, encephalopathy, and suicide.

Serious adverse events were reported infrequently: seven, four and eight patients in the NVP+ddI+ZDV, NVP+ZDV and ZDV+ddI arms, respectively. None of the events in the NVP+ddI+ZDV or ZDV+ddI arms appeared to be directly related to ddI.

6.4.2 All Adverse Events

One patient in each treatment arm reported peripheral neuropathy. Abnormal liver function tests, GI symptoms (nausea, vomiting, diarrhea), and rash occurred frequently but were reported with similar frequency between the treatment groups.

7.0 BMS START 2

An Open-Label, Randomized, Comparative Study of Zerit® + Videx™ + Crixivan® versus Retrovir® + Epivir™ + Crixivan® in HIV-Infected, Antiretroviral Naïve Subjects with CD4 Cell Counts of $\geq$200/mm^3 and HIV RNA Baseline Copy Number of $\geq$10,000 copies/mL.

7.1 Design

This was a 48-week, multi-center, randomized, open-label equivalence study that compared the immunologic and virologic effects of d4T+ddI+IDV versus ZDV+3TC+IDV in the treatment of antiretroviral-naïve patients who had $\geq$200 CD4 cells/mm^3 and plasma HIV RNA $\geq$10,000 copies/mL at baseline. The study was conducted between December 1996, and August 18, 1998.

The primary outcome measure was the proportion of patients with HIV RNA below the limit of assay detection (<500 copies/mL by the ( ) at weeks 18-24 and 40-48. HIV RNA samples <500 copies/mL were re-tested using , with a reported detection limit of 50 copies/mL. Secondary efficacy endpoints included changes from baseline in HIV RNA levels and CD4 cell counts at weeks 24 and 48.

START 2 was conducted and analyzed by a contract research organization on behalf of the sponsor. The sponsor submitted both interim (weeks 18-24) and end-of-study (week 48) analyses. A full study report, including virologic, immunologic and safety data were submitted along with CRF's for patients who discontinued study medication, experienced a serious adverse event or died.

Comment: Please see section 6.1 for an explanation of the acceptability of the assay. The is unapproved, and no data to validate the lower limit if detection of 50 copies/mL was submitted.

7.2 Patient Demographics and Disposition

A total of 205 patients entered the study and received study medication. Study patients were male (84.5%) and Caucasian (60%) with a mean age of 36 years. At baseline, patients had a mean CD4 cell count of 436 cells/mm^3 and mean HIV RNA of 4.5 log_{10} copies/mL.

Comment: The treatment arms were well balanced with regard to demographic and disease characteristics.

Of the 205 patients who entered the study, 122 (60%) completed all 48 weeks of study medications, 64 (63%) in the d4T+ddI+IDV arm and 58 (56%) in the ZDV+3TC+IDV arm. Adverse events and loss to follow-up accounted for the major reasons for study drug discontinuations and were equally distributed between the study groups. Two deaths were reported in the d4T+ddI+IDV arm.

7.3 Results: Efficacy

Table 4 presents the analysis of the primary endpoint: the proportion of patients below the detection limit of the assay (1200 copies/mL).

Table 4. Proportion of patients below detection limits, N(%)

	d4T+ddI+IDV (n=102)	ZDV+3TC+IDV (n=103)
Weeks 18-24	70 (69)	61 (59)
Weeks 40-48	64 (63)	50 (49)

At week 48, the mean increases in CD4 cell counts in the d4T+ddI+IDV and ZDV+3TC+IDV arms were 236 and 156 cells/mm^3, respectively.

Comment: The efficacy data support the conclusion that both three-drug regimens produce similar and durable antiviral and immunologic activity.

7.4 Results: Safety

7.4.1 Deaths and Serious Adverse Events

Two deaths were reported in patients treated with d4T+ddI+IDV. One death was due to pancreatitis, sepsis, and circulatory collapse attributed to ddI and d4T. The other death was due to heart failure.

A total of 17 patients reported serious adverse events, nine in the d4T+ddI+IDV arm and eight in the ZDV+3TC+IDV arm. The events reported in the d4T+ddI+IDV arm included pneumonia and chest pain, kidney stones, depression, seizures, appendicitis, fatty liver infiltrates with lactic acidosis, fatal heart failure and fatal pancreatitis. Kidney stones, anemia, dehydration due to gastroenteritis, diarrhea, hyperglycemia and hypertriglyceridemia, cocaine abuse, and headache were the event reported by patients in the ZDV+3TC+IDV arm.

Comment: Narratives for each patient were included in the study report. Fatty liver infiltrates with lactic acidosis has been reported with nucleoside analogues and all carry a warning in their labeling.

7.4.3 Adverse Events Leading to Discontinuation of Study Medication

Thirty-eight patients, 19 in each arm, discontinued study medication during the study due to an adverse event. Eight patients in the d4T+ddI+IDV arm discontinued study medication due to elevated liver function tests with or without other gastrointestinal symptoms such as nausea, vomiting, or abdominal pain, compared to one patient in the ZDV+3TC+IDV arm.

In the ZDV+3TC+IDV arm, gastrointestinal complaints, including nausea, vomiting, diarrhea, abdominal bloating, and abdominal pain were cited as the reason for study medication discontinuation by 11 patients compared to four in the d4T+ddI+IDV arm.

One d4T+ddI+IDV-treated patient discontinued due to peripheral neuropathy. Two patients in the d4T+ddI+IDV arm discontinued due to pancreatitis; one of these patients died. (See section 7.4.1).

7.4.4 Adverse Clinical and Laboratory Events

There were no statistically significant differences between treatment groups in the types of frequency of adverse events. Peripheral neuropathy (3 vs 0), parasthesias, fever (4 vs 0), dry skin (22 vs 12), pruritis (18 vs 7), and parasthesia (13 vs 8), occurred more frequently in patients treated with d4T+ddI+IDV compared to treatment with ZDV+3TC+IDV.

Table 5 presents liver function test abnormalities by treatment group. Significant (Grade 3/4) elevations in bilirubin and GGT occurred more frequently in patients treated with d4T+ddI+IDV.

Table 5. Liver function test abnormalities

	d4T+ddI+IDV	ZDV+3TC+IDV
Bilirubin		
-All	68%	55%
-Grade 3-4[1]	16%	8%
AST		
-All	53%	20%
-Grade 3-4[2]	7%	7%
ALT		
-All	50%	18%
-Grade 3-4	8%	5%
GGT		
-All	28%	12%
-Grade 3-4	5%	2%

Source: Adapted from Start 2 Final Study report, Table S08, January 13, 1999.
1. Grade 3 = 2.6-5 x ULN, Grade 4 = >5.1 x ULN
2. Grade 3 = >5-10 x ULN, Grade 4 = >10.1 x ULN

Comment: Pancreatitis, including one death, abnormalities in liver function, and peripheral neuropathy continue to be important adverse events associated with the use of ddI in combination with d4T.

8.0 Overall Summary of Safety and Efficacy

Five clinical trials, ACTG 241, ACTG 261, [redacted] 1046, BMS 053, and BMS START 2 were submitted to support amending the ddI labeling to include virologic and immunologic and safety data about the use of ddI in combination with other antiretroviral agents.

ACTG 241 demonstrated that the addition of NVP to ddI+ZDV produced marginally greater increases in CD4 cell counts and decreases in HIV RNA that were sustained over time compared to treatment with ZDV+ddI. A durable antiviral response was not documented in either treatment arm, thus precluding conclusions about the efficacy of ddI

in these combinations. Grade 3 and 4 abnormal hepatic, pancreatic, and hematologic values were reported with similar frequency between the two treatment groups.

ACTG 261 demonstrated that the triple combination of DLV+ZDV+ddI resulted in better mean responses in CD4 cell counts and HIV RNA than the double combination of DLV+ZDV. However, this trial was not designed or powered to determine if the addition of ddI was the factor resulting in the improved efficacy of the triple combination regimen. Rash, hematologic and liver function test abnormalities were the most commonly reported adverse events in this trial and they were reported with similar frequency across the four treatment arms.

BMS 053 demonstrated that d4T and ZDV when combined with ddI resulted in similar antiviral and immunologic activity after six months of treatment. Since ddI was in both treatment regimens, it was also not possible to assess ddI's specific contribution to efficacy. Peripheral neuropathy occurred twice as frequently in patients treated with d4T+ddI indicating the potential for increased risk of this overlapping toxicity when ddI and d4T are used together. Elevated liver function tests were reported by many patients, but with similar frequency between treatment groups.

In study — 1046, the addition of ddI to the combination of NVP+ZDV produced an increase in CD4 cell counts and a small decrease in HIV RNA levels that were greater than NVP+ZDV or ZDV+ddI. Because of the small number of patients available at weeks 60-76, it was not possible to determine if ddI influenced the long-term efficacy results. Peripheral neuropathy was reported infrequently, one patient in each treatment group. Abnormal liver function tests, GI symptoms (nausea, vomiting, diarrhea), and rash occurred frequently but were reported with similar frequency between the three treatment groups.

The results of START 2 demonstrated that d4T+ddI+IDV, when compared to an accepted combination of antiretroviral agents, ZDV+3TC+IDV, resulted in similar antiviral and immunologic activity after 48 weeks of treatment. Because there was more than one substitution of medications between the study arms, it was not possible to determine ddI's direct contribution to efficacy. Significantly more clinically relevant LFT abnormalities were observed in patients treated with d4T+ddI supports inclusion of this information in the label. The occurrence of peripheral neuropathy and the death due to pancreatitis in the d4T+ddI arm supports retaining these adverse events in the ddI label.

The data in the supplement support the conclusion that ddI is an acceptable component of combination therapy for the treatment of patients with HIV-1 infection, and support the use of ddI in combination with other approved antiretroviral agents for the treatment of HIV-1 infection. The potential for increased risk of abnormalities in liver function tests and peripheral neuropathy when ddI and d4T are used in combination were identified during the review of these studies and will be described in the revised label.

9.0 Labeling

The applicant submitted proposed labeling that provided selected data from all five studies, but failed to include either safety data or other information about the deficiencies of each trial. The applicant was informed that because of the problems associated with each trial, it would be difficult to accurately describe all the trials in the labeling. A revised draft label that included a revision to the indication section to provide for combination therapy, removal of descriptions of these clinical trials, revisions to the safety, and dosage and administration sections was forwarded to the sponsor. Labeling returned by the sponsor on July 1, 1999, adequately addressed the issues raised by the division by providing only a general description of the START 2 trial as well as information about the increased risk of peripheral neuropathy, abnormal liver function tests and the death due to pancreatitis in patients who received ddI+d4T. These revisions were determined to be acceptable.

10.0 Recommended Regulatory Action

Based on a review of the data submitted this supplement should be approved.

/S/

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Senior Clinical Analyst

Concurrence:
HFD-530/DivDir/HJolson 1/26/99
HFD-530/TLMO/TCvetkovich 1/23/99

CC:
HFD-530/DepDir/DBirnkrant
HFD-530/NDAs 20-154, 20-155, 20-164
HFD-530/Division File
HFD-725/Stats/MElashoff
HFD-530/Micro/LMishra/LConnors
HFD-530/BioPharm/KReynolds
HFD-530/MO/JToerner
HFD-530/PM/MTruffa
HFD-530/MO/RFleischer

Attachment A

64 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.