CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-705 / S-008

MEDICAL REVIEW

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 5-14-2001

FROM: Jeffrey S. Murray M.D., M.P.H.
Division of Antiviral Drug Products

SUBJECT: Group Leader's memorandum for NDA 20-705/S-008, Traditional Approval

TO: HFD-530/Division files

I. Recommendations

A. Approvability
I fully concur with the reviews and conclusions prepared by Dr. Linda Lewis, medical officer, and Dr. Thomas Hammerstrom, statistical reviewer. As both have stated, the results of two pivotal and several smaller supportive studies demonstrate the efficacy of Rescriptor (delavirdine) when used in combination with at least two other active antiretroviral drugs. This activity was demonstrated through 52 weeks of treatment. Therefore, traditional approval should be granted for delavirdine.

B. Labeling and Risk Management
The Usage section of the label includes statements that reflect a degree of uncertainty regarding how well a delavirdine-containing antiretroviral regimen compares to other "preferred" (according to current treatment guidelines) triple-drug regimens for the initial treatment of HIV. This uncertainty stems from the design of the two pivotal studies, 0021 Part II and 0013C, in which regimens containing delavirdine plus two nucleoside reverse transcriptase inhibitors were (NRTIs) compared to 2 NRTIs. These studies were conducted at a time when HIV management was rapidly evolving; the use of dual NRTI therapy has since fallen out of favor. Although the studies unambiguously showed that delavirdine contributed toward the antiviral activity of the regimen, we have no equivalence comparisons of delavirdine to other preferred agents when used with two NRTIs in treatment naïve populations. In addition the percentages of patients maintaining suppression of HIV RNA < 400 copies/mL through 52 weeks appeared to be relatively low in comparison to other more recent studies of similar regimens. However, studies 0021 (II) and 0013C enrolled some patients with previous experience to NRTIs. Inclusion of treatment experienced patients slightly lowered the overall response rate. In addition, there were a substantial

number of treatment discontinuations possibly related to the desire of participants to receive protease inhibitor based regimens. Such regimens were emerging as preferred regimens during the conduct of these studies. Given that discontinuations are treated as treatment failures in the Division's preferred analyses, high discontinuation rates may have unfavorably impacted the overall response rate.

No new toxicities were identified in this supplement over and above that identified in the application supporting the original accelerated approval. Rash is one of the few adverse events that can be conclusively attributed to delavirdine. Most of the time it is not treatment limiting, but infrequent to rare cases of very severe rashes, such as Stevens Johnson syndrome have been reported. All reported cases noted resolution without long-term sequelae. This adverse event has been included in product labeling since the initial approval.

Since delavirdine inhibits CYP450 3A and other CYP450 enzymes to a lesser extent, coadministration of delavirdine with other hepatically metabolized drugs may lead to important drug interactions. The new label will make the drug interactions section more reader friendly and add newly recognized drug interactions.

C. Recommendations for Phase 4 Studies

Currently, the applicant has several outstanding phase 4 commitments including the study of alternate dosing regimens (BID) and the study of delavirdine in children. In addition, since delavirdine is hepatically metabolized and inhibits its own metabolism and that of some other drugs, the division will ask the sponsor to conduct a study of delavirdine in individuals with hepatic impairment.

The applicant has previously conducted several pharmacokinetic studies with approved protease inhibitors. However, the division will also request a drug interaction study with Kaletra (ritonavir/lopinaivr), a new protease inhibitor that is likely to be used more widely in the future.

II Summary of Clinical Findings

A. Overview of Clinical Program

In 1997 Pharmacia & Upjohn obtained approval of RESCRIPTOR (delavirdine, DLV) 400 mg tid for the treatment of HIV infection under subpart H regulations (accelerated approval). DLV was the second nonnucleoside reverse transcriptase inhibitor NNRTI) to be approved by FDA. The initial approval was based on safety data from approximately 2,000 patients and efficacy data from two studies (0021 and ACTG 261) that demonstrated DLV's antiviral activity in combination with one or more antiretroviral drugs. In study 0021, HIV RNA reductions were greater among patients randomized to zidovudine (ZDV) + DLV than to those randomized to ZDV alone. In ACTG 261 patients randomized to

ZDV + didanosine (ddI) + DLV had greater reductions in HIV RNA than those randomized to ZDV + ddI. CD4 increases were not significantly greater on the DLV arms in these studies. In addition, a third study that compared DLV+ddI to ddI alone showed no difference in clinical disease progression. However, it is now known that two-drug therapy regimens including a NNRTI are doomed to failure because of the rapid emergence of resistance to the NNRTI. Consequently, in pursuit of traditional approval, the sponsor conducted trials of DLV in triple combination regimens in primarily naïve patients and in other "novel" three- and four-drug regimens with protease inhibitors for naïve and treatment experienced individuals.

Shortly after the data had been analyzed from the two principal phase 3 studies included in this current NDA supplement, Pharmacia & Upjohn sold DLV to Agouron, which is now owned by Pfizer.

B. Efficacy

The principal studies supporting traditional approval are study 0021-Part II and study 0013C. The primary objective of these studies was to assess the antiviral activity of DLV 400 mg tid as part of triple drug antiretroviral therapy in HIV infected patients with limited or no antiretroviral experience. In both studies the control arm consisted of dual nucleoside reverse transcriptase inhibitor (NRTI) therapy, which was acceptable at the time, but is currently not recommended. In both studies DLV 400 mg tid plus two NRTI was superior to two NRTI alone with respect to the proportion of patients sustaining HIV RNA levels < 400 copies through 52 weeks of therapy. The results were robustly statistically significant. In addition CD4 increases were also greater among patients receiving DLV + 2 NRTI than those receiving only 2 NRTI. Refer to the reviews prepared by Drs. Lewis and Hammerstrom for details on treatment responses.

The efficacy of DLV was further supported by ACTG 359, a six-arm, modified factorial study that allowed for a comparison of DLV vs. placebo on a background of two protease inhibitors with or without adefovir (an investigational nucleotide analogue).

Another study performed by ACTG compared the strategy of switching to delavirdine vs. continuing lamivudine when initiating a protease inhibitor based regimen in patients with previous NRTI experience. Those randomized to the delavirdine arm had a better virologic response rate than those continuing lamivudine.

B. Safety

This supplement contains safety data on over 2000 people receiving DLV for a mean duration of approximately 40-48 weeks. Overall the total safety database

included in the original and supplemental NDAs totals approximately 6000 individuals. No new safety concerns were identified in this supplement. The major toxicity of DLV is rash, which is usually mild to moderate in severity. Four cases of Stevens Johnson Syndrome were reported among patients receiving DLV in clinical trials. Three cases of Stevens Johnson Syndrome were identified in postmarketing reports, one of these involved concomitant use of nevirapine. One case had been reported at the time of initial approval. Labeling will be updated to include somewhat more detailed information on the frequency and severity of rash.

D. Dosing

The originally approved dose of DLV is 400 mg tid. This was the dose used in the pivotal studies included in this traditional approval supplement. Smaller studies have investigated a [redacted] dosing regimen of delavirdine; However, [redacted]

E. Special Populations

Although the majority of patients studied in this supplement and the original NDA were white males (paralleling the profile of the U.S. HIV epidemic at the time), women and people of color were included in the submitted studies. No gender or racial issues with respect to efficacy or safety could be identified.

Studies of delavirdine in children are to be addressed as an outstanding phase 4 commitment. The ability to conduct these studies has been limited in part by the previous sponsor's inability to develop a palatable pediatric formulation. A [redacted]

In that no [redacted] has been granted, this supplement did not trigger the pediatric rule.

Jeffrey S. Murray M.D., M.P.H.

Medical Officer Review
NDA 20-705, SE7-008

Date of submission: July 12, 2000
Date received: July 17, 2000
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Final Review: May 16, 2001

Applicant: Agouron Pharmaceuticals, Inc.
10350 North Torrey Pines Road
La Jolla, CA 92037-1020

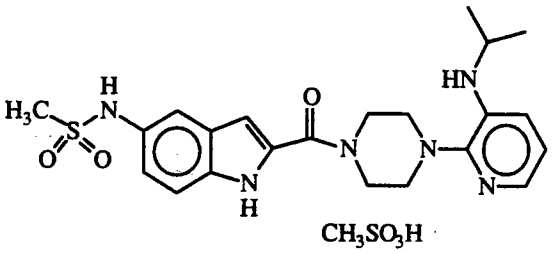
Drug name: Delavirdine mesylate

Trade name: Rescriptor

Formulation: 100 and 200 mg capsules

Proposed indication: Treatment of HIV infection in adults

Chemical structure:



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Executive Summary

Recommendations

Recommendations on Approvability:
Traditional approval should be granted for delavirdine mesylate tablets. This sNDA provides clear evidence of the antiretroviral activity of delavirdine when used in combination with at least 2 nucleoside reverse transcriptase inhibitors (NRTIs). Both of the pivotal trials were terminated early by their respective Data and Safety Monitoring Boards when interim analyses of the efficacy data revealed significant superiority of the 3-drug regimens containing delavirdine plus 2 NRTIs compared to the dual NRTI regimens. The Division's review of the data confirms the statistically significant and clinically relevant benefit conferred by delavirdine in these studies. There are no new or unexpected safety issues raised by the data in this submission to preclude traditional approval.

Recommendations on Phase 4 Studies and Risk Management Steps:
The current sponsor has been reminded of Phase 4 commitments agreed upon by Pharmacia & Upjohn (the previous sponsor) at the time of delavirdine's original approval in 1997. These include investigating the PK and optimal dosing of [redacted] and consideration of a BID dosing regimen. New Phase 4 commitments agreed upon during this review process include evaluation of delavirdine's P[redacted] and further investigation of appropriate dosing in combination with ritonavir and lopinavir/ritonavir.

Risk management has been addressed with labeling changes that fall into 3 main categories: appropriate drug usage, documentation of adverse events and improved information regarding drug-drug interactions. The review team had the difficult task of trying to integrate the statistically valid study results showing benefit of the delavirdine-containing treatment regimens with the clinical knowledge that the comparator treatment regimens are now considered supoptimal therapy. These studies were designed and conducted at a time when dual NRTI therapy was rapidly being replaced by regimens containing a protease inhibitor (PI). A significant number of patients discontinued their assigned study treatment because of a desire to pursue more aggressive therapy. Compared to the results of more recent 3-drug antiretroviral combinations the proportion of patients receiving delavirdine who achieved and maintained an undetectable viral load was relatively low. While cross-study comparisons are generally not wise, more recent studies evaluating other 3-drug combinations appear to achieve better results. This should make practitioners cautious in the selection of delavirdine as the anchor of a 3-drug regimen for initial therapy of HIV. The review team has included in the label's Indications and Usage section some information that would make a practitioner aware of the difficulties in extrapolating results of these older studies to current standard therapy recommendations.

The most significant adverse event encountered with use of delavirdine was drug-associated rash. This was noted at the time of the original NDA and rash was highlighted in the earlier label. While severe rash occurs rarely in patients receiving delavirdine, it has been reported in both clinical trials and spontaneous adverse event reports. The review team felt that it was appropriate to strengthen the precautions regarding frequency and severity of rash related to delavirdine use and has included additional information in the text of the label and a new table. No new drug-related toxicity was identified in the studies presented in this submission.

This submission contained several smaller studies investigating the use of delavirdine with other antiretroviral drugs including PIs. Data from the sNDA submission provided information that allowed revisions of the label including new PK data and expanded drug-drug interaction data. The Biopharmaceutics/Clinical Pharmacology reviewer confirmed recommendations for altering doses of some of the drugs that might be used in combination with delavirdine. The clinical pharmacology data has been presented in a revised format that the review team believes will be more readable than the original label.

Summary of Clinical Findings

Brief Overview of Clinical Program:
Delavirdine was originally granted accelerated approval in March, 1997, based on the results of 3 large trials. The NDA initially presented results from 2 studies: Study 0021, a dose ranging study that compared delavirdine plus zidovudine to zidovudine alone, and Study 0017, a large study comparing delavirdine plus didanosine to didanosine alone. While Study 0021 demonstrated the superiority of the 2-drug regimen compared to monotherapy in terms of reduced HIV-1 RNA levels after 24 weeks of treatment, Study 0017 failed to confirm that finding. At the time an Advisory Committee was split evenly on whether to recommend approval and data from a third study ACTG 261 was felt to be critical. ACTG 261 was a 4 arm study including delavirdine in 3 arms, one of which included delavirdine plus zidovudine and didanosine. Preliminary study results (submitted as a major amendment to the original NDA) revealed that the patients randomized to this 3-drug arm had greater improvements in both HIV-1 RNA and CD4 cell counts. On the basis of all 3 studies' results accelerated approval was granted.

Pharmacia & Upjohn then undertook a series of confirmatory trials. Study 0013B, a large clinical endpoint study comparing delavirdine plus zidovudine to zidovudine alone, was later modified to Study 0013C, evaluating delavirdine plus zidovudine and another NRTI (either didanosine, lamivudine or zalcitabine) compared to zidovudine and another NRTI using long-term viral suppression as its endpoint. Study 0021 Part II compared the 3-drug combination of delavirdine plus zidovudine plus lamivudine to zidovudine plus lamivudine and zidovudine plus delavirdine. Studies 0021 Part II and 0013C became the pivotal trials for this sNDA submission and Study 0013B and several smaller studies investigating delavirdine in different 3 and 4-drug combinations were submitted as supporting evidence of activity and safety. The

supportive studies were intended to identify drug interactions and appropriate regimens in combination with the PIs.

Efficacy:
As stated above, the large studies designed to confirm the activity and clinical benefit of delavirdine were conducted at a time when the management of HIV infection was rapidly evolving to multidrug regimens and real-time viral load monitoring. Both studies lost a number of subjects as patients and physicians decided that the studies' 2-drug regimens might not represent optimal care. In spite of this, however, interim analyses of the efficacy data for both studies by their respective Data and Safety Monitoring Boards revealed clear superiority of the delavirdine-containing 3-drug treatment arms in both studies and it was recommended that the studies be closed prematurely. FDA analysis of the data confirms that the delavirdine plus 2 NRTIs conferred significant benefit in terms of long-term suppression of HIV-1 RNA and improvements in CD4 cell counts. The proportion of patients receiving delavirdine who achieved and maintained a viral load < 400 copies/mL after 52 weeks of therapy was 45% in Study 0021 Part II and 29% in Study 0013C. In both studies, the patients who had received some prior therapy with NRTIs (16% of patients enrolled in 0021 Part II and 36% in Study 0013C) were significantly less likely to achieve long-term suppression of HIV-1 RNA, as would be expected.

In ACTG 359, a complex study using a 2 x 3 factorial design, delavirdine in combination with 2 PIs was compared to adefovir in similar PI regimens. In this case, the delavirdine-containing regimens appeared to have superior activity compared to the adefovir-containing regimens. Also in ACTG 370, a study investigating switching to delavirdine compared to continuing lamividine in NRTI-experienced patients beginning an indinavir/PI based regimen, the delavirdine regimen appeared to perform better at 44/48 weeks of therapy although there was no apparent benefit at 20/24 weeks. Most of the other supportive studies were too small to provide statistically meaningful results in favor of delavirdine-containing regimens. Many of these studies did suggest that the delavirdine treatment groups performed similarly to the comparator treatment groups.

Safety:
No new safety concerns were raised in reviewing the data submitted for this sNDA which included safety assessments on 2220 patients, 707 of whom received blinded delavirdine in the pivotal trials. The only adverse event significantly associated with delavirdine use was rash. While there were no reports of Grade 4 rash (erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis) among patients enrolled in the pivotal trials, there were a handful of reports of severe rash in the supportive studies and in spontaneous adverse event reports. All of these events resolved with discontinuation of delavirdine and none resulted in long-term sequelae. Other frequently encountered adverse events such as headache, nausea and fatigue were balanced across treatment groups. No specific laboratory abnormalities were associated with delavirdine use. There did seem to be some study-specific adverse events such as increased diarrhea in Study 0073B in which delavirdine was used in

combination with nelfinavir and didanosine and hyperlipidemia in ACTG 359 in which delavirdine was combined with ritonavir, saquinavir and nelfinavir. These types of events that were seen in the smaller studies were more likely attributed to other antiretroviral drugs included in the regimens.

Dosing:
The pivotal trials were conducted using 400 mg TID of delavirdine, the dose originally approved. None of the data presented suggested that this was an unacceptable dose in terms of efficacy, safety or tolerability. Three of the supportive studies (ACTG 359, Study 0073B and Study 0081) investigated a dose of 600 mg BID in combination with PIs. (16 to 24 weeks) and the data was incomplete. The alternate dose was not formally reviewed

Special Populations:
No specific differences were identified in minority subjects or women enrolled in the clinical trials, although, the numbers were relatively small. Numbers may be too small, however, to detect subtle differences in drug efficacy or toxicity. Similarly, it is impossible to determine whether elderly patients respond to DLV in the same way as younger subjects.

Clinical Review

1. Introduction and Background

Delavirdine mesylate (Rescriptor) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) active against HIV-1. It has been studied for use in the treatment of HIV-1 disease in adult patients over the last several years. Over the course of delavirdine (DLV) development, the standard of care in the treatment of HIV has evolved from single or dual drug therapy to multiple-drug regimens including members of different classes of antiretroviral agents. The studies submitted to support traditional approval of DLV reflect these changes in drug therapy. The studies originally designed as the long-term pivotal trials (0021 Part 2 and 0013C) were terminated early as the Data and Safety Monitoring Boards determined that the dual nucleoside reverse transcriptase inhibitor (NRTI) therapy comparator arms were significantly less effective than the arms containing DLV plus dual NRTIs. Both studies suffered from relatively large numbers of patients who discontinued prematurely because of interest in the protease inhibitors (PIs). Studies evaluating DLV in combination with PIs were initiated (Studies 0061, 0063, 0070, 0073A and 0073B, 0081, ACTG 359 and ACTG 370) and are included as supportive evidence of activity and to attempt to define an appropriate role for its use in a highly active multi-drug regimen. A single clinical endpoint study (Study 0013B) has also been included in support of the sNDA although changes in standard HIV care made this study impossible to complete without significant numbers of patient discontinuations. It provides information useful primarily in assessing DLV safety.

The initial NDA for DLV was submitted by Pharmacia & Upjohn and was granted accelerated approval by the FDA on April 4, 1997. This accelerated approval was based on changes in surrogate markers through 24 weeks in 2 large clinical trials. Results of these studies were discussed in detail at an FDA advisory committee meeting held in November, 1996. As required under the provisions of the accelerated approval process and to comply with their Phase 4 commitments, Pharmacia & Upjohn undertook a number of clinical trials designed to confirm long-term efficacy of DLV and to clarify the potential role of DLV in combination with PIs and in patients with more advanced disease. These studies were completed under Pharmacia and Upjohn sponsorship and plans were discussed for submission of the sNDA for traditional approval. On January 1, 2000, worldwide marketing rights for DLV were transferred to Agouron Pharmaceuticals, Inc. Agouron has re-analyzed the study data according to guidelines suggested in sponsor-FDA communications and now submits the sNDA for consideration. It must be noted that while Agouron is responsible for data analysis and submitting the sNDA for DLV, the company was not responsible for the design or conduct of the clinical trials.

Following U.S. approval in 1997, DLV has been approved for marketing in a number of other countries including Argentina, Aruba, Australia, Brazil, Canada, Chile, Columbia, Ecuador, Jamaica, Japan, Mexico, Peru, and Trinidad and Tobago. A marketing

Agouron Pharmaceuticals has made available financial disclosure statement summaries provided to them by Pharmacia & Upjohn. Access to financial disclosure information was a difficult issue in the transfer of DLV to Agouron. This information was not required and, therefore, had not been collected at the time the studies were conducted. After requests from Agouron, Pharmacia & Upjohn sent letters of inquiry to the physicians involved in the pivotal trials requesting financial disclosure information. Response rates were relatively poor and a significant number of inquiry letters were returned undeliverable. The summary information available indicates only 1 physician who had received significant compensation from Pharmacia & Upjohn. This is unlikely to impact the results of these multi-center trials.

2. Relevant Reviews from Other Disciplines

2.1. Chemistry

No new chemistry and manufacturing data was submitted with this sNDA. Please refer to the original NDA CMC review for background information.

2.2. Pharmacology/Toxicology

No new pharmacotoxicology data was submitted with this sNDA. Please refer to the original NDA pharm/tox review.

During review of the original NDA, it was noted that one of the toxicities identified in animal studies was vasculitis of small and medium size arteries, including the coronary arteries. This animal toxicity influenced the doses that were subsequently studied in humans. Although the mechanism of this toxicity, seen in 2 species other than humans, has not been elucidated, no significant vasculitic events have been associated with use of DLV in humans. The rash commonly seen in patients receiving DLV does not appear to be associated with vasculitis.

2.3. Microbiology

No new microbiology data was submitted with this sNDA. Dr. Narayana Battula, the Microbiology reviewer, requested that the sponsor provide updated information regarding the development of resistance to DLV and cross-resistance with other NNRTIs for inclusion in the package insert. This information was received late in the review cycle and consisted of previously published journal articles and a review of data submitted with the original NDA.

3. Pharmacokinetics and Pharmacodynamics

The initial pharmacokinetic (PK) evaluation and dose selection for DLV was reviewed in the original NDA. Several of the supportive studies submitted in support of this sNDA include PK data regarding DLV in combination with other antiretroviral agents and help

to define the extent of drug interactions with some of the PIs. These studies were reviewed in detail by Dr. Jenny Zheng, the Biopharmaceutics/Pharmacology reviewer. Please refer to her review for a more comprehensive assessment of these interactions.

In brief, the dose of DLV being evaluated in the pivotal trials is the currently approved dose of 400 mg TID. It is now known that DLV can act as a PK enhancer for some drugs and is in turn affected by co-administration with some of the PIs. These interactions have been evaluated in some of the supportive studies included in this submission. Study 0063 reveals that concomitant administration of DLV increased exposure to indinavir (IDV) while there was no effect of IDV on DLV exposure. Study 0073A confirmed results of an earlier study showing that DLV both increased exposure to nelfinavir (NFV) and prolonged its half-life and simultaneously decreased concentrations of NFV's active metabolite while NFV decreased DLV exposure by 30-35%. Study 0081 evaluated a dose of 600 mg DLV BID in combination with saquinavir soft gel capsules (SQV-SGC). This study demonstrated that this dose of DLV inhibited the clearance of SQV-SGC resulting in increases in SQV exposure without alteration in DLV's PK profile. Some of these studies provide the rationale for recommending dose adjustments of some PI's when given in combination with DLV.

Study 0061, which was included in the Pharmacology data submission but not the clinical data, evaluated the interaction with ritonavir (RTV) in HIV-infected patients. The sponsor notes that in this study concomitant administration of DLV and RTV resulted in increases in RTV concentrations. Dr. Zheng noted that many of the subjects in this study exhibited an unusual PK profile with markedly delayed peak concentrations of DLV and RTV making interpretations of the data difficult. The sponsor attributed this phenomenon to consumption of a high fat breakfast prior to PK sampling in some, but not all, of the subjects in the study.

Additional drug interactions are being investigated and the BID regimen of DLV is being further evaluated in on-going clinical trials that may be the subject of future supplements.

4. Description of Data Sources

4.1. Primary data

This sNDA contains clinical data from 10 trials conducted with DLV, including 2 large pivotal trials and 8 supportive studies. The submission consists of 138 volumes of study documents and electronic datasets containing Sections 11 and 12, the Case Report Tabulations and Case Report Forms. Clinical efficacy and safety data from the 2 pivotal studies, 0021 Part II and 0013C, and pharmacokinetic data from studies 0061, 0063, 0070, 0073A and 0081 were provided in SAS transport file format on CD-ROM. Case Report Forms for the pivotal trials were submitted as viewable PDF electronic documents on CD-ROM.

The clinical studies submitted include 2 large, controlled, efficacy studies and 8 supportive studies. Agouron divides these studies into 4 categories for purposes of

reporting. Group I includes the 2 pivotal trials. Study 0021 Part II investigated long-term efficacy (48 weeks) of triple therapy with DLV in combination with zidovudine (ZDV) + lamivudine (3TC) compared to ZDV + 3TC or ZDV + DLV in patients with limited or no prior antiretroviral therapy (ART). Planned enrollment was 480 subjects with 160 in each arm but the study was terminated early and actual enrollment was 373 subjects. Study 0013C was very similar in design. It also investigated long-term efficacy (48 weeks) of triple therapy with DLV but in combination with ZDV + ddX (a dideoxynucleoside, either didanosine [ddI], zalcitabine [ddC] or 3TC) compared to ZDV + ddX in patients with limited or no prior ART. Planned enrollment was 300 patients with 150 in each arm but actual enrollment reached 345 before this study was also halted prematurely.

Group II includes 2 controlled supportive studies, ACTG 359 and ACTG 370, which evaluated the use of DLV in combination with 1 or 2 PIs in patients with moderate to extensive prior ART use. ACTG 359 enrolled 277 patients into a randomized, partially-blinded, factorial design study with 6 arms comparing SQV-SGC + RTV + (adefovir [ADV] and/or DLV) and SQV-SGC + NFV + (ADV and/or DLV). ACTG 370 enrolled 159 patients in a randomized, open-label study in which 3TC-experienced patients either continued 3TC or switched to DLV in combination with IDV + ZDV or stavudine (d4T).

The Group III studies include 5 smaller supportive trials (Studies 0063, 0073A, 0073B, 0074, and 0081) which investigate the role of DLV in combination with a PI and 1 or more NRTIs in patients with limited or no prior ART. These studies provide additional PK data and information regarding safety and potentially important drug interactions. As noted, some of these studies use a BID dosing regimen for DLV in combination with other drugs presumed to act as pharmacologic enhancers.

Group IV includes Study 0013B, a controlled, clinical endpoint trial, that evaluated monotherapy with ZDV compared to dual therapy with DLV + ZDV in subjects with no prior treatment or experience with ZDV only.

4.2. Post-marketing experience

DLV has been marketed in the U.S. and many other countries since its approval in 1997. Through September 23, 1999, Pharmacia & Upjohn had received spontaneous reports of 273 adverse events in 108 patients. The adverse event profile in these spontaneous reports parallels that reported from the clinical trials. These adverse events will be summarized in more detail in Section 7.6 in the Integrated Review of Safety. Delavirdine has not been withdrawn from marketing in any country.

5. Review Methods

This clinical review is based on evaluation of Section 8 (clinical data) which includes study reports for the individual pivotal and supportive trials, the sponsor's Integrated Summary of Efficacy and Integrated Summary of Safety. The sponsor's conclusions

regarding safety and efficacy were confirmed by independent FDA analysis of the data. Dr. Thomas Hammerstrom performed the statistical analysis confirming the primary endpoint and some secondary endpoints in the pivotal trials. Pharmacokinetic data were reviewed and conclusions confirmed by Dr. Jenny Zheng as noted above. This MO reviewed study design, patient demographics, adverse events and laboratory safety monitoring data and reviewed the efficacy results and Dr. Hammerstrom's analysis using the JMP Statistical Discovery software. In this review, tables that were derived from the sponsor's presentation of the data are cited as to source in the table footnotes while those that are derived from reviewer-generated results are not referenced.

6. Review of Efficacy

6.1. Pivotal Trial – 0021 Part II

6.1.1. Study Design

Study 0021 Part II was designed as a randomized, placebo-controlled trial comparing the long-term virologic efficacy of the combinations ZDV + 3TC, ZDV + DLV and ZDV + 3TC + DLV given over 48 weeks. Study 0021 was originally designed as a comparison of ZDV vs. DLV + ZDV and results of the first 24 weeks of the study were reported in the original NDA. Because of the evolution of standard therapy for HIV the study was amended to the 2-drug vs. 3-drug design and new patients were enrolled in Part II. Some patients from Part I were transitioned into the amended study and described in a separate report. The changes that make up Part II were introduced in Study Amendment 9 dated 3/7/96. Several significant revisions to Study 0021 Part II were introduced with Study Amendment 10 dated 8/13/97 and Amendment 12 dated 1/15/98. The study was terminated by Amendment 13 dated 6/11/98. This study report summarizes only the patients who were enrolled and followed in Study 0021 Part II.

Study 0021 Part II initially planned to enroll 150 subjects per treatment arm in the analysis with provisions for replacing dropouts. This was revised to 160 total subjects per arm (no replacement) in Amendment 10. Major inclusion criteria included: male or female subjects with documented HIV infection, 14 years or older, CD4 cell count of 200-500 cells/mm3 at the time of screening, acceptable baseline organ function as measured by screening laboratory assays (ACTG severity score $\leq$ Grade 1), Karnofsky performance status $\geq$ 80, acceptable medical history and physical exam, EKG and chest X-ray at the time of screening. Women of child-bearing potential must have had a negative pregnancy test within 15 days of beginning study and had to agree to use an effective method of birth control. Major protocol exclusions included: greater than 6 months of prior ZDV use, prior therapy with any other NRTIs or NNRTIs, participation in clinical trials of other investigational agents or use of HIV-1 vaccines within 21 days of beginning the study, use of rifampin, rifabutin, astemizole, or terfinadine within 21 days of study, intolerance to ZDV, Grade 2 or worse peripheral neuropathy,

history of clinically significant CNS, muscle or psychiatric disorder, clinically significant active medical problems including opportunistic infections or malignancy (including TB sensitive to rifampin), history of pancreatitis, active substance abuse, impaired renal function, and prior PI experience within 21 days of study.

Patients were screened within 7 to 35 days prior to enrollment and if all criteria were met were seen again 2 to 7 days prior to beginning randomized study drug. Patients were randomized (1:1:1) and stratified according to prior ZDV experience. Baseline laboratory tests and a physical exam were performed on Day 1 prior to the first dose of study drug. The first dose of study medications was given in the clinic. Blinded DLV or placebo was to be taken as 4 100-mg tablets p.o. TID, with meals or on an empty stomach, one hour before or after antacids and could be given with ZDV and 3TC. Blinded 3TC or placebo was to be taken as 1 150-mg tablet p.o. BID. All patients received ZDV 2 100-mg capsules TID.

Study subjects were seen at Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 52. The study was originally written to provide 2 years of follow-up but this was shortened to 1 year by Amendment 10. Adverse events recording, physical exam, laboratory monitoring for toxicity, and immunologic and virologic assessments of efficacy were performed at regular intervals. Safety and efficacy laboratory assays were performed at a central laboratory facility. Amendment 10 provided real-time results of viral load assays to the investigators so that these data could be used in patient management.

Investigators assessed toxicity and adverse events using the standardized ACTG Toxicity Grading Table included as an appendix to the protocol. A uniform approach to toxicity management was described, including dose modifications, treatment interruptions and discontinuations. Based on the spectrum of adverse events known to occur with the use of DLV, ZDV and 3TC, specific management procedures were identified for anemia, neutropenia, skin rash or fever, nausea, vomiting and diarrhea, elevated liver function tests (bilirubin, ALT and AST), elevated amylase or lipase, pancreatitis, peripheral neuropathy, fatigue or headache, and myositis. Patients were to discontinue therapy for any Grade 4 rash or drug-related fever and were given a rechallenge packet of study meds which included a dose escalation of DLV/placebo. Amendment 10 altered the management of all Grade 3 and 4 toxicities to include interrupting all study medications until the toxicity had resolved (maximum interruption of 30 days) and then restarting all drugs at their full dose. Amendment 10 also instructed investigators to treat through Grade 1 or 2 rashes and interrupt drug for Grade 3 rash. In the final study report it is difficult to determine which patients had some drugs interrupted or reduced and which had all drugs interrupted, although this probably has little impact on the safety analysis.

Patients were discontinued from the study at their own request or for any of the following reasons: major or life-threatening toxicity, generalized debilitation or mental incapacity, patients with viral load > 5000 copies/ml, patients with viral burden > 400 on more than one occasion were encouraged to withdraw (viral load criteria for withdrawal were specified in Amendment 11, dated 11/4/97, because of changing standards of care), subject non-compliance or major protocol violation, need for chemotherapy, or pregnancy. Study subjects were asked to return for a follow-up visit 4 weeks after early discontinuation.

6.1.2. Analysis Plan

The primary efficacy parameters defined in Study 0021 Part II originally included the average change and average change from baseline over time through 16 and 52 weeks in HIV-1 RNA PCR. Serial changes in CD4 percent and absolute numbers were evaluated and the average change in CD4 and average change from baseline over time were identified as secondary endpoints by Amendment 10. Amendment 12 added the comparison of time to virologic failure using both 400 copies/mL and 50 copies/mL as the lower limits of the HIV-1 RNA PCR assays. Other secondary endpoints included: change from baseline and average change from baseline over time in p24 and ICDp24 antigens at different timepoints, clinical changes including new or recurrent OIs, number of AIDS-defining illnesses or malignancies, time to clinical progression (new AIDS-defining illness or death) or change in Karnofsky score over time.

Adverse events and laboratory abnormalities were recorded at every study visit and included non-scheduled clinic visits. Suspected drug-related toxicities were to be correlated with PK data, clinical stage of disease and other study parameters in an attempt to better define the toxicity profile of DLV. Time to the development of rash was to be measured as a specific safety endpoint. Additional outcomes to be measured included: the incidence of all treatment-emergent and drug-related medical events and laboratory abnormalities including the subgroup of Grade 3 and Grade 4 toxicities, the incidence of and time-to-toxicity resulting in study discontinuation, the incidence of death from all causes and the maximum intensity of all adverse events for each patient. Safety was monitored by an independent Data and Safety Monitoring Board (DSMB) on a regular basis throughout the study. Study amendment 12 also provided for an interim efficacy analysis to be performed by the DSMB.

All patients reported to have taken at least 1 dose of study medications (DLV or placebo) and who returned for at least one follow-up visit were assessed for safety. All subjects randomized into the study were to be included in the intent-to-treat (ITT) analysis of the clinical and surrogate efficacy endpoints. The ITT analysis for efficacy would group subjects according to their randomized treatment arm and utilize all available follow-up data. An on-treatment analysis was also planned and included in the study report. The original analysis plan was generated by Pharmacia & Upjohn and was reported in the study's technical

report. After discussion with the Division, Agouron re-analyzed the data submitted to them in accordance with current recommendations and submitted these analyses in the sNDA's Integrated Summary of Efficacy. Consequently, there are minor differences between the results presented in the individual study reports and those in the ISE.

The primary comparison for the efficacy analysis was between the DLV + ZDV + 3TC arm and the ZDV + 3TC arm. Some of the secondary endpoint analyses evaluated both the comparison of the triple drug arm to the ZDV + 3TC arm and the comparison of the 2 dual therapy arms. Survival analysis (Kaplan-Meier analysis) evaluating the event "time to virologic failure" was used for the primary endpoint. Treatment groups were compared using the logrank test, using both HIV-1 RNA PCR values of 400 copies/mL and 50 copies/mL as the virologic response criteria. The proportion of patients with viral load below 400 copies/mL or below 50 copies/mL was determined at each study timepoint to 52 weeks. In both of these analyses the ITT analysis used the "non-completer = failure" construct to manage missing data or early discontinuation. Treatment-emergent medical/adverse events were compared between arms using the COSTART system of medically equivalent terms. In evaluating the incidence of rash, all events recorded as COSTART terms "rash", "rash maculopapular" and "urticaria" were included. Demographic variables were summarized and compared between treatment groups. All hypothesis tests were 2-sided and statistical significance was defined prior to the final analyses.

6.1.3. Efficacy in treatment of HIV in previously untreated or minimally treated adults – Study 0021 Part II

Amendment 12 of the protocol provided for an interim efficacy analysis at a time when 50% of the enrolled patients could have reached 52 weeks on study. This analysis was conducted and the results were reviewed by the DSMB on 1/22/98. At that time there was a statistically significant difference between treatment regimens favoring the triple therapy arm in terms of antiviral efficacy and time to virologic failure and the DSMB recommended closing the study. No significant safety issues contributed to the recommendation for study termination.

The study population included 373 HIV-infected subjects enrolled between 7/29/96 and 9/15/97 and all had been enrolled long enough to complete 24 weeks of therapy prior to the study termination. At the time all subjects were asked to exit the study by 3/31/98 approximately 80% of patients had participated for long enough to have completed 52 weeks of study. Most of the study subjects were male and white and relatively few had received prior therapy. Patients in the 3 arms of the study were very similar in terms of demographics and baseline HIV characteristics as is shown in Table 1 below.

Table 1: Demographics and Baseline HIV Characteristics in Study 0021 Part II

	ZDV + DLV	ZDV + 3TC	ZDV + 3TC + DLV	Total
Enrolled	125	124	124	373
Evaluable[1]	123	123	119	365
Age – mean (range)	34.3 (19-67)	36.4 (17-66)	34.4 (18-56)	35.0 (17-67)
Sex – male (%)	111 (89%)	106 (85%)	107 (86%)	324 (87%)
Race/Ethnicity (%)				
White	74 (59%)	77 (62%)	74 (60%)	225 (60%)
Black	36	26	34	96
Asian	2	1	1	4
Hispanic	11	14	13	38
Other	2	6	2	10
Prior ZDV use (%)	20 (16%)	25 (20%)	14 (11%)	59 (16%)
Baseline HIV Labs – mean (median)				
CD4 cell count	362 (363)	361 (355)	355 (338)	359 (350)
Log HIV RNA	4.38 (4.40)	4.39 (4.45)	4.53 (4.58)	4.43 (4.47)
Prior AIDS-defining illness	31 (25%)	26 (21%)	24 (19%)	81 (22%)

[1]Patients considered "evaluable" if they received at least 1 dose of study medication and had at least 1 follow-up visit.

During the course of the study many subjects withdrew from Study 0021 Part II. Reasons for discontinuation were somewhat difficult to track since the accepted criteria for leaving the study changed over time (eg., initially no viral load criteria or CD4 count criteria for withdrawal). Increasing viral load was the most common reason for subjects to leave the study prematurely, especially in the dual therapy arms. At the time of study closure, the triple therapy arm had the greatest proportion of subjects who had completed the study. There were no differences among treatment arms in the proportion of patients discontinuing study because of reaching clinical endpoints. The following table summarizes the sponsor's reporting of patient discontinuations for all reasons in Study 0021 Part II.

Table 2: Patient Disposition for Study 0021 Part II (all enrolled patients)

Reason for Discontinuation	DLV + ZDV (N = 124)	ZDV + 3TC (N = 125)	DLV + ZDV + 3TC (N = 124)	Total (N = 373)
Study course completed	16	27	48	91
New or recurrent AIDS defining illness	0	1	0	1
Medical event – serious	2	3	2	7
Medical event – non-serious	19	14	14	47
Protocol non-compliance other than entry criteria	4	0	3	7
Subject's personal request	16	12	11	39
Viral load criteria	34	39	16	89
Sponsor terminated study	3	4	6	13
Subject lost to follow-up	16	14	19	49
Other	15	10	5	30

Source: Volume 35, Technical Report Study 0021 Part II, page 75.

Time to virologic failure was the primary efficacy endpoint in the final study analysis. The sponsor's final report confirms the interim analysis finding of a significant difference in the time to virologic failure among the 3 treatment arms of the study. The 3-drug regimen of DLV + ZDV + 3TC significantly extended the time to failure compared to the ZDV + 3TC arm regardless of whether the analysis was performed using 400 copies/mL ($p=0.0001$) or 50 copies/mL ($p=0.0001$) as the limit of the HIV-1 RNA PCR assay. Comparison of the 2 dual therapy arms revealed that the ZDV + 3TC arm performed significantly better than the ZDV + DLV arm in terms of time to virologic failure ($p=0.0001$).

Analysis of the proportion of subjects below the level of quantitation of the HIV-1 RNA PCR assay at each study visit revealed that the triple therapy arm was superior to the ZDV + 3TC arm beginning at 8 weeks and maintained through 52 weeks. Again, the ZDV + 3TC arm was superior to the ZDV + DLV arm at every study visit. Table 3 below displays the sponsor's ITT analysis comparing the proportion of patients with viral load below 400 copies/mL for each treatment arm at selected study timepoints.

Table 3: Percentage of patients with HIV-1 RNA levels below quantitation (400 copies/mL), ITT analysis – Study 0021 Part II

Treatment Week	Treatment Groups					
	ZDV + 3TC (N = 124)		DLV + ZDV (N = 125)		DLV + ZDV + 3TC (N = 124)	
	S	n (%)	S	n (%)	S	n (%)
2	124	61 (49.2)	125	41 (32.8) [a]	124	58 (46.8)
4	124	73 (58.9)	125	37 (29.6) [a]	124	67 (54.0)
8	124	53 (42.7)	125	16 (12.8) [a]	124	79 (63.7) [b]
12	124	40 (32.3)	125	9 (7.2) [a]	124	80 (64.5) [b]
16	124	31 (25.0)	125	7 (5.6) [a]	124	68 (54.8) [b]
24	124	24 (19.4)	125	7 (5.6) [a]	124	64 (51.6) [b]
32	123	22 (17.9)	125	5 (4.0) [a]	124	59 (47.6) [b]
40	115	15 (13.0)	121	3 (2.5) [a]	117	56 (47.9) [b]
52	104	12 (11.5)	115	3 (2.6) [a]	105	46 (43.8) [b]

S = number of patients with samples at the stated timepoint.
[a] Comparison of ZDV + 3TC and DLV + ZDV arms with $P < 0.05$.
[b] Comparison of ZDV + 3TC and DLV + ZDV + 3TC arms with $P < 0.05$.
Source: Volume 16, Integrated Summary of Efficacy, page 85.

An additional secondary efficacy endpoint included the change in CD4 counts from baseline. This information is critically important to health care providers who might use DLV in clinical practice. Those patients remaining on study had significant increases in CD4 cell counts over baseline for the 52 week trial period. These increases were greater among subjects receiving the 3-drug regimen and were significantly lower among patients receiving the DLV + ZDV combination. Table 4 summarizes the CD4 changes from baseline at selected study timepoints for those patients remaining on study.

Table 4: Mean Change from Baseline in CD4 Cell Count – Study 0021 Part II (patients remaining on study)

Study Timepoint	DLV + ZDV		ZDV + 3TC		DLV + ZDV + 3TC	
	S	Mean Change	S	Mean Change	S	Mean Change
Baseline	124	362[1]	123	361[1]	124	355[1]
Week 12	88	30	101	73	92	75
Week 24	69	20	89	75	84	107
Week 52	34	27	55	75	57	111

S = number of patients with samples at the stated timepoint.
[1] Mean Baseline CD4

The sponsor also evaluated the differences in efficacy parameters stratified according to previous treatment experience. In this study relatively few patients

were ZDV-experienced at entry, between 11% and 20% with the triple therapy arm enrolling the lowest proportion. In all analyses the treatment naïve population mirrors the results of the entire population. The small number of treatment-experienced patients also had responses that were consistent with the larger population but were of much smaller magnitude. In this study the proportion of patients who had prior therapy who reached undetectable was about half that of patients who were treatment naïve. Subgroup analysis to assess treatment effects according to gender and race were hampered by the low numbers of minority and female participants. There did not appear to be any major discrepancies in the responses of these subgroups compared to the entire population.

In summary, the sponsor's analyses of Study 0021 Part II revealed that the triple therapy arm of DLV + ZDV + 3TC was significantly more efficacious than the ZDV + 3TC arm in terms of time to virologic failure, proportion of patients below either a limit of 400 or 50 copies/mL, magnitude of the decrease in HIV-1 RNA PCR and improvement in CD4 counts over time. It also revealed that the dual therapy arm of DLV + ZDV was less efficacious than either the triple therapy arm or the ZDV + 3TC arm.

6.2. Pivotal Trial – 0013C

6.2.1. Study Design

Study 0013C was designed as a large, multicenter, randomized, placebo-controlled trial conducted in Europe and South Africa to evaluate the safety and efficacy of triple therapy with DLV in combination with 2 nucleoside analogues compared to dual nucleoside therapy. An earlier version of the protocol, Study 0013B, compared DLV + ZDV with ZDV alone and employed clinical benefit and changes in surrogate markers as the primary efficacy parameters. As with Study 0021, Study 0013B required major revision as the standard of care in HIV therapy evolved beyond monotherapy. Patients enrolled in Study 0013B were continued on study and this study report has been submitted as supportive evidence of safety of DLV therapy. The completely redesigned Study 0013C, evaluating dual vs. triple therapy, became effective with Amendment 4 dated 3/26/96 and enrolled a new cohort of patients. No patients transitioned from Study 0013B to Study 0013C. Other major revisions include Amendment 6, dated 8/22/97, that added a virologic endpoint as a primary efficacy parameter in addition to the clinical benefit parameter and provided for reporting of HIV-1 RNA data back to investigators for clinical use, and Amendment 7, dated 7/10/98, that finalized the clinical analysis plan.

Study 0013C was conducted in HIV-1 infected patients with CD4 counts < 350 cells/mm3 and limited or no experience with antiretroviral treatment. In this trial investigators were allowed to choose what they determined was the most appropriate regimen of 2 NRTIs that included AZT + either ddI, ddC or 3TC for

each patient. Patients were then randomized to receive DLV or DLV-placebo with stratification for: (1) treatment naïve vs. prior therapy; (2) AIDS at start of study; and (3) baseline therapy. Initially the study was designed to enroll 820 subjects per treatment arm with the intention of having 490 remain on study through final analysis for clinical benefit. When the virologic endpoint was added as a primary parameter of efficacy, the sample size was revised to include 150 evaluable subjects in each arm.

Inclusion criteria included: HIV-1 infected men and women over 16 years of age, CD4 cell counts < 350 cells/mm3, less than 6 months of prior therapy with NRTIs or PIs, Karnofsky score > 70, and laboratory values less than Grade 3 on the ACTG toxicity rating scale for hemoglobin, WBC, SGOT/AST, SGPT/ALT, GGT, amylase and platelets. Additional exclusion criteria included: prior therapy with NNRTIs, current hospital admission for unresolved AIDS-defining illness, need for any prohibited medication listed in the protocol (eg., cytochrome P450 inducers or inhibitors or chemotherapy), allergy to any NRTI or piperazine, infection with HIV-2, use of interferon within 21 days of study, failure to use adequate contraception, and pregnancy or lactation.

DLV was given at a dose of 400 mg TID and doses of the NRTIs were those considered appropriate at the time the study was being conducted. Dose reductions and interruptions were recommended in the protocol for management of specific toxicities. Dose reductions for Grade 3 and 4 toxicities (except rash and anemia) were permitted. Individual study medications could be interrupted until Grade 3 or 4 toxicities returned to Grade 2 or baseline. If ≥ Grade 3 toxicity recurred more than 30 days after resumption of study medication, the subject was withdrawn from the study. Patients were to be permanently withdrawn from study for any Grade 4 rash. A procedure to interrupt study medication in patients who developed rashes of Grade 3 or less and to re-challenge them after resolution was described in the protocol.

Safety and efficacy laboratory assays were performed at a central study laboratory. Study subjects were screened up to 28 days prior to dosing and were enrolled if they met all eligibility criteria. Subjects were evaluated at Weeks 2, 4, 8, 12, 18, 24, 30, 36, 42, 48 and 54 or study termination. They were monitored with physical exams, medical history, adverse event recording, safety laboratories, HIV-1 RNA PCR, lymphocyte subset analysis and pregnancy testing at regular intervals. Patients who withdrew early from the study were to have all end-of-study procedures performed.

Patients could be withdrawn permanently from study for a variety of reasons listed in the protocol including: patient's request, Grade 3 drug toxicity requiring drug discontinuation, investigator's judgement that further participation was detrimental to the subject's health, alteration of the background therapy was needed because of increasing disease burden, pregnancy, or reaching a primary study endpoint. The protocol's original primary study endpoints included: death,

clinical progression with new or recurring AIDS-defining illness, 50% decrease in CD4 counts from baseline, or return to within 0.3 logs of baseline HIV-1 RNA after 12 weeks on study. Subjects withdrawn from the study or who dropped out were not replaced.

6.2.2. Analysis Plan

Patients in Study 0013C were enrolled and randomized in a 1:1 ratio to receive either the dual therapy (ZDV + either ddI, ddC or 3TC + DLV placebo) or triple therapy (ZDV + either ddI, ddC or 3TC + DLV). Patients were stratified at entry according to prior nucleoside experience, AIDS at time of study start and baseline therapy (ddI, ddC or 3TC). Subjects were analyzed according to their original treatment assignment. All subjects who received at least one dose of study medications were included in the analysis of efficacy.

As in Study 0021 Part II, the sponsor's primary efficacy endpoint was amended to include the event "time to virologic failure". This was assessed using a survival analysis (Kaplan-Meier analysis). Other efficacy endpoints included change from baseline and average change from baseline over time for HIV-1 RNA, CD4 cell counts and CD4%, and proportion of patients below the limit of detection of the HIV-1 RNA PCR assay. Stratified analyses were performed for all these endpoints. Definitions of data collection "windows" and handling of data were determined by Pharmacia & Upjohn prior to analysis. The rules for handling missing data and conducting the primary analysis were revised by Agouron and the analysis was repeated according to guidelines provided by the FDA.

Safety and tolerance endpoints included: the incidence and severity of major toxicities, maximum ACTG Toxicity Scale scores for all medical events for a patient, incidence and severity of liver function test abnormalities in patients with known hepatitis B and C, time to these toxicities, time to Grade 3 or 4 rash, and change from baseline in laboratory measures. As with Study 0021 Part II, medical adverse events were tabulated according to COSTART terms. Events thought to be possibly related to blinded study medication or of unknown causality were included in all analyses of drug-related toxicity. Summaries of treatment-emergent rashes included the COSTART terms "rash", "rash maculopapular" and "urticaria". Treatment-emergent medical adverse events were compared between arms. Demographic variables were summarized and compared between treatment groups. All hypothesis tests were 2-sided and statistical significance was defined prior to the final analyses.

6.2.3. Efficacy in Treatment of HIV in previously untreated or minimally treated adults – Study 0013C

Amendment 6 of Study 0013C provided for a single interim safety and efficacy analysis when all of the patients were enrolled and had completed 12 weeks of study. The independent DSMB for Study 0013C reviewed the results of this

interim analysis and recommended closing the study on 8/20/98. As with Study 0021 Part II, the interim analysis showed a significant difference in outcome favoring the DLV-containing, triple therapy arm of Study 0013C. No safety issues contributed to the recommendation for study termination.

Study 0013C enrolled 345 patients between 7/4/96 and 8/27/97. No patients transitioned from the previous version of the protocol, Study 0013B, that is reported separately. Relatively few subjects chose to receive ddI or ddC as the second nucleoside in combination with ZDV and so the planned stratification for the efficacy analysis based on background treatment was not submitted. Only 57 subjects (16.5%) received ddI and 65 (18.8%) received ddC compared to 223 (64.6%) who received 3TC. Therefore, the sponsor's efficacy and safety analyses compared ZDV + ddX to ZDV + ddX + DLV.

The treatment arms were well matched in terms of demographics and baseline characteristics of illness. There were significantly more men than women enrolled in the trial but Study 0013C was more successful at enrolling women than Study 0021 Part II. This study population was also slightly more advanced in their disease with lower mean CD4 cell counts and a higher proportion of patients with AIDS-defining illnesses prior to enrolling than was observed in Study 0021 Part II. Table 5 summarizes the demographics and baseline HIV characteristics of the study population.

Table 5: Demographics and Baseline HIV Characteristics in Study 0013C

	ZDV + ddX	ZDV + ddX + DLV	Total
Enrolled	173	172	345
Evaluable[1]	172	170	342
Age – mean (range)	35.4 (18-59)	36.2 (20-72)	35.8 (18-72)
Sex – male (%)	114 (66%)	112 (65%)	226 (66%)
Race/Ethnicity (%)			
White	107 (62%)	111 (65%)	218 (63%)
Black	56	52	108
Asian	5	3	8
Other	5	6	11
Prior ZDV use (%)	61 (35%)	64 (37%)	125 (36%)
Baseline HIV Labs – mean (median)			
CD4 cell count	209 (221)	212 (241)	210 (231)
Log HIV RNA	4.86 (5.00)	4.86 (4.99)	4.86 (5.00)
Prior AIDS-defining illness	56 (32%)	64 (37%)	120 (35%)

[1]Patients were considered "evaluable" if they received at least 1 dose of study medication.

During the course of the study many patients withdrew or were discontinued from Study 0013C. At the time the study was prematurely terminated, the triple

therapy arm had the highest proportion of patients who discontinued prior to completing the study. Significantly more patients in the dual therapy arm discontinued study due to "lack of efficacy" although the number of clinical progressions were similar across treatment groups. Among those patients leaving the study for "administrative" reasons, 40 were categorized as withdrawing by "personal request" or for "other" reasons. These categories included patients' desires to begin PI therapy or an increasing viral load that did not meet study endpoint criteria. Table 6 lists the sponsor's reported disposition of all patients enrolled in the trial.

Table 6: Patient Disposition for Study 0013C (all enrolled patients)

Reason for Discontinuation	ZDV + ddX (N = 173)	DLV + ZDV + ddX (N = 172)	Total (N = 345)
Study course completed	110 (63.6%)	91 (52.9%)	201 (58.3%)
Lack of efficacy	17 (9.8%)	6 (3.5%)	23 (6.7%)
Death, HIV related	0	1 (0.6%)	1 (0.3%)
New or recurrent AIDS defining illness	9 (5.2%)	8 (4.7%)	17 (4.9%)
Medical event – serious	0	4 (2.3%)	4 (1.2%)
Medical event – non-serious	13 (7.5%)	24 (14.0%)	37 (10.7%)
Protocol non-compliance other than entry criteria	2 (1.2%)	4 (2.3%)	6 (1.7%)
Subject's personal request	10 (5.8%)	14 (8.1%)	24 (7.0%)
Subject lost to follow-up	7 (4.0%)	9 (5.2%)	16 (4.6%)
Other	5 (2.9%)	11 (6.4%)	16 (4.6%)

Source: Volume 50, Technical Report Study 0013C, page 92.

As with Study 0021 Part II, the sponsor's final analysis confirmed the interim analysis findings of a significant antiviral benefit for patients in the triple therapy arm. The primary efficacy endpoint of "time to virologic failure" was based on either HIV-1 RNA > 400 copies/mL or clinical progression. The triple therapy regimen significantly extended the "time to virologic failure" compared to the dual therapy arm through 54 weeks of study ($p = 0.0001$). This difference was maintained when the analysis used the lower limit of quantitation as 50 copies/mL.

The triple therapy regimen also yielded a greater proportion of subjects who achieved HIV-1 RNA levels < 400 copies/mL at some time during the study. The difference in the 2 treatment arms was evident at all timepoints from Week 12 through Week 54 ($p < 0.001$). This difference was maintained when the 50 copies/mL cut-off was used in the analysis. The sponsor notes that fewer viral load measurements were available at Week 48 than expected. They attribute this in part to the fact that this measurement was added to the study by Amendment 5, and some patients had already completed 48 weeks of study at the time the amendment was implemented. Table 7 below displays the sponsor's ITT analysis

comparing the proportion of patients with viral load below 400 copies/mL for each treatment arm at selected study timepoints.

Table 7: Percentage of patients with HIV-1 RNA levels below quantitation (400 copies/mL), ITT analysis – Study 0013C

Treatment Week	Treatment Groups			
	ZDV + ddX (N = 173)		DLV + ZDV + ddX (N = 172)	
	S	n (%)	S	n (%)
4	173	35 (22.5%)	172	52 (30.2%)
12	173	27 (15.6%)	172	77 (44.8%)*
24	173	18 (10.4%)	172	61 (35.5%)*
36	173	19 (11.0%)	172	53 (30.8%)*
48	173	13 (7.5%)	172	42 (24.4%)*
54	173	14 (8.1%)	172	46 (26.7%)*

S = number of patients with samples at the stated timepoint.
*Comparison of DLV + ZDV + ddX and ZDV + ddX arms with $P < 0.05$.
Source: Volume 16, Integrated Summary of Efficacy, page 91.

An additional secondary efficacy endpoint included the change in CD4 counts from baseline. The sponsor's analysis of change in mean CD4 cell counts revealed significant increases in both treatment arms at all timepoints in patients who remained on study. These increases were greater in the triple therapy arm. The following table summarizes the CD4 changes from baseline at selected study timepoints for those patients remaining on study.

Table 8: Mean Change from Baseline in CD4 Cell Count – Study 0013C (patients remaining on study)

Treatment Week	Treatment Groups			
	ZDV + ddX (N = 173)		DLV + ZDV + ddX (N = 172)	
	S	Mean Change	S	Mean Change
Baseline	171	209*	170	212*
12	151	59	139	68
24	138	56	124	74
54	97	56	83	101[a]

S = number of patients with samples at the stated timepoint.
*Mean baseline CD4
[a]Statistically significant difference between treatment groups, $p < 0.05$.

The sponsor also evaluated the differences in efficacy parameters stratified according to previous treatment experience. In this trial 35% and 37% of the dual and triple therapy groups respectively had limited prior therapy, defined as less

than 6 months (total) of NRTI or PI. For mean reduction in HIV-1 RNA, proportion of patients with viral load below quantitation, and mean increase in CD4 count the patients with prior treatment experience had responses that were consistent with the treatment naïve group or the entire population but were smaller. Treatment experienced subjects also received greater benefit from the triple therapy regimen. Subgroup analysis to assess treatment effects according to gender and race were hampered by the low numbers of minority and female subjects, although Study 0013C had more minority and female participants than Study 0021 Part II. There did not appear to be any major discrepancies in the responses of these subgroups compared to the entire population.

In summary, the sponsor's final data analysis supports the conclusion that triple therapy with DLV + ZDV + ddX provides greater therapeutic benefit than dual therapy with ZDV + ddX. The benefit was seen in both the primary efficacy analysis of "time to virologic failure" and the secondary efficacy analyses. These results were sustained over the 54 week study period.

6.3. Supportive Studies

6.3.1. Group II studies

The 2 ACTG studies were undertaken to determine the role of DLV in more heavily treatment-experienced patients in combination with PIs. Data collection and analyses for these studies were performed by the ACTG and the individual study reports and the sponsor's ISE were prepared from source data provided with the analysis report from the Statistical Analysis and Data Center, Harvard School of Public Health, the group providing statistical support for the ACTG.

6.3.1.1. Study ACTG 359

Study ACTG 359 was undertaken to investigate the activity of SQV-SGC in combination with either RTV or NFV along with DLV and/or ADV. It utilized a 2 x 3 factorial design leading to 6 study arms: 1) SQV-SGC 400 mg BID + RTV 400 mg BID + DLV 600 mg BID, 2) SQV-SGC 400 mg BID + RTV 400 mg BID + ADV 120 mg QD, 3) SQV-SGC 400 mg BID + RTV 400 mg BID + DLV 600 mg BID + ADV 120 mg QD, 4) SQV-SGC 800 mg TID + NFV 750 mg TID + DLV 600 mg BID, 5) SQV-SGC 800 mg TID + NFV 750 mg TID + ADV 120 mg QD, and 6) SQV-SGC 800 mg TID + NFV 750 mg TID + DLV 600 mg BID + ADV 120 mg QD. All subjects received L-carnitine 500 mg QD. The study was randomized and partially blinded (the DLV and ADV components) and subjects received study treatment for 24 weeks with the possibility of a 24 week extension for subjects reaching HIV-1 RNA < 5000 copies/mL by Week 16. Patients were eligible for enrollment if they were at least 16 years old with documented HIV infection, had HIV-1 RNA levels 2,000-200,000 copies/mL at screening, had taken IDV for at least 6 months, had received < 2 weeks of RTV or SQV hard gel capsules, had

received no NNRTIs or ADV, had not received other investigational agents within 30 days of study and were not pregnant or breastfeeding. Patients were stratified at entry according to HIV-1 RNA levels, 2,000-20,000 and 20,001-200,000.

Patients were seen at baseline and weeks 4, 8, 12, 16, 24 and also weeks 32, and 48 if they continued in the extension phase of the study. Routine hematology and chemistry laboratory tests were monitored at these visits, as well as virologic and immunologic markers. All HIV-1 RNA levels were collected and stored through week 16 and assayed in batches at 2 central laboratories. Adverse events were recorded at each visit and graded according to the ACTG Toxicity Scoring scale. Events of Grade 2 or higher were tracked and reported in the safety analysis.

The primary analyses compared RTV and NFV and compared DLV, ADV and DLV + ADV by pooling the appropriate treatment arms. The primary efficacy parameter was the proportion of subjects with undetectable HIV-1 RNA (in this study < 500 copies/mL) at Week 16 of the study. Secondary analyses included change in HIV-1 RNA, change in CD4 cell count and durability of the viral load suppression for the pooled comparisons and the 6 different treatment arms.

All major parameters were balanced among the 6 treatment arms at study entry. Table X summarizes the demographics and baseline HIV characteristics of patients enrolled in Study ACTG 359. Similar to the pivotal trials, the study participants in this trial were also predominantly white and male. As might be expected for a study that was conducted in 1997-98 and enrolled subjects with previous IDV use, there was a greater proportion of subjects in this study with a previous HIV-related OI than was seen in other studies.

Table 9: Demographics and Baseline HIV Characteristics in Study ACTG 359

	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	Total
Enrolled	47	47	45	48	45	45	277
Age – median	39	42	37	41.5	40	40	40
Sex – male (%)	39 (83%)	38 (81%)	38 (84%)	41 (85%)	38 (84%)	37 (82%)	231(83%)
Race							
White	26 (55%)	19 (40%)	24 (54%)	27 (56%)	19 (42%)	22 (49%)	137(49%)
Black	13	19	11	11	13	13	80
Hispanic	7	8	9	8	11	10	53
Asian	1	0	1	2	2	0	6
Other	0	1	0	0	0	0	1
Months Prior IDV (median)	13.0	12.2	14.3	15.5	15.1	15.4	14.4
Baseline HIV Labs – median							
CD4 cell count	228	230	242	202	193	258	229
HIV-1 RNA	28,950	48,466	35,704	22,428	32,122	22,551	31,746
Prior HIV OI	30 (64%)	37 (79%)	28 (62%)	35 (73%)	35 (78%)	38 (84%)	203(73%)

Source: Volume 80, Study Report Study PACTG 359, page 51-53.

Data for this study collected by the ACTG was recorded in a slightly different way compared to the Pharmacia & Upjohn sponsored studies. Disposition of study subjects was reported differently; subjects that were followed through at least 16 weeks regardless of whether they remained on their assigned treatment were considered to be on study. Two subjects never started their assigned treatment but were followed "on study" for 16 weeks. There were 48 subjects (17%) who were followed "on study" but off treatment for reasons other than completing protocol or reaching a protocol-defined endpoint. Six patients were listed as having completed the protocol, 3 refused further contact, 4 could not be contacted, 3 died during the study and 5 were listed as off study for "other" reasons. The sponsor notes no differences among the treatment groups in terms of duration of treatment or follow-up.

For this study the primary efficacy analysis was the proportion of patients with HIV-1 RNA below 500 copies/mL at 16 weeks. Treatment arms were pooled to compare RTV vs. NFV and to compare DLV vs. ADV vs. both. No identifiable differences between the RTV and NFV arms could be determined. However, both the ACTG's analysis and the sponsor's reanalysis revealed a difference in the proportion of subjects with undetectable viral load when comparing the DLV and ADV components in favor of the DLV-containing arms. Their analysis suggests that the addition of ADV to the DLV-containing treatment arms conferred no significant benefit, ie. the 4-drug regimens were not more efficacious than the corresponding 3-drug regimens.

The following table summarizes the sponsor's analysis of this data at selected timepoints.

Table 10: Proportion of Patients with HIV-1 RNA Levels Below 500 Copies/mL – Study ACTG 359

Treatment Week	Treatment Groups*					
	Control Groups		DLV-Containing Groups			
	SQV+RTV +ADV (N=47)	SQV+NFV +ADV (N=45)	SQV+RTV +DLV (N=47)	SQV+RTV +DLV +ADV (N=45)	SQV+NFV +DLV (N=48)	SQV+NFV +DLV +ADV (N=45)
4	8/43* (18.6%)	4/43 (9.3%)	13/41 (31.7%)	9/39 (23.1%)	16/45 (35.6%)	11/40 (27.5%)
8	10/43 (23.3%)	6/43 (14.0%)	17/42 (40.5%)	12/39 (30.8%)	15/42 (35.7%)	16/39 (41.0%)
16	9/44 (20.5%)	7/44 (15.9%)	14/42 (33.3%)	12/39 (30.8%)	20/43 (46.5%)	15/42 (35.7%)
24	7/35 (20.0%)	8/40 (20.0%)	11/37 (29.7%)	11/36 (30.6%)	15/37 (40.5%)	8/36 (22.2%)

Source: Volume 16, Integrated Summary of Efficacy, page 98.
*Note: The treatment arms in this table are not in the same order as listed in the text or Table 9. Here DLV treatment arms are grouped together to aid comparison to the Control Groups.

Subjects with HIV-1 RNA < 500 copies/mL at Week 16 were eligible to continue their original study regimen for an additional 24 weeks. Of the 277 subjects enrolled in the study, 107 were eligible to continue in the extension phase. At Week 48 the numbers of patients in the extension phase with undetectable HIV-1 RNA were 8, 5, 6, 8, 0, and 10 for treatment arms 1 to 6 respectively.

The secondary analysis of most interest was that evaluating the change in CD4 cell counts from baseline to week 16. For the 6 study groups the median change from baseline to Week 16 CD4 count was increased by 19, 30, 13, 44, 35, 5, and 8 cells/mm3 for arms 1 to 6 respectively. These increases were not significantly different for any of the treatment arms. There were also no discernable differences between the pooled RTV and NFV groups or the pooled DLV, ADV and DLV + ADV groups.

In assessing other baseline factors and their impact on suppression of viral load the ACTG statistical team used logistic regression to evaluate age, race, gender, weight and time of prior IDV use along with treatment arm and baseline HIV markers. Their model indicated that there was a higher probability of HIV-1 RNA suppression at Week 16 associated with: 1) being in a DLV-containing treatment arm, 2) lower baseline HIV-1 RNA, 3) female

gender, and 4) shorter duration of IDV use. Baseline CD4 count was not independent of baseline viral load but in the absence of viral load was a predictor of suppression.

In summary, the ACTG technical report of Study 359 supports the sponsor's conclusions that the DLV-containing treatment arms of the study provide antiviral benefit over 16 weeks in patients who have previously received a PI (in this case IDV). This benefit was similar whether RTV + SQV or NFV + SQV was combined with DLV in the salvage regimen. It is of interest to note that this study was also reviewed as part of an NDA submission for [redacted] with similar conclusions drawn by that review team.

6.3.1.2. Study ACTG 370

ACTG Study 370 was a randomized, open-label study comparing the efficacy of 3TC + IDV + ZDV, DLV + IDV + ZDV, DLV + IDV + d4T in 3TC or PI experienced patients. DLV was used at the 400 mg TID dose in this study. It was designed as a roll-over study from ACTG 306, an earlier study comparing monotherapy with ddI or d4T with dual therapy with ZDV + 3TC, d4T + 3TC or ddI + 3TC; the extension phase of ACTG 306 continued the dual therapy regimens. In ACTG 370, patients remained on dual NRTIs if their viral load was below 500 copies/mL but were randomized to one of the triple therapy arms if above that level. Essentially, this study evaluated the role of continuing 3TC vs. switching to DLV when adding a PI. Participants were required to have a CD4 count > 200 within 60 days of enrollment, have no evidence of significant organ dysfunction and no serious HIV-related comorbid conditions. Sites were also encouraged to enroll patients not previously on ACTG 306, randomizing these subjects to receive either 3TC + IDV + ZDV or DLV + IDV + ZDV.

Study subjects were followed at Weeks 2, 4, 8, 12, 16, 20, 24 and every 4 weeks thereafter. Safety laboratory monitoring was performed at each visit and adverse events were recorded. HIV-1 RNA levels and lymphocyte subsets were measured at each visit. Guidelines for managing anticipated common toxicities were included in the protocol. Subjects could be withdrawn from the study in the event of drug toxicity defined in the protocol, failure to comply with protocol requirements, withdrawal of consent, generalized debilitation making clinic visits impossible, requirement for a medication disallowed on the protocol and completion of the study.

The primary study analysis was comparison of the proportion of subjects with HIV-1 RNA > 200 copies/mL at Weeks 20 and 24 in the 2 ZDV-containing arms, thereby comparing the efficacy of the DLV and 3TC components in these regimens. Rates of adverse events requiring discontinuation of study drugs were compared between the treatment arms. Secondary analyses included the change from baseline to Week 24 in HIV-1 RNA between the 2

major treatment groups and the change from baseline to Week 24 in CD4 cell counts. Rates of resistance were to be calculated for IDV, DLV, ZDV and d4T in subjects developing resistance while on study. It is not clear from the study report how missing data was to be handled.

No statistical or clinical report of this study from the ACTG is submitted with this sNDA. Results are described in a very brief technical study report prepared by Pharmacia & Upjohn. According to this summary, 157 subjects were randomized in the study: 33 in the 3TC + IDV + ZDV arm, 30 in the DLV + IDV + ZDV arm and 40 in the DLV + IDV + d4T arm while 54 subjects continued treatment with previously assigned dual NRTI therapy. At Week 20/24 numerically more patients had reached the primary endpoint, virologic failure defined as HIV-1 RNA > 200 copies/mL in the 3TC treatment group compared to the DLV treatment group, although the difference was not statistically significant. The proportion of patients with viral load < 200 copies/mL was 73% in the DLV treatment group compared to 58% in the 3TC group. By Week 44/48 the technical report indicates that 83% of the DLV group had achieved a viral load < 200 copies/mL compared to 48% in the 3TC group, a statistically significant difference. There was no difference in change in CD4 counts from baseline to either 24 or 48 weeks across treatment arms. Patients who continued on dual NRTI therapy failed to show decreases in viral load or increases in CD4 counts at 24 or 48 weeks.

In summary, the sponsor suggests that in ACTG Study 370 there may be some benefit to changing to DLV from 3TC in a regimen beginning IDV as a new PI. These differences were only apparent in some of the parameters evaluated and at some of the timepoints studied. There were no significant differences in safety or tolerability of these regimens.

6.3.2. Group III Studies

These studies were all designed to investigate the use of DLV in combination with PIs in patients with limited or no previous therapy. These were all randomized, open-label, multicenter studies analyzed at Week 24; all of the studies had relatively few patients in each treatment group. Identifying pharmacokinetic interactions with the PIs being studied was an important consideration of these trials. Inclusion criteria for most of these studies (except Study 0081) were very similar with patients required to have CD4 cell counts > 50 cells/mm3, HIV-1 RNA levels > 20,000 copies/mL and no prior therapy with NNRTIs or PIs.

In Study 0063 patients were randomized to receive either DLV + ZDV + IDV (400 mg TID) or DLV + ZDV + IDV (600 mg TID) or ZDV + 3TC + IDV (800 mg TID). DLV was given at 400 mg TID. One of the primary objectives of this study was to define the interactions between DLV and different doses of IDV by measuring peak concentrations (Cmax), minimum concentrations (Cmin) and

drug exposure (AUC). A total of 45 subjects were enrolled and followed through 24 weeks. Primary efficacy variables included change from baseline in HIV-1 RNA and CD4 cell counts and proportion of subjects with viral load < 400 or < 50 copies/mL. At the Week 24 analysis the proportion of patients with HIV-1 RNA < 400 copies/mL was not statistically significantly different in any treatment arm with 27% for DLV + ZDV + IDV600, 33% for DLV + ZDV + IDV400 and 47% for ZDV + 3TC + IDV800.

Study 0073A randomized patients to receive either DLV (600 mg TID) + NFV (750 mg TID) + d4T + ddI or DLV (400 mg TID) + NFV (750 mg TID) + d4T + ddI. This study enrolled only 22 patients and included PK assessments of DLV and NFV. Efficacy parameters evaluated included change from baseline in HIV-1 RNA level, proportion of patient with HIV-1 RNA below 400 or 50 copies/mL and change from baseline in CD4 cell counts. Again there was no difference in proportion of patients with undetectable viral load between the treatment arms in this small study.

Study 0073B enrolled and randomized 137 subjects to receive either DLV + NFV + d4T, DLV + NFV + ddI, NFV + d4T + ddI or DLV + NFV + d4T + ddI. In this study the DLV was given at a dose of 600 mg BID and NFV was given at a dose of 1250 mg BID. Safety and efficacy monitoring was done at Weeks 1, 2, 3, 4, 8, 12, 16, and 24 with 3 optional 24-week extensions for patients who were doing well on their assigned regimen. Efficacy analyses were similar to those described for Study 0073A. In this study there were 23 treatment discontinuations in the quadruple-drug regimen compared to 8 to 11 in the triple therapy regimens. Not surprisingly the ITT analysis of the primary efficacy parameter revealed that the 4-drug regimen had significantly fewer patients with HIV-1 RNA below 400 and below 50 copies/mL at Week 24 compared to the NFV + d4T + ddI regimen. There was little difference in efficacy among the 3 triple therapy regimens and patients in all 4 treatment groups experienced mean increases in CD4 cell counts during the course of the study.

Study 0074 was the largest of this group of studies, enrolling 186 subjects into one of 4 treatment groups. Patients were randomized to receive either DLV + ZDV + IDV (600 mg TID), ZDV + 3TC + IDV (800 mg TID), DLV + 3TC + IDV (600 mg TID) or DLV + ZDV + 3TC + IDV (600 mg TID). Safety and efficacy monitoring was done at Weeks 2, 4, 8, 12, 16 and 24 with the option to continue for 3 24-week extensions. Efficacy variables were similar to those described in the other Group III studies. Again, discontinuations from study were most frequent in the quadruple therapy arm. At Week 24 there were no significant differences in proportion of patients with HIV-1 RNA < 400 copies/mL across treatment arms. At some of the earlier timepoints the analysis favored the non-DLV-containing treatment regimen (ZDV + 3TC + IDV800). When the 50 copies/mL cutoff was analyzed the 4-drug arm had fewer successes than the 3-drug arms. All treatment groups exhibited mean increases in CD4 cell counts from baseline to Week 24.

Study 0081 enrolled and randomized 97 patients into a PK, efficacy and safety study evaluating 4 regimens containing combinations of SQV-SGC and DLV. These regimens included: SQV (1400 mg BID) + 3TC + DLV (600 mg BID), SQV (1000 mg TID) + 3TC + DLV (400 mg TID), SQV (1200 mg TID) + 3TC + ZDV and SQV (1400 mg BID) + 3TC + DLV (600 mg BID) + ZDV. PK assessments were performed at Week 4 while safety and efficacy parameters were monitored at Weeks 1, 2, 3, 4, 8, 12, 16, 20, and 24 and every 8 weeks thereafter for patients on the extension phase. The primary efficacy analyses were the changes from baseline in HIV-1 RNA and CD4 cell counts. At the time data was collected for this submission less than half of the patients enrolled in this study had received 24 weeks of therapy. Consequently, numbers of patients reaching a primary endpoint were too small to show any differences between treatment groups. At the time of reporting, there were relatively few discontinuations from study. The sponsor notes, however, that at this early analysis the BID triple therapy regimen of SQV + 3TC + DLV appeared to be as efficacious as the TID regimen.

In summary, the Group III studies provided useful PK information regarding the interactions of DLV and some of the PIs. Most of the studies enrolled too few patients and were plagued by frequent discontinuations that made it unreliable to draw any conclusions regarding the antiviral benefit of a particular treatment regimen. There were numerical differences in some studies favoring the non-DLV-containing arms. There were, however, also some of the DLV-containing arms that performed as well as treatment arms including PIs.

6.3.3. Group IV Study

Study 0013B was initiated as a randomized, double-blind, multi-center, clinical endpoint study to investigate the safety and efficacy of DLV + ZDV compared to ZDV monotherapy. This study began enrolling in July, 1994 and was the predecessor to the pivotal trial that was submitted for the sNDA, Study 0013C. DLV was initially given at a dose of 300 mg TID but was increased to the currently approved dose of 400 mg TID mid-way through the study. Study subjects were required to have CD4 counts < 350 cells/mm3, meet the 1993 European AIDS/ARC criteria and be NRTI treatment naïve or receiving ZDV monotherapy at the time of enrollment. The primary efficacy parameters for this study were survival, progression to AIDS, requirement of a study-prohibited medication and changes in CD4 cell counts and HIV-1 RNA levels.

A total of 597 patients were randomized to receive either DLV + ZDV or ZDV with ddC available for patients requiring "salvage" for clinical or immunologic deterioration. Later in the study investigators were allowed to also prescribe ddC or ddI to all patients in addition to the assigned therapy. The study was truncated to proceed for 52 weeks rather than the originally planned 108 weeks. This study was in progress at a time when monotherapy was identified as inferior to

combination therapy. Over the course of the study many subjects withdrew from participation before reaching a study-defined endpoint, undoubtedly to pursue more aggressive therapy. A total of 239 subjects discontinued study due to a medical event and 131 subjects met the criteria of a clinical endpoint. There was no significant difference in the rate of clinical progression between the 2 study treatment arms using an ITT analysis, although the sponsor's on-treatment analysis favored the DLV + ZDV arm. The sponsor notes that there were significantly fewer patients in the dual therapy arm who developed an AIDS-defining OI during the study. There was no difference in the numbers of deaths between the 2 treatment groups. Relatively small changes from baseline in HIV-1 RNA and CD4 cell counts suggested some benefit of dual therapy at early timepoints but at later timepoints there were no significant improvements in these measures in either arm. The changes in standard therapy for HIV occurring during the time this study was being conducted and the resultant high withdrawal rate make it difficult to draw any firm conclusions regarding DLV use from this study.

6.4. Summary of FDA Statistical Analyses

The FDA confirmatory reanalysis was performed predominantly by Dr. Thomas Hammerstrom, the Statistical Reviewer for this sNDA. Some of the CD4 cell count analyses were performed by the Medical Reviewer. The methods of statistical analysis used are detailed in Dr. Hammerstrom's review. In brief, he utilized a non-completer equals failure, intent-to-treat analysis determining "time to virologic failure" as the primary analysis and proportion of subjects below the limit of quantitation of the HIV-1 RNA PCR assays (both < 400 copies/mL and < 50 copies/mL) as a secondary analysis. These analyses were calculated out through Week 48. In general, our conclusions regarding the antiretroviral activity of DLV are similar to those of the sponsor.

Kaplan-Meier survival curves were computed for "time to virologic failure", the primary efficacy endpoint for both of the pivotal trials. In the FDA reanalysis, failure was defined as the earliest confirmed rebound of viral load (> 400 or > 50 copies/mL), death, disease progression, discontinuation of assigned therapy or loss to follow-up. In Study 0021 Part II, the proportion of subjects who never achieved HIV-1 RNA < 400 copies/mL was about 20% and was equivalent for all arms. The difference between treatments favoring the DLV arm begins early in the study and increases through Week 48. For Study 0013C the Kaplan-Meier curves again confirm an early and persistent difference in treatment efficacy favoring the DLV-containing arm. In this case there was a greater proportion of subjects who never attained an undetectable viral load and the differences between the treatment arms decreased over 48 weeks. Overall, more subjects reached the endpoint of "time to failure" in Study 0013 C than in Study 0021 Part II.

Dr. Hammerstrom's reanalysis of the pivotal trial data confirm a statistically significant and clinically meaningful superiority in the proportion of subjects with

HIV-1 RNA levels below detection (using either < 400 or < 50 copies/mL) when DLV was added to dual nucleoside therapy. These results were equally evident whether the background nucleoside therapy was ZDV + 3TC or pooled ZDV + ddX, although the numbers of subjects receiving a second nucleoside other than 3TC were relatively small. In Study 0021 Part II the combination of DLV + ZDV as dual therapy was not as efficacious as ZDV + 3TC. The reanalysis also confirmed that the therapeutic benefit in both arms of Study 0021 Part II was greater in the subset of patients who were truly treatment naïve than in those with some prior ZDV treatment experience. This observation was also confirmed in Study 0013; subjects with limited ART experience were less likely to have undetectable viral load than those with no prior ART. The results of the FDA reanalysis reproduced from Dr. Hammerstrom's review are displayed in Tables 11 and 12.

Table 11: Proportion of Patients with HIV-1 RNA < 400 copies/mL at Week 48 – Study 0021 Part II (FDA Reanalysis)

Treatment Status	DLV + ZDV + 3TC	ZDV + 3TC	DLV + ZDV	P values
No prior ZDV	51/99 (52%)	12/109 (11%)	1/105 (1%)	< 0.001
Prior ZDV	6/25 (24%)	1/14 (7%)	1/20 (5%)	0.19
All Patients	57/124 (46%)	13/123 (11%)	2/125 (2%)	< 0.001

Table 12: Proportion of Patients with HIV-1 RNA < 400 copies/mL at Week 48 – Study 0013C (FDA Reanalysis)

Treatment Status	DLV + ZDV + ddX	ZDV + ddX	P values
No prior ZDV	42/105 (40%)	13/112 (12%)	< 0.001
Prior ZDV	9/64 (14%)	3/61 (5%)	0.08
All Patients	51/169 (30%)	16/173 (9%)	< 0.001

Reanalysis of the CD4 cell count data confirmed that patients receiving DLV in a multi-drug treatment regimen had significant improvements in CD4 cell counts. In the pivotal trials the increase in CD4 counts was significantly better in the subjects receiving DLV-containing triple therapy compared to those receiving dual nucleoside therapy. In the smaller studies presented there were no significant differences in the increase in CD4 counts across treatment arms but among these treatment-naïve patients almost all regimens resulted in substantial increases in CD4 counts sustained over the study period. Our results were essentially the same as those presented by the sponsor.

One of the difficulties encountered in reviewing the studies submitted in this sNDA was that many of the subjects enrolled in the pivotal and supportive studies discontinued therapy prior to the end of study. This occurred in large part because the pivotal trials were conducted at a time when the advent of PI therapy was dramatically changing the standard of care in HIV clinical practice. Patients during

this time period became much more focused on the level of HIV-1 RNA that could be achieved using the PIs in multi-drug combinations and were less willing to participate in blinded studies not including one of the new highly active agents. In the sponsor's listing of reasons for study discontinuations in the pivotal trials (shown in Sections 5.1.3 and 5.2.3 above) many patients were withdrawn from study because of "study completion", "personal request" or "other" reasons and relatively few are listed as withdrawing because of "failure" or "medical events". In reviewing these listings more carefully it appeared that many of the discontinuations due to "personal request" or "other" reasons were related to subjects' concern that they were not benefiting from study therapy and/or to subjects' desire to be treated with a PI. This raised concern that the sponsor's listings of discontinuations might not accurately reflect the studies' shortcomings and that some subjects might not have been correctly counted as virologic failures. Dr. Hammerstrom's reanalysis specifically evaluated the status of all patients at 48 weeks as related to virologic failure (as defined above). He noted that although the listed reasons for treatment discontinuation were not always viral failure, most patients who discontinued treatment before the end of the studies did have viral loads > 400 copies/mL. His re-classification of patient status at 48 weeks is reproduced in Table 13 below and is based on the end-of-study event that occurred first (virologic failure, medical event, etc.).

Table 13: Patient Status at Week 48 – Studies 0021 Part II and 0013C (FDA Reanalysis)

Status	DLV + ZDV + 3TC (or ddX)	ZDV + 3TC (or ddX)	ZDV + DLV
Study 0021 Part II	N = 124	N = 124	N = 125
Success at Week 48 (n)	57	13	2
Failure at Week 48			
HIV-1 RNA > 400 copies/mL	42	95	89
Medical event	12	10	18
Other	13	6	16
Study 0013C	N = 172	N = 173	NA
Success at Week 48 (n)	51	16	NA
Failure at Week 48			NA
HIV-1 RNA > 400 copies/mL	88	136	
New AIDS event/Death	3	2	
Medical event	18	9	
Other	12	10	

The conclusion reached after the efficacy reanalysis was that DLV confers virologic benefit when given in combination with other antiretroviral agents over a period up to 48 weeks. The 2 large pivotal trials clearly showed the superiority of a 3-drug regimen of DLV in combination with 2 NRTIs compared to a regimen of 2 NRTIs. Most of the studies submitted for review investigated DLV given at the currently

approved dose of 400 mg TID. ACTG Study 359, Study 0073B and Study 0081 evaluated a dose of 600 mg BID of DLV in combination with different PI's. These were relatively small, 16 to 24 week studies with multiple treatment arms, in some cases with significant missing data and, therefore, no definite conclusions could be drawn regarding the long-term efficacy of the BID dosing regimen. There is the

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7. Integrated Review of Safety

7.1. Overview of Adverse Events

A total of 2238 patients were enrolled and randomized in the 10 clinical trials submitted in the sNDA. Data for 2220 are included in the safety analysis. The following table summarizes the studies and patients who are represented in the sponsor's Integrated Summary of Safety.

Table 14: Disposition of Patients Included in the Integrated Summary of Safety

Study	Number randomized/ enrolled	Number evaluable for safety	Number discontinued before study end
Study 0021 Part II	373	365	282
Study 0013C	345	342	144
ACTG 359	277	277	NA*
ACTG 370	159	157	NA*
Study 0063	45	45	19
Study 0073A	22	22	10
Study 0073B	137	137	52
Study 0074	186	186	48
Study 0081	97	94	15
Study 0013B	597	595	453
Total all studies	2238	2220	

*NA, not available
Source: Volume 22, Integrated Summary of Safety

In almost all studies there were more discontinuations in the study arms with greater number of drugs in the regimen (ie, 4 drugs vs. 3 drugs, 3 drugs vs. 2 drugs). The notable exception to this was Study 0021 Part 2 in which the 3-drug arm (DLV+ZDV+3TC) had fewer discontinuations than either of the 2-drug arms (DLV+ZDV or 3TC+ZDV). The proportion of discontinuations was highest in Study 0013B since this was a clinical endpoint study (131 patients met a study endpoint) conducted at a time when the standard of care evolved beyond the study's monotherapy regimen (171 discontinuations due to "personal request" or "other" reasons). The number of discontinuations was not listed for the 2 studies conducted through the ACTG.

Although Studies 0021 Part II and 0013C were intended to be 52 and 54 weeks in duration respectively, both studies were stopped before all patients could reach these timepoints. Additionally, because of the large number of discontinuations in the pivotal trials the long-term exposure to DLV may not be as extensive as with some other antiretroviral drugs. The following table summarizes the duration of exposure to study drug for all patients by treatment group in the 2 pivotal studies. The shorter duration of exposure in the DLV + ZDV treatment arm of Study 0021 Part II is consistent with the higher rate of study discontinuations in that arm.

Table 15: Delavirdine Exposure in Pivotal Trials – Studies 0021 Part II and 0013C

Duration of Treatment (weeks)	Treatment Groups in Study 0021 Part II		
	ZDV + 3TC (N = 124)	DLV + ZDV (N = 125)	DLV + ZDV + 3TC (N = 124)
Mean	44.8*	33.4*	46.4*
Range	0.1-98.6	0.1-79.4	0.1-92

*Statistically significant differences among treatment groups
Source: Volume 22, Integrated Summary of Safety, page 100.

Duration of Treatment (weeks)	Treatment Groups in Study 0013C	
	ZDV + ddX (N = 173)	ZDV + ddX + DLV (N = 172)
Mean	44.3	39.6
Range	0.1-71.9	0.1-67.6

Source: Volume 22, Integrated Summary of Safety, page 100.

The sponsor analyzed adverse event data collected continuously during the clinical trials. At each visit patients were asked to identify any new or recurrent events and these episodes were scored in terms of intensity/severity and relationship to study drugs. Events were summarized using defined COSTART medically equivalent terms corresponding to the investigator's description of the event. In analyzing the occurrence of rash, the COSTART terms "rash", "rash maculopapular" and "urticaria" were evaluated together to give a clearer picture of the extent of these events.

Adverse events were extremely common in all of the studies submitted as part of the sNDA. The pattern of these events was very similar across studies with a few study-specific exceptions that will be noted. The FDA safety analysis will therefore concentrate on the combined safety data from the 2 large pivotal trials. In these studies, 707 patients were evaluable for safety with 412 receiving a DLV-containing regimen and 295 receiving a non-DLV-containing regimen. A total of 664 of the 707 patients (93.9%) in the pivotal trials reported at least one adverse event while they were followed on study. Most of these events were graded as mild to moderate in intensity/severity. There was no difference in the total number of adverse events reported actoss the different treatment arms.

The most commonly reported events were nausea, headache and fatigue. All of these events were reported more frequently in Study 0021 Part II than in Study 0013C although subjects in Study 0013C as a whole were more advanced in their HIV disease. Rash was the only adverse event reported more frequently in subjects receiving DLV and will be described in more detail below. The following table summarized the most commonly reported adverse events reported in the 2 pivotal trials.

Table 16: Adverse Events Reported Most Frequently by Patients Enrolled in Studies 0021 Part II and 0013C

Adverse Event	Patients Receiving DLV 400 mg TID (N = 412)	Patients not Receiving DLV (N = 295)	All Patients in Studies (N = 707)
Patients reporting at least one adverse event	391 (94.9%)	273 (92.5%)	664 (93.9%)
Nausea	165 (40.0%)	118 (40.0%)	283 (40.0%)
Headache	129 (31.3%)	95 (32.2%)	224 (31.7%)
Infection[1]	121 (29.4%)	99 (33.6%)	220 (31.1%)
Rash[2]	146 (35.4%)	52 (17.6%)	198 (28.0%)
Fatigue/Asthenia	110 (26.7%)	79 (26.8%)	189 (26.7%)
Diarrhea	73 (17.7%)	63 (21.4%)	136 (19.2%)
Vomiting	74 (18.0%)	51 (17.3%)	125 (17.7%)

[1]Evaluation of infections includes the COSTART terms "infection", "infection bacterial", "infection viral" and "urinary tract infection". This category included predominantly upper respiratory infections.
[2]Statistically significant difference between DLV-containing regimens and non-DLV-containing regimens.

In general the adverse events reported in the supportive studies mirrored those seen in the pivotal trials with few exceptions. Study 0073B had a slightly higher frequency of diarrhea in the DLV + NFV + ddI and DLV + NFV + d4T + ddI arms. This may reflect the effects of NFV and ddI more than the DLV component. In ACTG Study 359 2 patients were identified as having proximal renal tubular dysfunction, an adverse event associated with ADV.

Rash was the only adverse event that occurred in significantly more patients receiving DLV than in those receiving comparator regimens. It occurred in approximately one third of subjects receiving DLV in all the clinical trials and was reported most frequently in the clinical endpoint study 0013B. The rash typically occurred within the first 3 weeks of DLV use as was described in earlier clinical trials with DLV. In study 0021 Part II the sponsor attempted to identify co-factors that might predispose to development of rash. Severe rash was not correlated with prior history of skin rashes, allergies or concomitant use of trimethoprim-sulfa. The table below gives a breakdown of the frequency and severity of rashes reported in the 2 pivotal trials.

Table 17: Percent of Patients with Treatment-Emergent Rash[1] in Pivotal Trials (Studies 0021 Part II and 0013C)[2]

ACTG Toxicity Grade of Rash	Description of Rash Grade	Delavirdine 400 mg TID (N = 412)	Control Group Patients (N = 295)
Grade 1 Rash	Erythema, pruritis	69 (16.7%)	35 (11.9%)
Grade 2 Rash	Diffuse maculopapular rash, dry desquamation	59 (14.3%)	17 (5.8%)
Grade 3 Rash	Vesiculation, moist desquamation, ulceration	18 (4.4%)	0 (0.0%)
Grade 4 Rash	Erythema multiforme, Stevens-Johnson syndrome, toxic epideral necrolysis, necrosis requiring surgery, exfoliative dermatitis	0 (0.0%)	0 (0.0%)
Rash of any Grade		146 (35.4%)	52 (17.6%)
Treatment discontinuation as a result of rash		12 (2.9%)	1 (0.3%)

[1] Includes events reported as COSTART term "rash", "rash maculopapular", and "urticaria".
[2] Includes events reported regardless of causality.

While Grade 4 (life-threatening) rash was not reported in any patients enrolled in the pivotal trials, 5 patients enrolled in the supportive studies developed Grade 4 rash thought to be related to study drugs. Three of the 5 patients were enrolled in Study 0013B, the clinical endpoint study, and only one of the 5 was not receiving DLV. It has been suggested that patients with advanced immunosuppression may be more likely to have severe rash reactions and this could account for the slightly higher numbers of Grade 4 rashes seen in Study 0013B. The case descriptions of the patients with Grade 4 rashes from Study 0013B do not provide sufficient detail to assess the severity of these adverse events or determine causality. These events were not specifically identified as Stevens-Johnson syndrome, in some cases were described as "non-serious" and were not included in the sponsor's description of reported cases of Stevens-Johnson syndrome. The few reported cases of Stevens-Johnson syndrome are described in Section 6.6, Post-marketing Safety Reports.

In the original NDA review of DLV, both nervous system complaints and palpitations were identified as events that might require additional study. In the registrational studies submitted with the accelerated approval package there was the suggestion that these events might be associated with the use of DLV. In reviewing these events in the current sNDA pivotal trials there appeared to be no increase in either nervous system or cardiovascular complaints with the use of DLV. Somnolence was reported numerically more often in Study 0013C in patients using DLV and dizziness was reported more often in patients not receiving DLV but neither of these associations

were seen in Study 0021 Part II and the numbers of these specific complaints were small.

In most of the studies, reporting of laboratory abnormalities as medical adverse events was at the discretion of the investigator if the laboratory finding was felt to be clinically important. Consequently, not all marked laboratory abnormalities were identified as adverse events. Laboratory abnormalities will be discussed briefly as they relate to discontinuation from study and in detail in Section 6.5.

7.2. Drug Discontinuations due to Adverse Events

Data were available regarding discontinuations from study due to adverse medical events for 8 of the 10 studies submitted; this information was not available for the 2 studies conducted by the ACTG. Except for Study 0013C there were no differences among treatment groups in proportion of subjects who discontinued therapy due to an adverse event. In Study 0013C more subjects in the DLV-containing arm discontinued study because of an adverse event compared to the non-DLV-containing arm. As would be expected, more patients in Study 0013B withdrew due to medical adverse events than in the other studies since this was a clinical endpoint study enrolling more advanced patients. Table 18 summarizes the numbers of patients discontinuing study due to adverse events in the 8 studies for which these data are available.

Table 18: Patients Reporting at Least 1 Adverse Event Leading to Study Discontinuation

Study	Patients Receiving DLV	Patients Not Receiving DLV	Total
Study 0021 Part II	34/242 (14.0%)	16/123 (13.0%)	50/365 (13.7%)
Study 0013C	36/170 (21.2%)	22/172 (12.8%)	58/342 (17.0%)
Study 0063	3/30 (10.0%)	1/15 (6.7%)	4/45 (8.8%)
Study 0073A	3/22 (13.6%)	NA	3/22 (13.6%)
Study 0073B	15/103 (14.6%)	4/34 (11.8%)	19/137 (13.9%)
Study 0074	20/140 (14.3%)	4/46 (8.7%)	24/186 (12.9%)
Study 0081	9/70 (12.9%)	5/24 (20.8%)	14/94 (14.9%)
Study 0013B	124/299 (41.5%)	115/296 (38.9%)	239/595 (40.2%)
All Studies	244/1076 (22.7%)	167/710 (23.5%)	411/1786 (23.0%)

In all studies reporting a specific medical cause for withdrawal (Studies 0021 Part II, 0013C, 0063, 0073A, 0073B, 0074 and 0013B) rash, nausea and anemia were the events that prompted discontinuation in the most subjects. A variety of other medical events were cited as prompting study discontinuation in small numbers of patients including: serious infections, fatigue, elevated liver transaminases, neutropenia, vomiting, kidney stones (seen in patients receiving IDV), neuropathy, pancreatitis, depression and others. It should be noted that in Study 0073B more subjects withdrew from study secondary to diarrhea than in any of the other studies and 4/5 of

these patients were receiving the quadruple-drug therapy which included both ddI and NFV, both associated with diarrhea.

Rash was the only adverse event causing a disproportionate number of withdrawals in the DLV-containing treatment groups. Of the patients receiving DLV in these studies (N = 1006) a combined 46 patients discontinued therapy due to rash, 32 discontinued due to nausea and 14 discontinued due to anemia. Among the study patients not receiving DLV (N = 686) the corresponding numbers of discontinuations are 4 for rash, 15 for nausea and 11 for anemia. Over half of the discontinuations due to rash were observed in Study 0013B.

7.3. Serious Adverse Events

Serious adverse events are defined in the pivotal studies as those medical events that meet one or more of the following criteria: death, life-threatening, require or prolong hospitalization, cancer, congenital anomaly or overdose. In the supportive studies there were additional criteria by which an event could be designated as serious. In the 2 ACTG studies all Grade 3 and 4 events were considered serious adverse events. Because of the differing criteria it is somewhat difficult to compare all studies. In the pivotal trials a relatively small number of patients experienced events that were classified as serious, 39 in Study 0021 Part II and 62 in Study 0013C. Table 19 summarizes the serious adverse events reported by at least 2 patients in any treatment group in either of the pivotal trials. These events are grouped according to use of DLV and do not represent all of the serious adverse events occurring in the 2 studies.

Table 19: Serious Adverse Events Reported by ≥ 2 Patients in Any Treatment Group in Studies 0021 Part II and 0013C

Adverse Event	Patients Receiving DLV (N = 412)	Patients Not Receiving DLV (N = 295)
Patients with at least 1 serious adverse event	59 (14.3%)	42 (14.2%)
Abscess	2 (0.5%)	1 (0.3%)
Anemia	10 (2.4%)	6 (2.0%)
Appendicitis	0	2 (0.7%)
Fever	3 (0.7%)	3 (1.0%)
Gastroenteritis	4 (1.0%)	0
Kaposi's sarcoma	2 (0.5%)	2 (0.7%)
Kidney stone	2 (0.5%)	0
Mycobacterium tuberculosis	4 (1.0%)	1 (0.3%)
Nausea	1 (0.2%)	2 (0.7%)
Pneumonia	6 (1.5%)	3 (1.0%)
Rash	4 (1.0%)	0
Sepsis	2 (0.5%)	0
Substance abuse	2 (0.5%)	0
Trauma	4 (1.0%)	3 (1.0%)
Vomiting	1 (0.2%)	2 (0.7%)

Three patients in Study 0021 Part II and 6 patients in Study 0013 experienced serious adverse events, some with multiple events, that were felt by the investigator to be related to blinded study drug (or specifically to DLV). These events included episodes of anemia (4 patients), rash (3 patients), cardiac insufficiency, neutropenia, allergic reaction, fever, nausea and paresthesias.

The most frequently reported serious adverse events in ACTG Study 359 were hypertriglyceridemia in 24 (8.7%) patients and neutropenia in 11 patients (4.0%). All but 1 of the episodes of Grade 4 hypertriglyceridemia were identified in patients receiving RTV, however, there was significant overlap in the drug regimens and 9 of the 10 events were seen in subjects also receiving DLV. One of the patients experiencing Grade 4 rash was enrolled in Study 359. ACTG Study 370 reported relatively few Grade 3 and 4 events with the most common serious events being increased SGPT, hyperbilirubinemia and hypertriglyceridemia. The ACTG studies did not assign causality in their assessments of serious adverse events.

Serious adverse events reported in the Group III studies were similar in spectrum to those seen in the pivotal trials. These events included stupor, anemia, pancreatitis, depression, gastroenteritis, liver function abnormalities, fever, pneumonia, vomiting, rash, allergic reaction and hyperbilirubinemia. A very small number of these serious adverse events were classified as drug-related by the investigators.

There were 4 unintended pregnancies reported during the 2 pivotal trials, 1 during Study 0021 Part II and 3 during Study 0013C. All 3 of the patients in Study 0013 had therapeutic abortions and no obvious fetal anomalies were observed. The woman who became pregnant while participating in Study 0021 Part II delivered an apparently healthy male infant with no observed abnormalities. She had received ZDV + 3TC for 12 weeks prior to learning of the pregnancy and discontinued her study medications 28 weeks prior to delivery. Not all of the pregnancies were classified as serious adverse events by the investigators or the sponsor.

Regardless of whether an event met the criteria for a serious adverse event or was reported as a Grade 3 or 4 event, the most common serious events associated with the DLV clinical trials that might be of concern to health care providers included rash, anemia, neutropenia and liver function abnormalities. Rash was the only one of these events that occurred more frequently in patients receiving DLV. The occurrence of anemia, neutropenia and liver function abnormalities were reported as serious adverse events in similar proportions of patients receiving DLV or not and will be discussed in more detail in Section 6.5, Laboratory Abnormalities.

7.4. Deaths

There were 22 deaths reported during treatment or within 30 days of stopping study treatment for the 10 studies included in the safety analysis. Eighteen of the deaths were in patients receiving DLV and 4 were not receiving DLV or 1.4% and 0.4% respectively of the evaluable patients in those groups. Sixteen of the 22 deaths occurred in Studies 0021 Part II, 0013C and 0013B and no deaths were recorded in Studies 0063, 0073A, 0081 or ACTG 370. In reviewing the narratives of the deaths it appeared that some of the reported deaths occurred beyond the 30-day reporting window but this is not clear from the sponsor's ISS report. Conditions resulting in the death of more than one patient included: disseminated TB, toxoplasmic encephalitis, sepsis, malignancy, cardiovascular disease and trauma. As can be seen from this listing, many of the deaths were due to AIDS-related conditions and OIs. Although a majority of the deaths occurred in patients receiving DLV, no deaths were directly attributed to DLV during the studies and no pattern emerges from the review suggesting that DLV contributed significantly to the patients' demise.

7.5. Laboratory Abnormalities

Analysis of the laboratory monitoring data submitted with the sNDA clinical trials revealed no unexpected laboratory abnormalities associated with DLV use. The sponsor expressed laboratory abnormalities by both the shift of ≥ 2 grades from baseline and the incidence of Grade 3 and 4 abnormalities. My review focused on the incidence of Grade 3 and 4 abnormalities and the mean change from baseline in some specific laboratory test values observed in the 2 pivotal trials. In general, my review agreed with the sponsor's findings and where differences occurred they were minor. These discrepancies were probably related to using slightly different cut-offs for the

upper limit of normal values for some laboratory assays performed in Study 0013C which used a number of clinical laboratories with varying reference ranges.

The most commonly identified laboratory abnormalities resulting in ≥ Grade 3 toxicity included neutrophil count (or segmented neutrophils), hemoglobin, ALT, AST, bilirubin and serum amylase. The table below summarizes Grade 3 and 4 laboratory abnormalities reported in the pivotal trials grouped according to use of DLV. The original NDA suggested that increased bilirubin might be associated with DLV use but in the pivotal trials submitted with this sNDA there was no difference in frequency of marked increase in bilirubin across treatment groups. Marked increases in triglycerides were rarely observed in Study 0013C (1 patient in each treatment group) but triglycerides were not routinely monitored in Study 0021 Part II.

Table 20: Number of Patients Reporting Grade 3 and 4 Laboratory Abnormalities for Selected Laboratory Tests Performed during Studies 0021 Part II and 0013C

Laboratory Value (limit of ≥ Grade 3)	Patients Receiving DLV (N = 412)	Patients Not Receiving DLV (N = 295)
Hemoglobin (< 7.0 mg/dL)	10 (2.4%)	8 (2.7%)
Neutrophils (< 750 cells/mm3)	23 (5.6%)	24 (8.1%)
Platelets (< 50,000/mm3)	1 (0.2%)	2 (0.7%)
ALT (> 215 U/L or 5 x ULN*)	18 (4.4%)	9 (3.1%)
AST (>180 U/L or 5 x ULN)	10 (2.4%)	5 (1.7%)
Bilirubin (> 3.0 mg/dL or 2.5 x ULN)	5 (1.2%)	3 (1.0%)
Serum amylase (> 220 U/L or 2.5 x ULN)	9 (2.2%)	3 (1.0%)
BUN (> 120 mg/dL or 5 x ULN)	0	0
Creatinine (> 4.8 mg/dL or 3 x ULN	1 (0.2%)	0
Glucose (> 250 mg/dL)	4 (1.0%)	4 (1.4%)

*ULN = upper limit of normal.

One interesting point in evaluating the proportions of subjects with abnormal laboratory values involves those with markedly increased ALT and AST. A total of 15 of 27 of the patients in the pivotal trials experiencing ≥ Grade 3 ALT increases were co-infected with hepatitis B, hepatitis C or both. In these studies, all patients who experienced Grade 4 elevations of either ALT or AST (> 10 x ULN) were co-infected with hepatitis B and/or hepatitis C. These designations were based on hepatitis screening performed at baseline and not all patients had repeat testing for

hepatitis B and C during their episodes of elevated transaminases. Additionally, the sponsor suggests that patients co-infected with either hepatitis B or C (118 of the 718 patients enrolled) might have been more likely to have elevations of ALT or AST if they received DLV as part of their regimen. However, the number of patients in this post hoc analysis was small and it is difficult to determine if these findings represent a signal of a possible unfavorable drug-disease interaction.

Among the supportive studies there were some study-specific laboratory trends. These were probably related to the variety of other drugs included in the treatment regimens. In ACTG Study 359 there were smaller numbers of patients with Grade 3 and 4 laboratory abnormalities reported in the SQV + RTV + ADV and SQV + NFV + ADV treatment arms than in the other groups. Hypertriglyceridemia was reported in a total of 10 patients in Study 359 with 6 of these receiving SQV + RTV + DLV (12.8% of the patients in that treatment arm). In Study 0074 the sponsor reported statistically larger percentages of patients with increased bilirubin and increased amylase in the patients receiving DLV + 3TC + IDV600 and DLV + ZDV + 3TC + IDV600. The sponsor also reported abnormal prothrombin time in a significantly larger percentage of patients receiving DLV in Study 0013B compared to those not receiving DLV (3.1% compared to 0.7%), although there was no difference between groups in partial thromboplastin time. In many of these smaller studies low neutrophil counts and elevated ALT and AST were encountered relatively frequently but were not observed more often in any treatment group.

Over the course of the pivotal studies, mean changes from baseline through the end of study in either ALT or AST did not appear to be significant. These variables were increased by 0.3 to 2.9 mg/dL in Study 0013C and decreased by 1.6 to 5.3 mg/dL in Study 0021 Part II. For both studies the mean final laboratory values for ALT and AST were within the normal range. No significant differences were identified in mean hemoglobin, neutrophil counts or platelet counts from baseline to 52 Weeks in Study 0021 Part II among the different treatment arms. However, in Study 0013C there were statistically significant differences in mean change from baseline to Week 54 in neutrophil and platelet counts between the 2 study arms. Over 54 weeks the segmented neutrophil counts decreased by 109 cells/mm^3 in the dual therapy arm and increased by 369 cells/mm^3 in the triple therapy arm. Platelet counts increased by 18,000/mm^3 in the dual therapy arm while they increased by 41,000/mm^3 in the triple therapy arm. For both of these hematologic parameters, mean baseline and final neutrophil and platelet counts were within the normal ranges. These changes could reflect the benefit of better HIV therapy.

Overall, the occurrence of significant neutropenia, anemia and elevated liver transaminases was relatively common but not significantly different across study treatment groups. The increased incidence of hypertriglyceridemia observed in Study 359 is more likely attributed to use of PIs although some contribution from the DLV cannot be ruled out. None of the laboratory abnormalities observed in these studies could be clearly attributed to use of DLV and it is difficult to determine which may be related to HIV disease rather than its treatment.

7.6. Post-marketing Safety Reports

Prior to transfer of DLV to Agouron Pharmaceuticals, Pharmacia & Upjohn received 273 spontaneous reports of adverse events in 108 patients receiving the drug. These events may be related to DLV use or may be attributed to underlying HIV disease, co-morbid conditions or other medications. The following table lists the total numbers of events by body systems and those specific events (using Pharmacia & Upjohn's Medical Event Dictionary identifiers) reported at least twice. As with any reporting system, many of the specific event listings could be grouped together to get a clearer idea of the numbers and types of events being reported. For example, rashes are listed as "rash", "maculopapular rash", "papular pruritic skin rash" and "erythematous rash" and it is impossible to determine if these merely represent the spectrum of vocabulary that investigators use to describe the same type of event or if they represent distinct adverse reactions.

Table 21: Number and Type of Events Reported from the Voluntary Reporting System*

Body System/Event	Number of Reports	Number of Patients
Endocrine	1	1
Metabolic	11	7
Weight loss	2	
Ankle swelling	2	
Hematologic	7	5
Neutropenia	2	
Psychiatric	23	10
Anxiety	2	
Hallucinations	2	
Fatigue	4	
Neurologic	33	17
Headache	2	
Unusual dreams	2	
Insomnia	3	
Dizziness	4	
Tingling	2	
Weakness (not otherwise specified)	2	
Warm flushing feeling	2	
Special senses	6	6
Conjunctivitis	2	
Cardiovascular	11	11
Arrhythmia (not otherwise specified)	2	
Respiratory	11	7
Coughing	3	

Gastrointestinal	36	28
Hepatitis	2	
Pancreatitis	3	
Mouth ulcers	2	
Buccal oral disorders NEC/NOS	2	
Nausea	8	
Diarrhea	5	
Mucositis	2	
Urinary tract	3	2
Dermatologic	69	54
Rash	35	
Maculopapular rash	6	
Papular pruritic skin rash	3	
Erythematous rash	4	
Stevens-Johnson syndrome	2	
Hair loss	2	
Pruritis	4	
Itching	5	
Musculoskeletal	20	15
Myalgia	6	
Allergy	3	3
Miscellaneous	26	22
Lack of efficacy	4	
Fever	11	
Chills	3	
Drug interaction	12	8
Cytotoxic antineoplastic interaction	2	
Antiviral agent interaction	7	

Source: Volume 22, Integrated Summary of Safety, pages 216-221.

The sponsor noted that there were 3 reports of Stevens-Johnson syndrome prior to submission of the sNDA. Two are included in the list of spontaneously reported events while the third was described in a published report. The published case describes a patient enrolled in an earlier investigational trial but the trial is not identified and the sponsor cannot give further information regarding the event which occurred prior to transfer of DLV to Agouron. The sponsor was asked to provide any additional information available regarding the occurrence of Stevens-Johnson syndrome but only brief summaries of the cases were returned.

Case 1: A 33 year old male patient with AIDS received combination therapy with DLV and nevirapine. Within 2 weeks of beginning the combination the patient developed a "severe rash and mild Stevens-Johnson syndrome," a swollen face, shorness of breath, flushing and "puffiness of the skin with chest and nasal congestion like a histamine reaction." Concomitant medications included Neupogen, ganciclovir, MS-Contin, fluconazole, azithromycin, oxandrolone, prenatal vitamins, Phenergan and ethembutol. The patient's medical history

included past disseminated CMV, disseminated MAC, HIV wasting syndrome and chronic abdominal pain. The patient required hospitalization for this episode. The physician reported that the Stevens-Johnson syndrome may have been due to the DLV. The events resolved after DLV was discontinued. The nevirapine was also discontinued. There is no mention of what other medications the patient may have received or what treatment was given for the episode. This case was also reported through the FDA surveillance system, AERS.

Case 2: A 42 year old male patient developed Stevens-Johnson syndrome-like symptoms shortly after beginning DLV. The patient had previously been treated with ZDV, 3TC and SQV. Treatment was changed to DLV in combination with IDV and ddC. The patient developed a "severe pruritic truncal rash associated with conjunctivitis" with "significant perioral and labial inflammation that degenerated into a desquamative rash." DLV was discontinued after 16 days of treatment and the rash slowly resolved. The patient was not hospitalized for the episode. Subsequently d4T was substituted for the DLV but the patient tolerated the combination of d4T, IDV and ddC poorly. No recurrence of the rash was reported.

Case 3: A 35 year old male patient enrolled in an early clinical trial (1996-97) using DLV developed a generalized "diffuse, pruritic, erythematous, maculopapular rash" accompanied by mildly injected conjuctivae and oral ulcerations. He had a history of having had a milder rash prior to this presentation and was being treated through it. The patient had mild hepatomegaly without splenomegaly and otherwise physical examination and laboratory tests were reported to be unremarkable except for an LDH = 292 U/L. The patient refused hospitalization so DLV was discontinued and the patient was managed as an outpatient with oral prednisone. He had marked improvement in the rash within 72 hours. There was no evidence of bacterial or viral illnesses reported. All symptoms of Stevens-Johnson resolved and no recurrence was noted.

Since the submission of the sNDA in July, 2000, Agouron reports no additional cases of Stevens-Johnson syndrome reported through the spontaneous reporting system. None of the events reported through this mechanism have suggested new or unexpected toxicity attributable to DLV use.

8. Use in Special Populations

The pivotal clinical trials submitted for review included subjects of both sexes and varied ethnic and racial backgrounds. Study 0013C made special efforts to recruit and enroll women. In spite of these efforts, DLV was investigated in a population of patients that was primarily male and Caucasian. Though the numbers of women and minority subjects were relatively small it does not appear that there are significant differences in adverse events in these subpopulations. Numbers may be too small, however, to detect subtle differences in drug efficacy or toxicity. Similarly, it is impossible to determine whether elderly patients respond to DLV in the same way as younger subjects.

9. Review of Package Insert

A number of changes have been made in the product label, last revised in 1997. Several of these changes had been requested over the past year and were suggested for all antiretroviral drugs metabolized through the CYP3A4 system or for all antiretroviral drugs. These included rewording or adding sections related to the Antiretroviral Pregnancy Registry, use in geriatric patients, recommendations against breastfeeding, and statements regarding interactions with HMG-CoA reductase inhibitors, St. John's wort, sildenafil and other drugs. Additionally, an alert warning to health care providers to find out about medications that should not be taken with DLV has been added to the label and also placed directly on the product's bottle label.

Label changes that were specific to DLV and the Rescriptor label included the following:

1. In the MICROBIOLOGY section the subsections describing drug resistance and cross resistance were re-worded. As previously noted, no new information regarding resistance was submitted but the review team felt that there was enough experience with the drug's use to warrant removing mention of a mutation at position 236 conferring hypersusceptibility to the NNRTIs in vitro.

2. The tables describing the potential interactions affecting levels of concomitantly administered drugs and the effects of other drugs on DLV have been revised. For a more detailed description of these changes based on review of the PK data included in the NDA please see the Biopharmaceutics/Clinical Pharmacology review submitted by Dr. Jenny Zheng.

3. The INDICATIONS AND USAGE section was revised to make clear that DLV should be prescribed in combination with at least 2 other active antiretroviral agents. The following statements have been added to the section in an attempt to provide health care providers with information regarding the potential weaknesses of the DLV pivotal studies.

The following should be considered before initiating therapy with Rescriptor in treatment naïve patients. There are insufficient data directly comparing Rescriptor containing antiretroviral regimens with currently preferred 3-drug regimens for initial treatment of HIV. In studies comparing regimens consisting of 2 NRTIs (currently considered suboptimal) to Rescriptor plus 2 NRTIs, the proportion of patients receiving the Rescriptor regimen who achieved and sustained an HIV-1 RNA level < 400 copies/mL over 1 year of therapy was relatively low (See DESCRIPTION OF CLINICAL STUDIES).

4. In the DESCRIPTION OF CLINICAL STUDIES section the review team requested that the sponsor recalculate the proportion of patients with HIV-1 RNA levels below 400 copies/mL according to the algorithm used by the Division's statisticians. In this analysis "only subjects who achieved confirmed suppression and sustained it through Week 52 are regarded as responders. All other subjects (including never suppressed, discontinued, and those who rebounded after initial suppression of < 400 copies/mL) are considered failures at Week 52." The proportions of patients who were virologic successes, virologic failures and who discontinued study according to this algorithm have been displayed in tabular format for each of the pivotal trials. Tables 3 and 4 of the label display the first event occurring for each patient since it was possible in these studies for patients to rebound > 400 copies/mL and continue on study, then discontinue at a later time because of an adverse event or other reason.

5. The sponsor was asked to include a statement in the DESCRIPTION OF CLINICAL STUDIES section stating that the studies were closed at the recommendation of the DSMB after interim analyses of the efficacy data revealed the superiority of the triple therapy arms compared to dual therapy.

6. The sponsor was asked to remove a description of ACTG Study 359 from the label since the dose of DLV investigated in this study was 600 mg BID rather than the approved 400 mg TID. It was felt that describing the study in the label might provide the sponsor with the means to market a dose regimen that has not been formally reviewed and approved. We have suggested that the sponsor consider submitting a formal supplement to review the 600 mg BID dose regimen in the future since it was investigated in 3 of the smaller studies presented in this sNDA. Long-term data from those studies may now be available. The sponsor was also asked to remove a brief description of Study 0074 claiming activity for a specific combination regimen and substitute a more general statement regarding potential activity in 3 or 4-drug regimens in combination with PIs and NRTIs.

7. The first 2 paragraphs of the Drug Interactions section of the label WARNINGS have been revised for clarity and combined. The new wording is as follows:

Because DLV may inhibit the metabolism of many different drugs (e.g., antiarrhythmics, calcium channel blockers, sedative hypnotics and others),

serious and/or life threatening drug interactions could result from inappropriate co-administration of some drugs with DLV. In addition, some drugs may markedly reduce DLV plasma concentrations, resulting in suboptimal antiviral activity and subsequent emergence of drug resistance. All prescribers should become familiar with the following tables in this package insert: **Table 5, Drugs That Are Contraindicated with Rescriptor; Table 6, Drugs That Should Not Be Co-administered with Rescriptor; and Table 7, Established and other Potentially Significant Drug Interactions for Which Alteration in Dose or Regimen May Be Recommended.** Additional details on drug interactions can be found in Tables 1 and 2 under the **Clinical Pharmacology Section.**

8. The subsection describing Skin Rash in the PRECAUTIONS section has been revised and reformatted to highlight the possibility of rare but severe forms of rash. The first paragraph of this subsection now reads:

Skin Rash: Severe rash including rare cases of erythema multiforme and Stevens-Johnson syndrome have been reported in patients receiving Rescriptor. Erythema multiforme and Stevens-Johnson syndrome were rarely seen in clinical trials and resolved after withdrawal of Rescriptor. Any patient experiencing severe rash or rash accompanied by symptoms such as fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches should discontinue Rescriptor and consult a physician. Two cases of Stevens-Johnson syndrome have been reported through post-marketing surveillance out of a total of 339 surveillance reports.

9. The Drug Interactions subsection of the PRECAUTIONS section has been revised according to the recommendations of the Biopharmaceutics/Clinical Pharmacology review team. Table 6, Drugs That Should Not Be Co-administered with Rescriptor and Table 7, Established and other Potentially Significant Drug Interactions for Which Alteration in Dose or Regimen May Be Recommended have been modified to improve readability.

10. The ADVERSE REACTIONS section has been substantially modified from the sponsor's original proposal. A text description of skin rash is now followed by Table 8, Percent of Patients with Treatment-Emergent Rash in Pivotal Trials (Studies 0021 Part II and 0013C). This table, similar to ones found in the labels for the 2 other approved NNRTI drugs, displays the proportions of patients developing rash of different grades of severity in patients receiving DLV or the control regimen regardless of the assigned causality.

11. The sponsor had originally proposed documenting the frequency of medical adverse events in a table displaying events of moderate to severe intensity that were thought by the investigator to be related to DLV (or blinded study drug) or of unknown causality. The review team felt that this method of displaying the data failed to give an adequate representation of the extent of adverse events observed

during the pivotal trials. In these trials, investigators were required to assign causality of an adverse event to one of a list of medications or conditions (ie., ZDV, 3TC, DLV or blinded study medication, HIV disease) rather than the more current method of assigning causality as possibly, probably, definitely or not related to study drug. It is unlikely that investigators with limited experience with DLV would be able to accurately assign causality. We felt that the label should display adverse events of moderate or greater severity regardless of causality that occurred in more than 5% of patients in the trial. Some medical event terms were combined in the table (eg., "rash" and "rash maculopapular"). Adverse events resulting from laboratory abnormalities were deleted from this table and captured in Table 10, Marked Laboratory Abnormalities Reported by > 2% of Patients. Minor changes were suggested in Table 10 to improve readability.

10. Phase 4 Commitments

Many of the Phase 4 commitments and Post-Accelerated Approval commitments that were agreed upon by Pharmacia & Upjohn and the Division in 1997 have been fulfilled. Unfulfilled commitments remaining from those original agreements include the following:

[ ]

2. Consideration will be given to investigate the use of higher doses of DLV, including twice daily dosing regimens.

We would remind the sponsor that these commitments are now their responsibility. Additional Phase 4 commitments negotiated with this sNDA include:

1. Evaluate delavirdine pharmacokinetics in subjects with hepatic impairment, to allow the determination of dosing recommendations.

2. Establish appropriate dosing recommendation for the coadministration of delavirdine with lopinavir/ritonavir.

3. Establish appropriate dosing recommendation for the coadministration of delavirdine with ritonavir.

11. Conclusions

This sNDA provides clear evidence of the antiretroviral activity of DLV when used in combination with at least 2 NRTIs. The studies submitted to support traditional approval include 2 relatively large pivotal trials of similar design comparing 3-drug regimens containing DLV to similar background 2-drug regimens and 8 smaller exploratory studies

evaluating different 3 and 4 drug regimens including DLV and a variety of PIs and NRTIs. Both of the pivotal trials were terminated early by their respective DSMB when interim analyses of the efficacy data revealed significant superiority of the 3-drug regimens containing DLV plus 2 NRTIs compared to the dual NRTI regimens. This benefit was evident whether the analysis was performed as a time-to-event/survival plot of patients who reached the endpoint "time to virologic failure" or as a proportion of patients who reached and maintained an undetectable viral load (either < 400 copies/mL or < 50 copies/mL). From a statistical perspective the results are overwhelmingly in favor of the benefit of DLV use in HIV-infected patients with limited or no prior NRTI therapy over a 1 year period.

The difficulty comes in assigning the appropriate clinical weight to these statistical results. In order to assess the drug's potential clinical utility the studies submitted for this sNDA must be viewed in the context of when and how they were conducted. The DLV clinical trials were in progress during a time of rapid evolution in HIV management as the new technology allowing accurate measurement of HIV-1 RNA levels was becoming a standard monitoring tool in clinical practice. Health care providers and patients became aware that an undetectable viral load was an achievable and desirable goal. Study 0021 Part II was originally designed to keep investigators and patients blinded to HIV-1 RNA levels. Patients and investigators became increasingly unwilling to accept this information deficit and the study was ultimately amended to provide real-time viral load monitoring.

The then-new 3-drug regimens containing a PI and 2 NRTIs improved CD4 counts and lowered viral load to undetectable in large numbers of patients at all stages of HIV disease. These improvements were very significant in patients with no prior antiretroviral therapy, however, the most dramatic and visible results were seen in patients with very advanced HIV. Patients and physicians clamored for the new regimens. A relatively large number of patients left the pivotal trials because they or their physicians chose to institute PI-based therapy. Fortunately, these discontinuations are balanced across the treatment arms, and many of the patients who chose to leave the studies had actually reached the virologic endpoints that were added to the study analyses after the studies were in progress. It was, therefore, possible to assess the virologic results for all patients who had HIV-1 RNA measurements regardless of their sponsor-stated reason for discontinuing study.

The DLV pivotal trials confirmed the results seen in trials comparing 2 and 3-drug combinations investigating other drugs (including PIs). A regimen of 2 NRTIs provides much poorer antiretroviral activity than a regimen of 2 NRTIs plus a drug of another class. For this reason these studies were among the last which used a 2-drug comparator regimen. The review team was faced with the task of assessing results of clinical trials completed 3 years ago, using comparator arms that are now considered sub-standard therapy. New antiretroviral drugs being developed now would not be allowed to use this study design or the DLV studies' original analysis plan. The final study results of 29% (Study 0013C) to 45% (Study 0021 Part II) percent of patients achieving and maintaining an undetectable viral load through 1 year of therapy are considered barely adequate by

current standards. It is difficult to make any cross-study comparisons of efficacy of antiretroviral drugs since details of study design and patient population may be significantly different. However, there are many examples of similar 3-drug regimens providing apparently greater benefit. For example, NFV given either on its TID or BID schedule plus 2 NRTIs achieved undetectable viral load in about 60% of patients with limited or no prior treatment experience and efavirenz plus 2 NRTIs given to patients with prior NRTI experience reported 60-68% patients with HIV-1 RNA < 400 copies/mL in its registrational trials. A recent meta-analysis of the effectiveness of 3-drug combinations in treatment naïve patients revealed that the average proportion of patients achieving < 400 copies/mL at 48 weeks was 52% for those receiving a PI plus 2 NRTIs regimen and 61% for those receiving an NNRTI plus 2 NRTIs regimen (including 1 DLV study was included in the analysis). DLV in combination with 2 NRTI's did not perform as well in a population of patients with limited prior therapy as we have come to expect from more contemporary studies but this may be partly because the study populations were somewhat more advanced.

In reviewing the smaller supportive studies designed to better identify an appropriate patient population and regimen in which DLV might best be used, the review team could not confirm a particular niche for DLV. In Study 359, a complicated, 6-arm study, DLV in combination with 2 PIs performed better than ADV plus 2 PIs. This may have been an unfortunate comparison since ADV was not approved for treatment of HIV infection and it is unclear how to assess it as part of a comparator regimen. In some of the supportive studies, DLV as a fourth drug appeared to add nothing to a 3-drug regimen. In some studies, however, the 4-drug regimens were not tolerated as well as the 3-drug regimens. In some studies, DLV combined with 2 other drugs provided similar benefit compared to NFV or IDV combined with the same drugs. None of these studies were large enough or extended [illegible]

Assessing the safety of the studied doses of DLV is easier. Rash was the only medical adverse event that was associated with DLV use, occurring in approximately one third of patients receiving the drug in the pivotal trials. The rash associated with DLV typically developed within the first 3 weeks of use and resolved completely with discontinuing drug. As the pivotal studies progressed, patients with milder forms of rash were encouraged to continue study drug in spite of rash rather than stop drug and gradually re-introduce DLV. No additional skin biopsy data was submitted with this sNDA but the rash does not appear to be the result of a systemic vasculitis. Most of the rash events were mild or moderate in severity and few resulted in patients discontinuing study or requiring hospitalization. Severe forms of rash, including erythema multiforme and Stevens-Johnson syndrome, have been reported during DLV use and patients and physicians will require information regarding this possibility. The review team has attempted to make this information available in both the label and the Patient Package Insert. Other medical adverse events occurred at similar frequencies in patients receiving DLV and those receiving other drug regimens without DLV. Interestingly, there has been no evidence of systemic vasculitis in the patients enrolled in the clinical trials, either

those submitted with the original NDA or those included in this submission. This had been a concern at the time of the original approval because of animal toxicology studies revealing vasculitis in a significant proportion of dogs.

Significant laboratory abnormalities did not occur more frequently in patients receiving DLV in the clinical trials. There was a suggestion that patients who were co-infected with hepatitis B and/or hepatitis C might be more susceptible to developing elevations of liver transaminases. This may be an area for future surveillance as DLV becomes more widely used, especially since another drug in the NNRTI group (nevirapine) has been associated with hepatotoxicity. Neutropenia and anemia developed in a small but significant number of patients participating in the pivotal trials but the frequency was no greater in patients receiving DLV. It is most likely that the concomitant use of ZDV played an important role in the development of cytopenias in these studies.

For the reasons described above, the review team felt that it was appropriate to extend traditional approval for DLV but also to provide some information in the label regarding the potential weaknesses of the studies and the relatively low rate of sustained virologic suppression in the pivotal trials. A statement has been included in the INDICATIONS AND USAGE section of the label indicating that the proportion of patients achieving and maintaining an undetectable viral load was relatively low. It is hoped that physicians would consider this carefully when initiating therapy with DLV in treatment naïve HIV-infected patients. In spite of some ambivalence regarding the pivotal trial design, the review team confirmed the contribution of DLV in large pivotal trials and ACTG-sponsored studies in 3 and 4-drug combinations and is confident that it will fulfill a useful role in the treatment of HIV-infected individuals.

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/s/

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5/16/01 04:47:37 PM
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Traditional approval recommended.

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