Bristol-Myers Squibb Company

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ATAZANAVIR BRIEFING DOCUMENT MAY-2003

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SUMMARY

Current therapies for HIV-infected patients are highly effective but their success is limited by the need to adhere to complex regimens with multiple daily doses and large pill counts, intolerance and long-term safety issues. Treatment with highly active antiretroviral therapy (HAART) combination regimens represents the standard of care combining the use of three separate classes of antiretroviral (ARV) therapies — nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). Nonetheless, potential areas for improvement in the use of HIV therapies still exist. In fact, long-term treatment with HAART regimens is increasingly linked with important safety and tolerability issues, including the emergence of drug-resistant HIV strains and toxicity associated with the use of PIs and NNRTIs.

In this briefing document, we present data demonstrating that atazanavir (BMS-232632, ATV) is an effective PI for treating HIV-infected patients. Atazanavir is a true once-a-day PI with the single daily administration of two capsules. Review of clinical trial efficacy data demonstrates that in ARV treatment-naive patients ATV dosed at 400 mg daily is as effective as efavirenz (EFV), an ARV standard of care for HIV-infected patients. Atazanavir is also as effective as the commonly used PI nelfinavir (NFV) in ARV treatment-naive patients. ATV was also effective in ARV treatment-experienced subjects, and preliminary data in ARV treatment-experienced patients also suggest that ATV 300 mg dosed in combination with ritonavir (RTV) appears as efficacious as lopinavir/ritonavir (LPV/RTV), a standard of care in this patient population.

Importantly, ATV has been shown to exhibit a distinct resistance profile that contributes to an overall maintenance of ARV treatment efficacy for HIV-infected patients by potentially limiting the development of resistance to other PI agents. Atazanavir possesses a distinct and advantageous resistance profile involving the induction of a unique I50L substitution.

Atazanavir has been shown to possess a unique benefit/risk profile that addresses the hyperlipidemia currently emerging in the HIV-infected patient population chronically

treated with HAART regimens. Prospective studies in large cohorts of HIV-infected patients have demonstrated that hyperlipidemia with both hypercholesterolemia and/or hypertriglyceridemia frequently develops with long-term use of antiretrovirals and may ultimately be associated with an increase in cardiovascular risk among patients on maintenance HAART regimens. Compared to other PIs, ATV has no adverse impact on cholesterol, triglyceride, and other metabolic parameters, including insulin and glucose. In addition, in patients who developed hyperlipidemia due to prior HAART regimens, ATV has been shown to decrease lipid concentrations to near normal levels.

The high pill burden of HAART regimens and the often unavoidable drug interactions that may occur when these therapies are dosed multiple times per day often interfere with the effective choice and use of other medicines designed to treat these newly developing metabolic disorders.

Across the clinical trials program, ATV was shown to be very safe and tolerable and in general similar to other commonly used drugs in HAART regimens. It was not associated with the frequently observed side effects of other PIs (eg, diarrhea with NFV) or NNRTIs (eg, rash and CNS symptoms with EFV). Two topics of special interest, unconjugated hyperbilirubinemia and cardiac conduction effects are reviewed in this briefing document. Elevation in unconjugated bilirubin is the most notable laboratory abnormality during treatment with ATV. These increases in bilirubin are reversible, manageable in the clinic, and dissociated from hepatocellular toxicity as indicated by a lack of concomitant rises in ALT or AST transaminases, except as a consequence of unrelated causes, such as co-existing viral hepatitis. The etiology for hyperbilirubinemia due to ATV is inhibition of the uridine diphosphate-glucuronosyl transferase 1A1 (UGT 1A1) enzyme, a mechanism previously elucidated with another PI, indinavir (IDV). Hyperbilirubinemia was common on ATV and occasionally associated with clinical jaundice and/or scleral icterus. No long-term clinical sequelae related to hyperbilirubinemia have been observed.

Finally, extensive electrocardiographic (ECG) assessments of ATV during the clinical development program have contributed to the understanding of the limited potential significance of *in vitro* assay findings and clinical ECG abnormalities. Overall, the incidence of QT_c and PR interval prolongations in ATV-treated patients is low and comparable to standard of care regimens. Thus, ATV is judged to possess no greater ECG liability than currently marketed ARV agents. Nonetheless, appropriate consideration of

drug interactions with ATV that could lead to cardiac conduction abnormalities (due to effects on exposure of the co-administered agent) will need to be provided to the treating physician.

In summary, ATV is a novel PI with important differentiating characteristics. In addition to efficacy comparable to other reference agents, ATV provides the convenience of once-a-day dosing and a decreased pill-burden (two capsules once-daily), along with the lack of increases in serum lipid parameters, which obviates the need for lipid lowering therapy in many patients and which may provide long-term cardiovascular benefit. Atazanavir's distinct resistance profile is characterized by a signature substitution of isoleucine for leucine at codon 50 (I50L) in the PI gene. This signature mutation strengthens its uniqueness and its potential benefit for treatment-naive and treatment-experienced patients. Atazanavir represents an important addition to enhancing and improving the management of HIV infection. The pharmacokinetic, efficacy, and safety data generated during the ATV clinical development program support the indication sought for its use in combination with other ARV agents for the treatment of HIV-1 infection in both ARV treatment-naive and ARV treatment-experienced patients.

1 INTRODUCTION

The development of PIs and NNRTI for the treatment of HIV-1 infection has led to the implementation of ARV combination regimens that result in durable suppression of HIV replication in HIV-infected patients. The therapeutic use of HAART regimens has led to measurable declines in morbidity and mortality due to HIV-1 infection and its complications. Along with sensitive monitoring of viral load and resistance testing, HAART regimens are considered key components of state-of-the-art care for HIV-infected patients.

Primary determinants of successful virologic suppression for patients receiving HAART regimens include the potency of the combination and the ability of the patient to remain compliant with the regimen. For ARV regimens, patient compliance is a function of the complexity and tolerability of the regimen. In general, patients that can maintain greater than 95% compliance with their HAART regimen are able to demonstrate sustained virologic responses. Regimens that are well tolerated and easy to administer (eg, few pills, once-daily frequency of dosing) are likely to encourage the high patient compliance that is necessary to enhance viral response clinical outcomes.

Atazanavir represents a therapeutic advance for the treatment of HIV-infected patients based on three important features: 1) simplicity of dosing administration with two capsules given once-daily; 2) demonstrated efficacy in both ARV treatment-naive and treatment-experienced patients; and 3) a good safety and tolerability profile that is most notable among current PIs for its unique lipid neutrality, having no adverse impact on cholesterol, triglycerides, and other metabolic parameters, including insulin and glucose. Finally, a unique benefit of ATV is the preservation of future treatment options because HIV resistance is slow to develop and because cross-resistance to other PIs does not appear to evolve even when decreased susceptibility to ATV develops due to the selection of viral isolates with a specific resistance mutation.

1.1 Pharmacologic Class

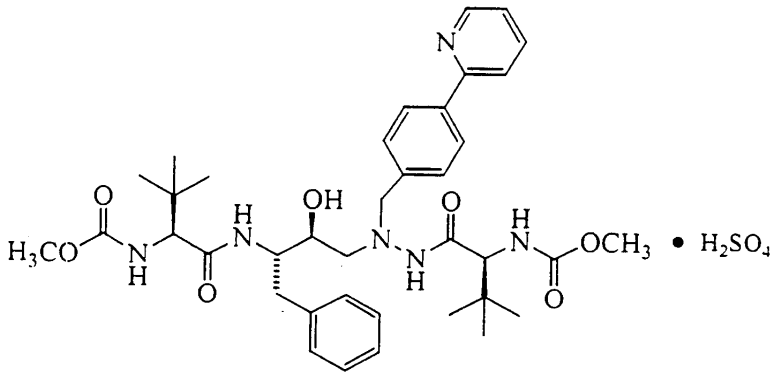
Atazanavir (BMS-232632, ATV) is an azapeptide PI that has demonstrated *in vitro* antiviral potency (EC_{50} 2 - 5 nM) against a variety of HIV isolates that exceeds that of

marketed PIs. HIV isolates taken from patients not previously exposed to ARV therapy have been shown to be extremely sensitive to ATV. Atazanavir has been shown to have a pharmacokinetic (PK) profile that clearly supports once-daily administration. This profile has been demonstrated in both Phase I studies in healthy individuals and in Phase II/III studies in HIV-infected patients.

1.2 Description and Structure of Atazanavir

The chemical name for atazanavir sulfate is (3*S*,8*S*,9*S*,12*S*)-3,12-Bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl]methyl]-2,5,6,10,13-pentaazatetradecanedioic acid dimethyl ester, sulfate (1:1). Its molecular formula is $C_{38}H_{52}N_6O_7 \bullet H_2SO_4$, which corresponds to a molecular weight of 802.9 (sulfuric acid salt). The free base molecular weight is 704.9. Atazanavir sulfate has the following structural formula (Figure 1.2):

Figure 1.2: Structural Formula of Atazanavir Sulfate



2 NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

During the course of its development, the nonclinical safety profile of ATV has been extensively evaluated in safety pharmacology, pharmacokinetic/ADME, and toxicology studies using test systems and protocols accepted by ICH and international health authorities. As clinical development of ATV progressed, studies of up to 9 months duration in three different species (rats, mice, and dogs) established support for the doses used in the clinical trials of healthy volunteers and HIV-infected patients. Overall, the safety pharmacology, pharmacokinetic, and toxicology studies supported the use of ATV in Phase I, II, and III studies. Details describing the results of these comprehensive nonclinical studies are available in Appendix 2.

3 MICROBIOLOGY AND RESISTANCE

The emergence of resistance mutations among HIV isolates or strains can severely limit treatment options for HIV-infected patients. Atazanavir has been extensively studied *in vitro* and *in vivo* in order to understand how *in vivo* HIV resistance may limit and guide optimum therapy approaches to the use of ATV. Overall, the occurrence of ATV resistance among HIV isolates from infected patients is infrequent. Importantly, when viral resistance to ATV does emerge in treatment-naive patients, a unique signature mutation in the HIV genome is identified (I50L). This mutation may not confer cross-resistance to other PIs. Thus, the use of ATV as an HIV treatment option does not limit the subsequent use of other drugs in the PI class. Supportive *in vitro* virology and resistance experiments and important clinical aspects related to the development of *in vivo* resistance to ATV are described in more detail below.

3.1 *In Vitro* Virology

Atazanavir was tested in a fluorescence-based *in vitro* protease assay in parallel with several commercially available HIV PIs. Atazanavir inhibited the cleavage activity of HIV-RF protease with a K_i of 0.75 nM which is comparable to the inhibitory activity of other PIs. Indinavir (IDV), nelfinavir (NFV), saquinavir (SQV), and ritonavir (RTV) resulted in K_i values of 0.73 nM, 1.05 nM, 0.39 nM and 1.01 nM, respectively, in this assay. Atazanavir is a highly specific inhibitor of protease, displaying IC_{50}s against a panel of human cellular aspartyl proteases > 10,000-fold higher than observed for HIV-1 protease.

Antiviral evaluation against a variety of HIV strains and host cell types showed that ATV displays EC_{50}s ranging from 2 - 5 nM. Comparative studies revealed that ATV is 2- to 20-fold more potent than other PIs including IDV, NFV, RTV, SQV and amprenavir (APV). Cytotoxicity determinations (CC_{50}) in each host cell revealed that the selectivity index of ATV (range > 174 to 19,084) is comparable to other approved HIV PIs. Atazanavir inhibited the cleavage of gag protein (p55) by HIV protease in chronically-infected cells with an EC_{50} of 47 nM, indicating that the inhibitory effect of ATV in cells is the result of blocking HIV-1 protease activity.

To determine the effect of human serum proteins on the antiviral activity of ATV, 40% human serum was included in a series of cell culture assays. Addition of human serum increased the ATV EC_{50} from 1.5 nM to 7.8 nM (5-fold), similar to the other PIs but significantly less than NFV (≥ 17-fold). In addition, ATV in the presence of 40% human serum is still 3- to 19-fold more potent than the other approved PIs.

3.2 *In Vitro* Resistance

To assess the potential for resistance development, three strains (RF, LAI, and NL4-3) of HIV-1 were serially passaged in cell culture in the presence of increasing concentrations of ATV for up to 4.8 months. For comparative purposes, the RF virus was also passaged in parallel with each of the clinically available HIV PIs. Results showed that ATV selected for RF resistant variants less readily than NFV or RTV, but at a similar rate compared to IDV and APV. Genotypic and phenotypic analysis indicated that an N88S substitution appeared first during passage of the RF and LAI viruses. The LAI virus exhibiting a 93-fold reduced susceptibility to ATV contained five amino acid changes (L10Y/F, I50L, L63P, A71V, N88S), while the NL4-3 virus showing a 96-fold decrease in susceptibility contained 4 amino substitutions (V32I, M46I, I84V, L89M). The NL4-3 variant has a well-documented resistance substitution (I84V) located near the protease active site; whereas, the resistance phenotype of LAI is attributed to the appearance of I50L and N88S substitutions, in combination with other secondary substitutions at residues 10, 63 and 71. Substitutions were also observed at the protease cleavage sites in all three viruses following drug selection. The evolution to resistance seemed distinct for each of the three strains used, suggesting the potential for multiple pathways to resistance and indicating the importance of viral genetic background.

3.3 *In Vitro* Cross Resistance

The ATV-resistant viruses generated *in vitro* were profiled for susceptibility to five available PIs. Mixed results were obtained depending on the virus studied and the level of ATV resistance. In general, ATV-resistant virus remained susceptible to SQV, while it showed varying levels (0.06 to 71-fold change) of cross-resistance to NFV, IDV, RTV and APV. Interestingly, ATV-resistant LAI viruses (harboring the unique I50L substitution) exhibited increased susceptibility to RTV and APV.

To obtain a greater understanding of the overall resistance profile of ATV relative to other available PIs, the susceptibility profile of ATV and several marketed HIV-1 PIs was evaluated against a diverse set of HIV-1 clinical isolates. A cross resistance profile was determined for the 551 clinical isolates exhibiting resistance to one or more of the currently marketed PIs by assaying for susceptibility to ATV and six other PIs: APV, IDV, LPV, NFV, RTV and SQV. Atazanavir susceptibility was retained by 86% of the isolates resistant to one or two PIs and by 34% of the isolates resistant to three PIs. However, susceptibility to ATV was quickly lost when viruses displayed cross-resistance to four or five of the PIs. The overall ATV resistance profile and coverage of this panel of resistant isolates indicated that ATV is distinct from the other PIs, with some possible relatedness to NFV noted. All of the isolates in this evaluation contained multiple mutations, although no clear mutation patterns predictive of ATV resistance could be discerned. The ATV median fold change (FC) for all 551 resistant isolates was 3.9, with a median FC of 9.5 for the subset of 311 isolates showing an ATV FC of > 3.0-fold. In general, reductions in ATV susceptibility required several amino acid changes, were relatively modest in degree and was retained among isolates resistant to one or two of the currently approved PIs.

Analysis of the genotypic profiles of 943 of the 950 PI susceptible and resistant clinical isolates identified a strong correlation between the presence of the specific amino acid changes at 10I/V/F, 20R/M/I, 24I, 33I/F/V, 36I/L/V, 46I/L, 48V, 54V/L, 63P, 71V/T/I, 73C/S/T/A, 82A/F/S/T, 84V and 90M and decreased susceptibility to ATV. While no single substitution or combination of substitutions is predictive of ATV resistance, the presence of at least five of these substitutions correlated strongly with loss of ATV susceptibility. This observation is consistent with an earlier result as substitutions at five of the residues identified, 10, 33, 46, 63, 71 and 84, also emerged during *in vitro* selection of resistant viruses.

3.4 Resistance Profile Amongst Viral Isolates From Atazanavir Clinical Studies

Phenotypic and genotypic analyses of clinical isolates were conducted to monitor resistance to ATV and to determine changes emerging in ATV-containing regimens. The clinical isolates were obtained from patients who had displayed virologic failure on regimens containing ATV and who exhibited decreased susceptibilities to ATV

(FC ≥ 2.5-fold). Distinct resistance patterns emerged. Treatment-naive patients who developed resistance on ATV-containing regimens all developed specific resistance to ATV through the emergence of a unique I50L substitution, accompanied by an A71V change about 40% of the time. The I50L substitution was identified in all 23 treatment naive subjects who developed ATV resistance (defined by phenotype greater than 2.5 fold increase from wild-type). None of the other amino acid changes observed appeared to correlate with resistance to ATV, and these changes occurred in a variety of genetic backgrounds. Phenotypic data on these clinical-failure isolates showed that emergence of resistance was modest in degree and specific for ATV. An important finding was that a reduced susceptibility to ATV was not associated with the loss of susceptibility to other PIs, but rather an increased susceptibility to all of the other PIs was observed.

The I50L resistance pathway was also observed with ATV therapy in treatment-experienced patients when they contained isolates displaying susceptibility to ATV and lacking cross-resistance to other PIs at baseline. In contrast, phenotypic and genotypic evaluation of viral isolates from patients receiving an ATV/SQV-containing regimen showed no evidence of the I50L substitution. In these patients, isolates displayed decreased susceptibility to multiple PIs along with resistance to ATV and SQV; this decreased susceptibility coincided with the accumulation of several additional amino acid substitutions, including I84V. This was an expected result, since presence of the I50L substitution would be resistant to ATV, but have increased susceptibility to SQV. A similar pathway was also observed when ATV was used as the only PI in those patients exhibiting cross-resistance to other PIs and decreased susceptibility to ATV.

The I50L substitution, sometimes in combination with an A71V change, appears to be the signature resistance mutation for ATV. To further evaluate its impact, a number of recombinant viral clones have been created containing the I50L substitution, expressed in a variety of genetic backgrounds. Phenotypic profiling of these recombinant viruses with ATV and six other PIs showed that resistance was specific to ATV and coincided with enhanced susceptibility to APV, IDV, LPV, NFV, RTV, and SQV. These recombinant viruses containing the I50L and the I50L/A71V substitutions were also shown to be significantly growth impaired. There was no evidence of cross-resistance between ATV and APV, despite the known relationship between the I50V substitution and APV resistance.

The resistance pattern observed among treatment-naive subjects who experience virologic failure on ATV studies and the effect of baseline mutations and resistance on virologic response among treatment-experienced subjects is further described within the efficacy section of this document.

4 CLINICAL PHARMACOLOGY AND DOSE SELECTION

4.1 Clinical Pharmacokinetics

Atazanavir has been evaluated in 27 clinical pharmacology studies conducted in healthy volunteers to elucidate the single dose and steady-state pharmacokinetics (PK), the effect of food, age, gender, and hepatic impairment or drug interaction potential of ATV. In addition, the pharmacokinetics of ATV have been studied in HIV-infected subjects as part of PK sub-studies or population PK assessments within Phase II clinical trials (refer to Appendix 1 Clinical Trials Directory).

4.1.1 Pharmacokinetics of Atazanavir in Healthy vs HIV-Infected Subjects

The steady-state PK parameter values for ATV at 400 mg in the fed state in healthy or HIV-infected subjects are provided in Table 4.1.1.

Table 4.1.1: Steady-State Pharmacokinetic of ATV in Healthy or HIV-infected Subjects in the Fed State Following ATV 400 mg QD

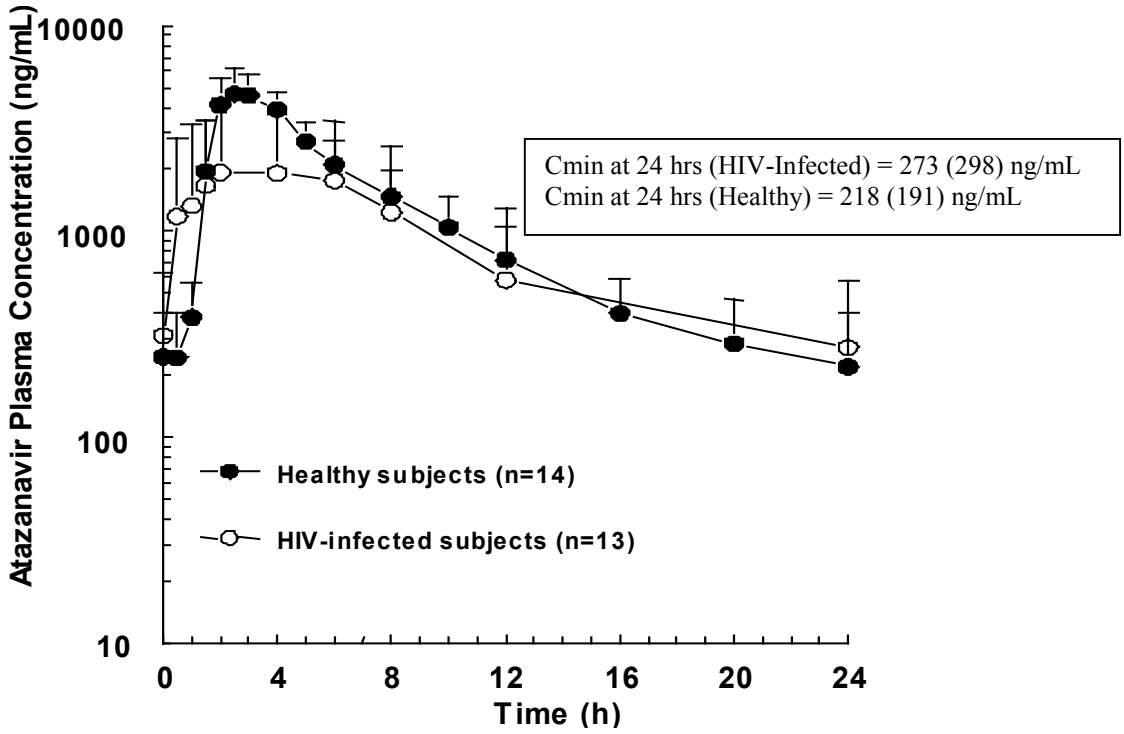
PK Parameters	Healthy Subjects (n = 14)	HIV-Infected Subjects (n = 13)
C_{max} (ng/mL)		
Geometric Mean (CV%)	5199 (26)	2298 (71)
Mean (SD)	5358 (1371)	3152 (2231)
Range	(3166 - 7970)	(448 - 7446)
T_{max} (hr)		
Median	2.5	2.0
Range	(1.5 - 4.0)	(0.5 - 6.0)
AUC (ng.hr/mL)		
Geometric Mean (CV%)	28132 (28)	14874 (91)
Mean (SD)	29303 (8263)	22262 (20159)
Range	(14756 - 46532)	(3009 - 75882)
T-Half (hr)		
Mean (SD)	7.9 (2.9)	6.5 (2.6)
Range	(3.0 - 15.2)	(2.8 - 12.6)
C_{min} (ng/mL)		
Geometric Mean (CV%)	159 (88)	120 (109)
Mean (SD)	218 (191)	273 (298)[a]
Range	(12 - 840)	(12 - 890)

Source: AI424013 Clinical Study Report and AI424008 Pharmacokinetic Study Report

[a] n = 12

Figure 4.1.1 displays the mean plasma concentration-time profile of ATV in healthy and HIV-infected subjects in the fed state following ATV 400 mg QD.

Figure 4.1.1: Mean (SD) Plasma Concentration-Time Profile of ATV in Healthy and HIV-Infected Subjects Following ATV 400 mg QD at Steady-State



Source: AI424008 Pharmacokinetic Report and AI424013 Clinical Study Report

The key findings were:

- ATV exposures (C_{max} and AUC) were lower in HIV-infected compared with healthy subjects. There was, however, considerable overlap in the range of exposure values in these two subject groups.
- In contrast, C_{min} values appeared similar in these two subject groups. This similarity was noted in the context of the inherent variability of this parameter.

4.1.2 Absorption

The key findings related to ATV absorption were:

- ATV was rapidly absorbed with a T_{max} of approximately 2.5 h;
- ATV is recommended to be administered with food as food enhances bioavailability and reduces pharmacokinetic variability;
- ATV demonstrated non-linear PK with greater than dose proportional increases in AUC and C_{max} values over the dose range of 200 - 800 mg QD;
- Steady-state was achieved between Days 4 and 8 in both healthy and HIV-infected subjects, with an accumulation index of approximately 2 to 3.

4.1.3 Distribution

The key findings related to ATV distribution were:

- ATV exhibited concentration independent protein binding to albumin and α1-acid glycoprotein of approximately 86%. This suggested minimal potential for drug-drug interactions on the basis of displacement of protein bound drugs and/or for effects of fluctuating concentrations due to changes in plasma protein content;
- ATV was found to distribute into the cerebrospinal (CSF) and seminal fluid. The CSF/plasma ratio for ATV in HIV-infected subjects (n = 4) ranged between 0.0021 and 0.0226 and seminal fluid/plasma ratio (n = 5) ranged between 0.11 and 4.42.

4.1.4 Metabolism

The key findings related to ATV metabolism were:

- CYP3A4 is the major isoform responsible for ATV metabolism;
- Three minor metabolites of ATV, BMS-421419, BMS-551160 and an unidentified keto metabolite [M41] have been noted in the systemic circulation. BMS-421419 and BMS-551160 are inactive against HIV, show no appreciable CYP inhibition, do not produce significantly greater effects than ATV in the HERG and Purkinje fiber assays and are not viewed as clinically important. The structure of the M41 metabolite is currently being confirmed via synthesis;
- ATV is a competitive inhibitor of CYP3A4 (Ki, inhibition rate constant = 2.35 μM) and UGT1A1 (Ki = 1.9 μM) at clinically relevant concentrations. ATV also competitively inhibits CYP1A2 and CYP2C9, but the Ki values (Ki ≥ 12.2 μM) were higher than steady-state plasma concentrations, suggesting that ATV is unlikely to inhibit CYP1A2 and CYP2C9 substrates at the recommended dose.

4.1.5 Elimination

The key findings related to ATV elimination were:

- The kidneys play a minor role in the elimination of ATV and/or its metabolites as approximately 13% of a [^{14}C]-labeled dose was excreted in the urine with approximately 7% of the dose excreted as unchanged drug;
- Approximately 79% of a [^{14}C]-labeled dose was recovered in the feces, suggesting that biliary elimination is a major pathway for the elimination of ATV and/or a fraction of the dose is unabsorbed.

4.1.6 Special Populations

The key findings related to ATV in special populations were:

- No clinically important PK differences due to age or gender were noted;
- A 45% increase in AUC in hepatically-impaired subjects versus healthy subjects suggests that a reduction in dose, for example to 300 mg once-daily, may be warranted in subjects with mild to moderate hepatic impairment. ATV is not recommended in patients with severe hepatic impairment;
- As the kidneys play a minor role in the elimination of ATV, a study in renally impaired subjects has not been conducted and a dose modification is not warranted in these patients.

4.1.7 Drug Interactions

The treatment of HIV infection and the care of co-morbid diseases in these patients often requires the concomitant administration of numerous drug therapies. Understanding the effects of concomitantly administered agents upon one another is critical to the safe and efficacious use of these medicines. Important considerations in determining the drug-drug interactions examined in a drug development program include: (1) the pharmacokinetic and pharmacodynamic properties of the drug development candidate; (2) drugs which may be commonly concomitantly administered; (3) the potential for a concomitantly administered agent to reduce or enhance the absorption, distribution, metabolism or elimination pathways of the drug development candidate or vise versa; and (4) the potential for antagonism or synergy for desired or unwanted pharmacologic effects.

Atazanavir is an HIV protease inhibitor which is primarily metabolized in the liver. Atazanavir is a substrate and a moderate inhibitor of CYP3A4 (Ki = 2.35 μM; ketoconazole Ki < 0.1 μM), and also a competitive inhibitor of UGT1A1 (Ki = 1.9 μM). Thus, ATV may have the potential to alter the metabolic clearance of drugs that are metabolized by CYP3A4 and/or conjugated by UGT1A1. Furthermore, ATV may have its metabolic clearance altered by drugs which have the potential to inhibit or induce CYP3A4. In addition, ATV may be a substrate of an apically located efflux pump (eg, P-glycoprotein, P-gp) and a weak inhibitor of P-gp with an IC_{50} value of ~29 μM based on *in vitro* Caco-2 cell model studies. However, P-gp inhibition by ATV may be of minimal clinical consequence as this effect has been observed at concentrations several-fold higher than the steady-state plasma concentrations in humans.

The drug-drug interaction profile for ATV was evaluated in a series of clinical pharmacology studies. Considerations for the selection of drugs to be evaluated included: (1) drugs that could be commonly co-administered including NRTIs such as stavudine, lamivudine, zidovudine, didanosine, other PIs such as saquinavir or ritonavir, and an NNRTI such as efavirenz; (2) drugs that could be commonly co-administered for co-morbid diseases such as clarithromycin, diltiazem, atenolol, and rifabutin; (3) drugs that could inhibit the metabolism of ATV such as ritonavir, clarithromycin, diltiazem, and ketoconazole; (4) drugs that could inhibit the absorption of ATV such as ddI buffered tablets; (5) drugs that could induce the metabolism of ATV such as efavirenz and rifabutin; (6) drugs that could have their metabolism inhibited by ATV such as saquinavir, rifabutin, clarithromycin, diltiazem and oral contraceptives; (7) drugs that could have their conjugation (elimination) inhibited by ATV such as zidovudine and ethinyl estradiol; and (8) drugs with the potential for a pharmacodynamic interaction such as atenolol, diltiazem, and clarithromycin.

The results of the interaction studies with ATV are summarized in Tables 4.1.7A and 4.1.7B.

Table 4.1.7A: Drug Interactions: Pharmacokinetic Parameters for ATV in the Presence of Coadministered Drugs

Coadministered Drug	Coadministered Drug Dose/Schedule	ATV Dose/Schedule	N	Geometric Mean Ratios (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00	
				C_{max}	AUC
atenolol	50 mg QD, d 7-11 and d 19-23	400 mg QD, d 1-11	19	1.00 (0.89, 1.12)	0.93 (0.85, 1.01)
clarithromycin	500 mg QD, d 7-10 and d 18-21	400 mg QD, d 1-10	29	1.06 (0.93, 1.20)	1.28 (1.16, 1.43)
didanosine (ddI) (buffered tablets) plus stavudine (d4T)	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose	400 mg x 1 dose simultaneously with ddI and d4T	32[a]	0.11 (0.06, 0.18)	0.13 (0.08, 0.21)
	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose	400 mg x 1 dose 1 hour after ddI + d4T	32[a]	1.12 (0.67, 1.18)	1.03 (0.64, 1.67)
diltiazem	180 mg QD, d 7-11 and d 19-23	400 mg QD, d 1-11	30	1.04 (0.96, 1.11)	1.00 (0.95, 1.05)
efavirenz	600 mg QD, d 7-20	400 mg QD, d 1-20	27	0.41 (0.33, 0.51)	0.26 (0.22, 0.32)
efavirenz and ritonavir	efavirenz 600 mg QD 2 h after ATV and ritonavir 100 mg QD simultaneously with ATV, d 7-20	400 mg QD, d 1-6 then 300 mg QD d 7-20	13	1.14 (0.83, 1.58)	1.39 (1.02, 1.88)
ketoconazole	200 mg QD, d 1-13	400 mg QD, d 7-13	14	0.99 (0.77, 1.28)	1.10 (0.89, 1.37)
rifabutin	150 mg QD, d 15-28	400 mg QD, d 1-28	7	1.34 (1.14, 1.59)	1.15 (0.98, 1.34)
ritonavir	100 mg QD, d 11-20	300 mg QD, d 1-20	28	1.86 (1.69, 2.05)	3.38 (3.13, 3.63)

Source: NDA Summary of Clinical Pharmacology Studies

[a] one subject did not receive ATV

Table 4.1.7B: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of ATV

Coadministered Drug	Coadministered Drug Dose/Schedule	ATV Dose/Schedule	N	Geometric Mean Ratios (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without ATV; No Effect = 1.00	
				C_{max}	AUC
atenolol	50 mg QD, d 7-11 and d 19-23	400 mg QD, d 1-11	19	1.34 (1.26, 1.42)	1.25 (1.16, 1.34)
clarithromycin	500 mg QD, d 7-10 and d 18-21	400 mg QD, d 1-10	21	1.50 (1.32, 1.71) OH-clarithromycin: 0.28 (0.24, 0.33)	1.94 (1.75, 2.16) OH-clarithromycin: 0.30 (0.26, 0.34)
didanosine (ddI) (buffered tablets) plus stavudine (d4T)	ddI: 200 mg x 1 dose d4T: 40 mg x 1 dose	400 mg x 1 dose simultaneous with ddI and d4T	32[a]	ddI: 0.92 (0.84, 1.02) d4T: 1.08 (0.96, 1.22)	ddI: 0.98 (0.92, 1.05) d4T: 1.00 (0.97, 1.03)
diltiazem	180 mg QD, d 7-11 and d 19-23	400 mg QD, d 1-11	28	1.98 (1.78, 2.19) desacetyl-diltiazem: 2.72 (2.44, 3.03)	2.25 (2.09, 2.16) desacetyl-diltiazem: 2.65 (2.45, 2.87)
ethinyl estradiol & norethindrone	Ortho-Novum® 7/7/7 QD, d 1-29	400 mg QD, d 16-29	19	ethinyl estradiol: 1.15 (0.99, 1.32) norethindrone: 1.67 (1.42, 1.96)	ethinyl estradiol: 1.48 (1.31, 1.68) norethindrone: 2.10 (1.68, 2.62)
rifabutin	300 mg QD, d 1-10 then 150 mg QD, d 11-20	600 mg QD, d 11-20	3	1.18 (0.94, 1.48) 25-O-desacetyl-rifabutin: 8.20 (5.90, 11.40)	2.10 (1.57, 2.79) 25-O-desacetyl-rifabutin: 22.01 (15.97, 30.34)
saquinavir (soft gelatin capsules)	1200 mg QD, d 1-13	400 mg QD, d 7-13	7	4.39 (3.24, 5.95)	5.49 (4.04, 7.47)

Table 4.1.7B: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of ATV

Coadministered Drug	Coadministered Drug Dose/Schedule	ATV Dose/Schedule	N	Geometric Mean Ratios (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without ATV; No Effect = 1.00	
				C_{max}	AUC
lamivudine + zidovudine	150 mg lamivudine + 300 mg zidovudine BID, d 1-12	400 mg QD, d 7-12	19	lamivudine: 1.04 (0.92, 1.16) zidovudine: 1.05 (0.88, 1.24) zidovudine glucuronide: 0.95 (0.88, 1.02)	lamivudine: 1.03 (0.98, 1.08) zidovudine: 1.05 (0.96, 1.14) zidovudine glucuronide: 1.00 (0.97, 1.03)

Source: NDA Summary of Clinical Pharmacology Studies

[a] one subject did not receive ATV

The key findings related to drug interactions with ATV were:

- Studies directed towards commonly co-administered NRTIs (ie, lamivudine, zidovudine, stavudine/didanosine administered one hour before ATV) did not appear to show appreciable interaction;
- Studies directed towards assessing ATV as a CYP3A4 substrate showed that steady-state exposure to ATV was substantially increased by a potent CYP3A4 inhibitor, RTV, but not substantially increased by other CYP3A4 inhibitors, ketoconazole and diltiazem. Clarithromycin, a known CYP3A4 and P-gp inhibitor and commonly used agent among the HIV-infected population, modestly increased ATV concentrations.;
- Conversely, ATV concentrations were appreciably reduced by the NNRTI EFV but not by rifabutin, both of which are CYP3A4 inducers. Of note, the interaction between EFV and ATV was reversed by co-administration of RTV;
- Since, the exposure of ATV may be altered when ATV is co-administered with drugs that are potent inhibitors or inducers of CYP3A4, an adjustment in the recommended ATV dose may be necessary;

- Conversely the dose of the co-administered drug may need to be modified. For example, a 50% dose reduction of diltiazem and clarithromycin, a schedule reduction (ie, TID to QD) for saquinavir (soft gel capsule), and a dose and schedule alteration for rifabutin (ie, 300mg QD to 150 mg thrice weekly) is recommended when administered simultaneously with ATV;
- ATV does not appear to inhibit the UGT2B7 isoform as the formation of zidovudine glucuronide was unaffected by ATV co-administration;
- The potential of ATV to inhibit the UGT1A1 isoform is typified by the benign, reversible hyperbilirubinemia associated with ATV administration. The potential for drug-drug interactions via this pathway is less clear, as drugs that are glucuronidated often have the possibility of being conjugated by alternate UGT isoform(s) and/or metabolized by CYP 450 mediated pathways. For example, the exposure to ethinyl estradiol, the elimination of which is mediated by multiple pathways (eg, CYP3A4 and UGT1A1), was only moderately increased by ATV;
- Pharmacodynamic interaction studies focused on the potential of ATV to affect cardiac conduction. The addition of atenolol or ritonavir to ATV did not result in significant PR interval or QT_c interval prolongation, respectively. In addition, ATV did not affect the steady-state exposure of atenolol. The addition of diltiazem to ATV resulted in a statistically significant increase in PR interval duration relative to ATV alone, however, it is anticipated that this effect can be managed with a 50% dose reduction of diltiazem. The addition of clarithromycin to ATV resulted in a statistically significant increase in QT_c interval duration relative to ATV alone, and it is anticipated that this effect can be managed with a 50% dose reduction of clarithromycin.

4.1.8 Pharmacokinetics of Atazanavir 300 mg Combined With Ritonavir 100 mg

Co-administration of ATV with low-dose RTV (acting as a metabolic inhibitor ie, "boosting") was evaluated, and a regimen of ATV 300 mg/RTV 100 mg QD (ATV 300/RTV) was subsequently studied in a Phase III clinical trial. The key findings related to the use of ATV combined with RTV were:

- The PK of ATV in healthy subjects with the ATV 300/RTV regimen relative to the ATV 400 mg QD regimen are presented in Table 4.1.8A. The steady-state profiles of ATV for these regimens are presented in Figure 4.1.8;

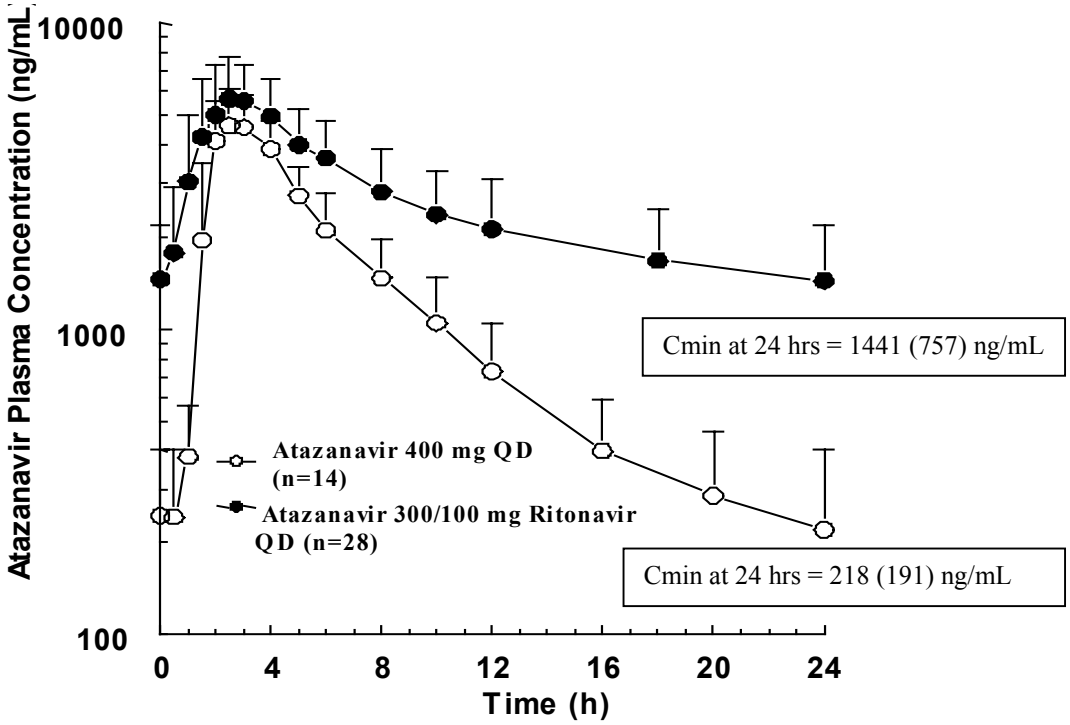
- The "boosted" regimen of ATV 300/RTV increases the C_{max} modestly, but doubles the AUC of ATV. Of note, the minimum concentration of ATV (C_{min}) increased by several-fold compared to minimum concentrations of ATV 400 mg QD.

Table 4.1.8A: Mean (SD) Pharmacokinetics of ATV at Steady-State in Healthy Subjects

PK Parameter	ATV 400 mg QD (n = 14)	ATV 300/RTV QD (n = 28)
C_{max} (ng/mL)	5358 (1371)	6450 (2031)
AUC (ng.h/mL)	29303 (8263)	61435 (22911)
C_{min} (ng/mL)	218 (191)	1441 (757)

Source: AI424056 and AI424013 Clinical Study Reports

Figure 4.1.8: Mean (SD) Plasma Concentration-Time Profiles of ATV 300/100 mg QD and 400 mg ATV 400 mg QD at Steady-State



Source: AI424056 and AI424013 Clinical Study Reports

The PK of ATV in HIV-infected subjects with ATV 300/RTV QD relative to ATV 400 mg QD is presented in Table 4.1.8B. In HIV-infected subjects, the pharmacokinetic parameters of the "boosted" regimen demonstrate that the C_{min} concentration would be expected to provide antiviral efficacy for strains with elevated ATV EC_{50}s as might be seen in ARV treatment-experienced subjects.

Table 4.1.8B: Mean (SD) Pharmacokinetics of ATV at Steady-State in HIV-Infected Subjects

PK Parameter	ATV 400 mg QD (n = 13)	ATV 300/RTV QD (n = 10)
C_{max} (ng/mL)	3152 (2231)	5233 (3033)
AUC (ng.h/mL)	22262 (20159)	53761 (35294)
C_{min} (ng/mL)	273 (298)[a]	862 (838)

Source: AI424008 Pharmacokinetic Study Report, Collaborative Puzzle II Pharmacokinetic Report

[a] n = 12

4.2 Dose Selection

4.2.1 Antiretroviral Treatment-Naive Population

4.2.1.1 Overview

Dose selection for ATV involved consideration of both viral sensitivity and systemic exposure to the drug. An initial estimate of viral sensitivity was derived from a representative wild-type HIV strain in a cell-based assay, and was defined as the ATV concentration which inhibited virion production by 50% (EC_{50}). To reflect the protein binding of ATV to albumin and alpha-1-acid glycoprotein, the viral sensitivity was adjusted by dividing the EC_{50} value by the free fraction (0.14) to yield a protein binding adjusted viral sensitivity of approximately 26 ng/ml. An *in vitro* hollow fiber model was employed to demonstrate that the pharmacodynamically-linked variable for ATV was the time above a threshold concentration. This value was most closely associated with C_{min}. The dose (exposure)-response relationship for ATV was evaluated in treatment-naive patients in Phase II studies, with efficacy of 400 mg QD to be confirmed in the Phase III program.

4.2.1.2 Establishing the Target of In vitro *and Phase I studies*

An initial estimate of viral sensitivity was derived from a representative wild-type HIV strain in a cell-based assay, and defined as the ATV concentration which inhibited virion production by 50% (EC_{50}). To reflect the protein binding of ATV to albumin and alpha-1-acid glycoprotein of 86%, the viral sensitivity was adjusted by dividing the EC_{50} value by the free fraction (0.14) to yield a protein binding adjusted viral sensitivity of approximately 26 ng/ml.

An *in vitro* hollow fiber model was employed to demonstrate that the pharmacodynamically-linked variable is the time above a threshold concentration. This value was most closely associated with C_{min}. The association of C_{min} with antiretroviral activity is consistent both with HIV being a continuously replicating virus, and with drug needing to be present at all times in concentrations that equal or exceed those concentrations required to inhibit viral replication. Simulation of the concentration-time profile of a 400 mg dose of ATV was sufficient to completely suppress a wild-type strain employed in the hollow fiber model.

4.2.1.3 The Evaluation of Dose In Treatment-Naive Patients in Phase II and Phase III

The Phase II study AI424007, included an initial two-week PI monotherapy phase prior to the addition of the dual nucleoside backbone. In this study, doses of ATV 200, 400, and 500 mg once-daily were evaluated. The relationship between the probability of achieving a 1.5 $\log_{10}$ decrease from baseline in HIV RNA and ATV exposure was evaluated by logistic regression. Doses at and above 400 mg were associated with a higher probability of achieving the target change from baseline of HIV RNA. Furthermore, the 400 mg dose was associated with a lower probability of achieving a total bilirubin value > 2.5 mg/dL.

Two Phase II studies, AI424007 and AI424008, were undertaken to assess the effectiveness and durability of several doses of ATV versus NFV (with two nucleosides) in treatment-naive patients. A population PK/PD assessment of studies AI424007 and AI424008 in Phase II confirmed the antiretroviral activity of the 400 mg dose of ATV in treatment-naive patients at 48 weeks of treatment.

Subsequently in Phase III, the efficacy of ATV 400 mg QD in a treatment-naive population was shown to be non-inferior to the comparator EFV 600 mg QD.

4.2.2 Antiretroviral Treatment-Experienced Population

4.2.2.1 Overview

Consistent with the approach to dose selection used for treatment-naive patients, consideration must be given to both viral sensitivity and systemic drug exposure when considering dose selection in ARV treatment-experienced patients. Since development of resistance is a commonly encountered occurrence in the treatment of HIV infection, it was anticipated that reduced viral sensitivity will be noted and increased drug exposure would be required in treatment-experienced patients. The ATV exposure following a 400 mg dose was anticipated to be adequate to address virus previously exposed to a limited number of PIs.

Since the 400 mg dose might not be adequate for all experienced patients, additional dosing options were developed. Therapeutic options focused on maximizing ARV activity while minimizing the potential for safety and tolerability concerns. Under these circumstances, treatment regimens either could include an increase in the dose of ATV or could include the addition of RTV for pharmacologic "boosting". Since C_{min} is the pharmacodynamically-linked parameter for ATV, RTV "boosting" was investigated with the desire to increase C_{min} without a substantial increase in C_{max}, which would have occurred by increasing the ATV dose above 400 mg QD.

The efficacy of ATV is currently being evaluated in ARV treatment-experienced patients administered as ATV 400 mg QD alone or in combination with SQV or as ATV 300 mg QD in combination with RTV, all as part of combination ARV therapy.

4.2.2.2 Evaluation of ATV/RTV Regimens

Dose selection for the combination of ATV with RTV was based on selecting the minimum dose of ATV to be combined with RTV that would maximize antiviral efficacy and minimize potential safety and tolerability concerns. Thus, in selecting a dose for

ATV with RTV, the objective was to focus on a regimen that would maximize the increase in ATV C_{min} and minimize the increase in ATV C_{max} with the addition of RTV.

The steady-state pharmacokinetics of ATV were evaluated following selected regimens of ATV, including: (1) ATV 400 mg QD in Study AI424013; (2) ATV 200/RTV 100 and ATV 400/RTV 100 QD in Study AI424028; and (3) ATV 300/RTV 100 QD in Study AI424056. In each of the trials in which ATV and RTV were combined, RTV was co-administered with ATV for 10 days. The steady-state pharmacokinetic values of ATV are provided in Table 4.2.2.2 below:

Table 4.2.2.2: Mean (SD, Range) Steady - State Pharmacokinetic Parameters of ATV

PK Parameter	ATV 200/ RTV 100 (n = 6)	ATV 300/ RTV 100 (n = 28)	ATV 400/ RTV 100 (n = 8)	ATV 400 (n = 14)
C_{max} (ng/mL)	2876 (1353) (579 - 4124)	6450 (2031) (2829 - 11910)	7754 (1060) (6310 - 8931)	5358 (1371) (3166 - 7970)
AUC (ng.h/mL)	25780 (13989) (5690 - 47920)	61435 (22911) (19338 - 121766)	70345 (10520) (48920 - 83922)	29303 (8263) (14756 - 46532)
C_{min} (ng/mL)	378 (286) (122 - 913)	1441 (757) (214 - 3323)	1023 (293) (528 - 1303)	218 (191) (12 - 840)

Source: Clinical Study Reports for AI424028, AI424056, and AI424013

- The AUC and C_{min} values for ATV with the ATV 200/RTV 100 regimen were generally comparable to 400 mg of ATV alone and provided only minimal increase in drug exposure.
- Compared to the 400 mg ATV regimen, the "boosted" regimen of ATV 300/RTV 100 increased the C_{max} modestly, but doubled the AUC of ATV. More importantly, the minimum concentration of ATV (C_{min}) increased by several-fold compared to the minimum concentration of ATV 400 mg QD.
- The ATV 400/RTV 100 regimen was noted to offer no substantial increase in the C_{min} of ATV compared to the ATV 300/RTV 100 regimen, but with the potential for an increase in C_{max}. Thus, in order to best balance maximization of C_{min} with minimization of potential C_{max} associated adverse effects, the ATV 300/RTV 100 regimen was selected.

4.2.2.3 Evaluation of ATV/RTV in Treatment-Experienced Patients in Phase III

Two studies in treatment-experienced patients (AI424043 and AI424045) are currently being conducted.

- In AI424043, ATV at 400 mg QD alone was evaluated in a treatment-experienced population versus LPV/RTV. In a limited preliminary evaluation of ATV C_{min} concentrations (n = 48), the values observed were similar to those noted in patients in Phase II.
- In AI424045, ATV was evaluated in combination with two PIs: SQV or RTV in two regimens versus LPV/RTV.
  - An ATV dose of 300 mg QD, with the 100 mg RTV, produced robust C_{min} values with mean C_{max} values only modestly above those noted with ATV at 400 mg alone. The ATV 300/RTV combination produced C_{min} values several-fold above those of 400 mg QD, with a lower coefficient of variation.
  - In the other regimen, SQV was added at 1200 mg QD to ATV 400 mg QD. ATV increased SQV exposure several-fold to a value similar to SQV alone at 1200 mg TID. ATV exposure was similar to historical controls.
  - In a limited preliminary review of ATV C_{min} values, the mean ATV concentration values for the ATV 300/RTV combination were approximately 4-fold higher than those for the ATV 400/SQV combination.

4.2.3 Summary

During development, viral sensitivity was established using a wild-type cell based assay. The pharmacodynamically-linked variable of time above a threshold concentration was demonstrated, and was most closely associated with C_{min}. In an initial two-week monotherapy treatment with ATV, doses at and above 400 mg had a high probability of producing a decrease in HIV RNA from baseline of 1.5 $\log_{10}$. In addition, the 400 mg dose provided a balance between ARV efficacy and the occurrence of hyperbilirubinemia in treatment-naive patients in Phase II (AI424007 and AI424008) and Phase III (AI424034). The efficacy of ATV was further evaluated in treatment-experienced patients who were to be administered ATV 400 mg QD alone or in combination with SQV or as ATV 300 mg QD in combination with RTV, all as part of combination ARV

therapy. In a limited preliminary review of ATV C_{min} values, the mean ATV concentration values for the ATV 300/RTV combination were approximately 4-fold higher than those for the ATV/SQV combination.

5 CLINICAL DEVELOPMENT PROGRAM

The ATV clinical development program consisted of 15 clinical studies (Refer to Appendix 1 Clinical Trials Directory). Eight BMS studies (three in ARV treatment-naive subjects [AI424007, AI424008, AI424034], three in ARV treatment-experienced subjects [AI424009, AI424043, AI424045], and two long-term rollover studies [AI424041, AI424044]) were evaluated for efficacy and safety. An additional study in ARV treatment-experienced subjects (AI424037) was terminated early due to administrative reasons and contributed to the safety evaluations.

For pediatric subjects, pharmacokinetic, safety and minimal antiviral activity data are available from an ongoing study (AI424020) being conducted by the Pediatric AIDS Clinical Trials Group (PACTG). Safety data are available from four collaborative studies (AI424038 and AI424069 conducted by NIAID and ACTG, respectively, AI424049 conducted by Aaron Diamond AIDS Research Center [ADARC], and AI424074 conducted by Agence Nationale de Rescherches surle SIDA [ANRS]). In addition, the Sponsor is conducting an Early Access Program (AI424900).

6 EFFICACY

Efficacy analyses included data collected on a total of 2266 randomized subjects evaluable for efficacy (Table 6). Efficacy evaluations were measured at 24 weeks (primary timepoint for Studies AI424043 and AI424045) and 48 weeks (primary timepoint for AI424034 and all Phase II studies). Long-term (> 72 weeks) exploratory efficacy analyses were performed in AI424041 and AI424044.

Table 6: Number of Subjects Included in Efficacy Analyses

Study Number	Number of Subjects		
Treatment Group	**Randomized**	**Treated**	**Evaluable for Efficacy**
ARV Treatment-Naive Studies			
AI424034			
ATV 400 mg	405	404	404
EFV	405	401	401
AI424007/041[a]			
ATV 200mg	104	102	83[b]
ATV 400mg	103	101	78[b]
ATV 500mg	110	107	79[b]
NFV	103	100	82[b]
AI424008/044[a]			
ATV 400mg	181	178	181
ATV 600 mg	195	195	195
NFV	91	91	91
Total	**1697**	**1679**	**1594**

Table 6: Number of Subjects Included in Efficacy Analyses

Study Number	Number of Subjects		
Treatment Group	**Randomized**	**Treated**	**Evaluable for Efficacy**
Treatment-Experienced Studies			
AI424043			
ATV 400 mg	150	144	114[c]
LPV/RTV	150	146	115[c]
AI424009			
ATV400mg/SQV	34	32	34
ATV600mg/SQV	28	27	28
RTV/SQV	23	23	23
AI424045			
ATV 300mg/RTV	120	119	120
ATV 400mg/SQV	115	110	115
LPV/RTV	123	118	123
Total	**743**	**719**	**672**
All Populations	**2240**	**2398**	**2266**

Source: NDA Background and Overview of Clinical Studies

[a] Does not include subjects who were switched to ATV 400 mg from another ATV dose or a comparator after entry into a rollover study.

[b] Includes only subjects treated in Stage II of Study AI424007.

[c] Includes subjects who were randomized through 02-Apr-2002 and eligible to complete Week 24 assessments prior to last patient last visit date of 16-Sep-2002.

For clarity and consistency throughout this document, the preferred intent to treat (ITT) analysis, time to loss of virologic response (TLOVR), is depicted. This analysis defines 'responders' as subjects maintaining a minimum of two sequential HIV RNA measurements < LOQ through the scheduled visit without intervening replicated rebounds or treatment discontinuations. The as treated (AT) analysis, virologic response (VR), is the proportion of subjects with HIV RNA measurements < LOQ among those subjects who remain on treatment at the time of the scheduled HIV RNA measurement. Subjects who discontinued study therapy prior to that study visit are not included.

Virologic response may be presented for observed cases (VR-OC) or for completers (VR-C).

6.1 Efficacy in Treatment-Naive Subjects

6.1.1 Efficacy Analyses in the Phase II Study AI424007

Study AI424007 was a Phase II, two-stage, randomized, active-controlled, multi-national, four-arm study designed to evaluate and compare the safety, tolerability, and antiviral activity of ATV at three different doses (200 mg, 400 mg and 500 mg) with NFV over two weeks of monotherapy and a minimum of 46 additional weeks of the triple therapy (study drug of ATV or NFV with didanosine [ddI] and stavudine [d4T]) in ARV treatment-naive subjects. Because a double-blind design would have required an unacceptable number of study drug capsules, only the dose level of ATV was blinded. A total of 420 HIV-infected subjects were randomized (98 in Stage I and 322 in Stage II). Data are only presented for Stage II subjects because this population was larger and subjects were routinely taking ATV with food.

Overall, the baseline demographic characteristics of the subjects in Stage II were comparable among treatment regimens (Table 6.1.1A). The study population was predominantly male (62%), with a median age of 33 years. Non-white racial groups comprised 42% of the population. A total of 322 HIV-infected subjects were randomized in Stage II. The disposition of subjects is presented in Table 6.1.1B.

Table 6.1.1A: Study AI424007 Baseline Characteristics - Randomized Subjects

	Treatment Regimen: ddI/d4T/PI				
	ATV (QD)			NFV (TID)	Total
Characteristic	**ATV 200 mg N = 83**	**ATV 400 mg N = 78**	**ATV 500 mg N = 79**	**NFV 750 mg N = 82**	**N = 322**
Age (years):					
Mean (SE)	33.9 (0.8)	34.3 (0.8)	35.0 (1.0)	34.3 (0.9)	34.4 (0.5)
Median	33.0	34.0	33.0	32.5	33.0
Range	19 - 53	21 - 54	18 - 65	21 - 55	18 - 65
Gender: N (%)					
Male	54 (65)	48 (62)	46 (58)	52 (63)	200 (62)
Female	29 (53)	30 (38)	33 (42)	30 (37)	122 (38)
Race: N (%)					
White	50 (60)	45 (58)	44 (56)	47 (57)	186 (58)
Black/Mixed[a]	28 (34)	28 (36)	26 (33)	29 (35)	111 (34)
Hispanic/Latino	5 (6)	5 (6)	8 (10)	5 (6)	23 (7)
Other	-- --	-- --	1 (1)	1 (1)	2 (<1)
Region: N (%)					
Europe	32 (39)	30 (38)	30 (38)	34 (41)	126 (39)
Africa	28 (34)	25 (32)	27 (34)	27 (33)	107 (33)
North America	10 (12)	10 (13)	10 (13)	9 (11)	39 (12)
South America	13 (16)	13 (17)	12 (15)	12 (15)	50 (16)
IV Drug Use: N (%)	12 (14)	12 (15)	9 (11)	13 (16)	46 (14)
AIDS: N (%)	5 (6)	3 (4)	4 (5)	4 (5)	16 (5)
HIV RNA level (log_{10} c/mL) Median	4.60	4.66	4.76	4.77	4.71
CD4 cell count (cells/mm^3) Median	305	305	268	343	307

Source: AI424007 48 Week Clinical Study Report, Appendix 8.3A

[a] Includes mixed, biracial, colored.

Table 6.1.1B: Study AI424007 Subject Disposition Randomized Subjects

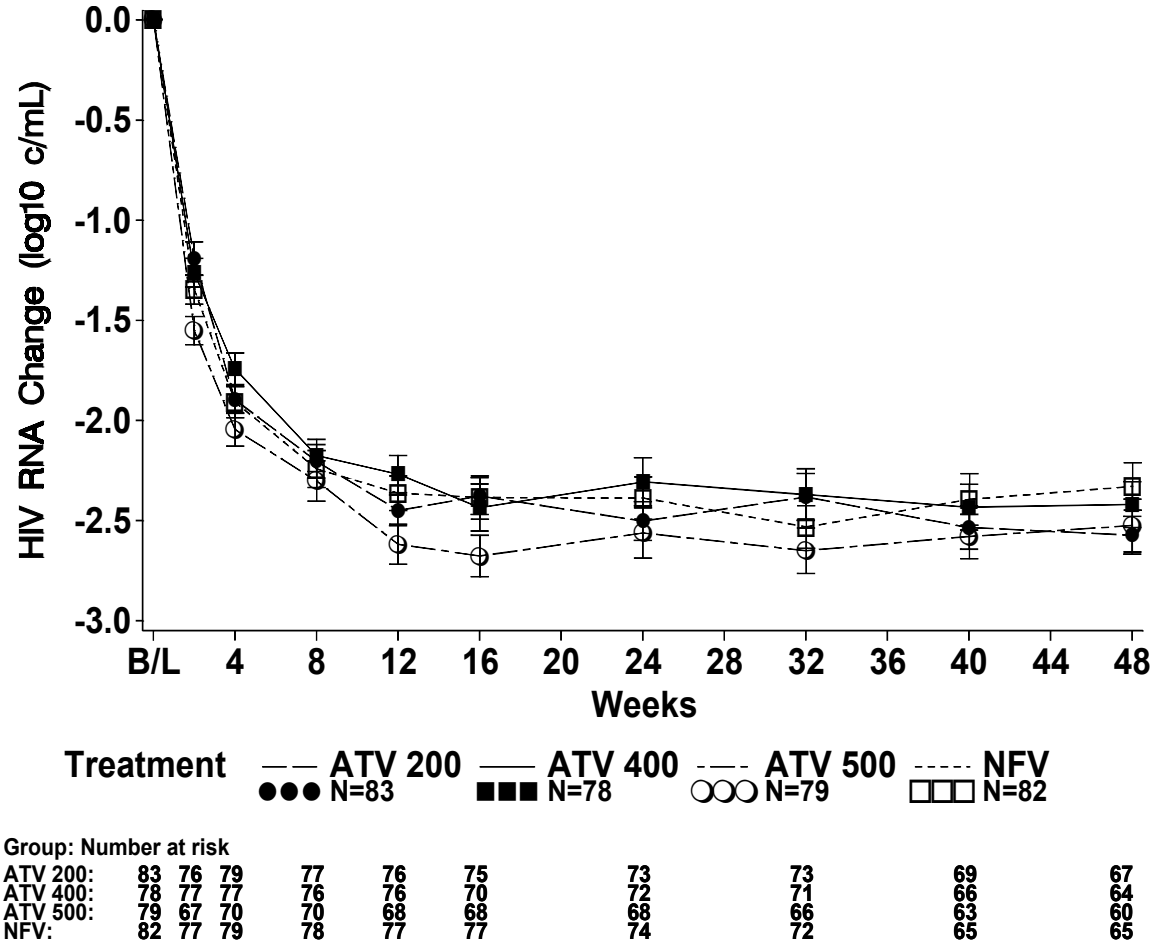
	Number of Subjects (%)				
	Treatment Regimen: ddI/d4T/PI				
	ATV (QD)			NFV (TID)	Total
	ATV 200 mg N = 83	ATV 400 mg N = 78	ATV 500 mg N = 79	NFV 750 mg N = 82	N = 322
Randomized	**83 (100)**	**78 (100)**	**79 (100)**	**82 (100)**	**322 (100)**
Never treated	-- --	-- --	2 (3)	2 (2)	4 (1)
Treated	**83 (100)**	**78 (100)**	**77 (97)**	**80 (98)**	**318 (99)**
Discontinued prior to Week 48	14 (17)	12 (15)	13 (16)	14 (17)	53 (16)
Discontinued after Week 48	4 (5)	6 (8)	5 (6)	7 (9)	22 (7)
Continuing on treatment beyond 48 Weeks	65 (78)	60 (77)	59 (75)	59 (72)	243 (75)

Source: AI424007 48 Week Clinical Study Report Appendix 8.1

6.1.1.1 Longitudinal Virologic Suppression

In Study AI424007, the antiviral activity of ATV at all three doses studied (200, 400, and 500 mg) was similar to NFV (750 mg TID) as measured by the primary endpoint of HIV RNA change from baseline through Week 48 (Figure 6.1.1.1).

Figure 6.1.1.1: Mean Change (SE) in HIV RNA Levels from Baseline - Study AI424007 Randomized Subjects



Source: AI424007 48 Week Clinical Study Report

6.1.1.2 Proportions in Response at Week 48

Using the TLOVR definition, the proportion of subjects with HIV RNA below LOQ for both 400 and 50 c/mL were comparable among all dosing regimens of ATV and NFV (Table 6.1.1.2).

Table 6.1.1.2: Proportions with HIV RNA Response at Week 48 (LOQ Equals 400 and 50 c/mL): Study AI424007 ARV Treatment Naive - Randomized Subjects

	Responders / Evaluable (%) Difference Estimate (ATV - comparator) (95% CI) Treatment			
Analysis	**ATV 200 N = 83**	**ATV 400 N = 78**	**ATV 500 N = 79**	**NFV N = 82**
LOQ = 400 c/mL				
TLOVR (ITT)	53/83 (64)	48/78 (62)	50/79 (63)	50/82 (61)
	2.5 (-12.0, 16.9)	0.5 (-14.5, 15.5)	2.8 (-11.9, 17.5)	--
VR-C (AT)	52/69 (75)	50/66 (76)	47/64 (73)	46/66 (70)
	5.2 (-9.6, 19.9)	6.5 (-8.5, 21.5)	4.4 (-10.8, 19.6)	--
LOQ = 50 c/mL				
TLOVR (ITT)	25/83 (30)	26/78 (33)	29/79 (37)	23/82 (28)
	1.8 (-11.9, 15.4)	5.2 (-9.0, 19.4)	9.2 (-4.9, 23.3)	--
VR-C (AT)	23/69 (33)	28/66 (42)	33/64 (52)	32/66 (48)
	-15.5 (-32.0, 0.9)	-5.6 (-22.3, 11.2)	3.9 (-12.8, 20.6)	--

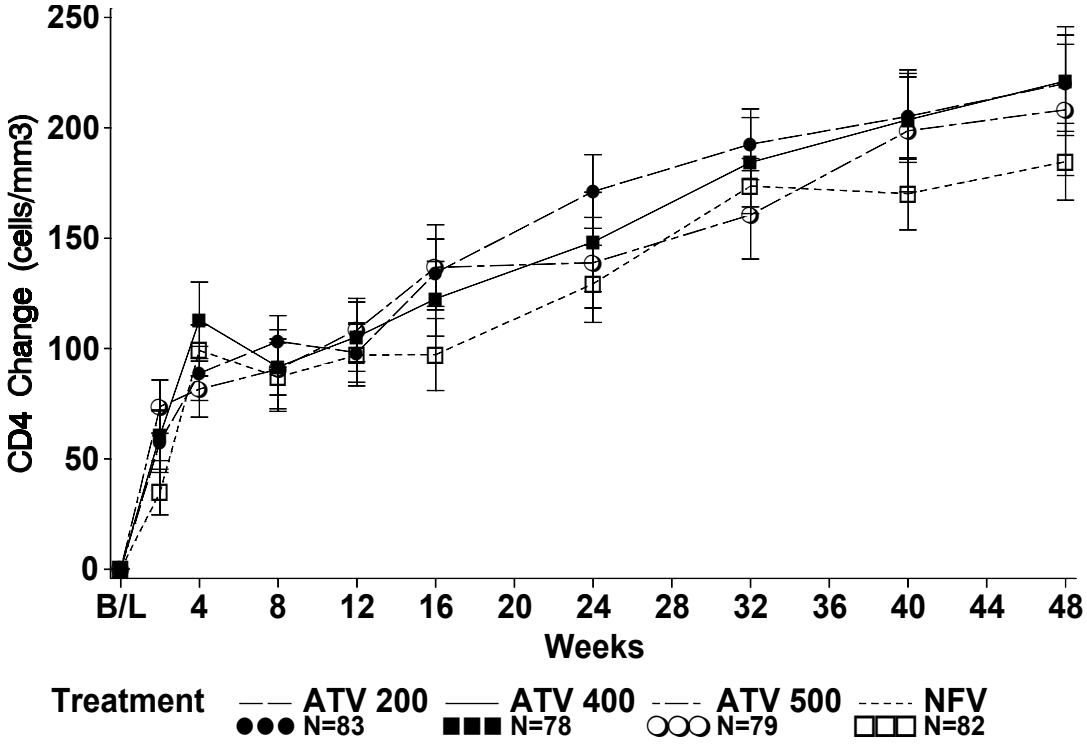
Source: AI424007 48 Week Clinical Study Report

6.1.1.3 Longitudinal Immunologic Response

As shown in Figure 6.1.1.3, immunologic response in Study AI424007 continued to improve over time and continued to increase through 48 weeks.

Pairwise TAD estimates (ATV - NFV) and 95% CI for the change from baseline in CD4 cell counts demonstrated comparable immunologic response. Results were consistent when missing data were replaced with the last observation carried forward (LOCF).

Figure 6.1.1.3: Mean Change (SE) in CD4 Cell Counts From Baseline - Study AI424007 Treated Subjects



Source: AI424007 48 Week Clinical Study Report

6.1.2 Efficacy Analyses in the Phase II Study AI424008

Study AI424008 was a Phase II, randomized, active-controlled, multi-national, three-arm study designed to evaluate and compare the safety, tolerability, and antiviral efficacy of ATV at two different doses (400 mg and 600 mg) in combination with d4T and 3TC to NFV in combination with d4T and 3TC through 48 weeks in ARV treatment-naive subjects. Subjects were enrolled in a 2:2:1 ratio for ATV 400:ATV 600:NFV. Only the specific dose level of ATV was blinded. Three hundred forty-six (346) subjects who completed Study AI424008 were enrolled in an observational, open-label study (AI424044); 63 of these subjects were in the NFV treatment regimen and were switched to ATV (designated as NFV⇒ATV) in order to assess lipid parameters.

Overall, the baseline demographic characteristics of the randomized subjects were comparable across treatment regimens (Table 6.1.2A). The study population was predominantly white (55%) and male (63%), with a median age of 34 years. A total of 467 HIV-infected subjects were randomized in this clinical trial. The disposition of subjects is presented in Table 6.1.2B.

Table 6.1.2A: Study AI424008 Baseline Characteristics - Randomized Subjects

	Treatment Regimen: d4T/3TC/PI			
	ATV (QD)		NFV (BID)	Total
Characteristic	400 mg N = 181	600 mg N = 195	1250 mg N = 91	N = 467
Age (years):				
Mean (SE)	34.3 (0.7)	34.7 (0.6)	35.3 (1.0)	34.7 (0.4)
Median	33	34	34	34
Range	18 - 64	18 - 58	19 - 69	18 - 69
Gender: N (%)				
Male	110 (61)	125 (64)	57 (63)	292 (63)
Female	71 (39)	70 (36)	34 (37)	175 (37)

Table 6.1.2A: Study AI424008 Baseline Characteristics - Randomized Subjects

Characteristic	Treatment Regimen: d4T/3TC/PI			
	ATV (QD)		NFV (BID)	Total
	400 mg N = 181	600 mg N = 195	1250 mg N = 91	N = 467
Race: N (%)				
White	100 (55)	104 (53)	52 (57)	256 (55)
Black/Mixed[a]	47 (26)	59 (30)	24 (26)	130 (28)
Asian/Pacific Islander	27 (15)	26 (13)	12 (13)	65 (14)
Hispanic/Latino	7 (4)	5 (3)	3 (3)	15 (3)
Other	--	1 (< 1)	--	1 (< 1)
Region: N (%)				
Europe	53 (29)	61 (31)	28 (31)	142 (30)
Africa	38 (21)	40 (21)	23 (25)	101 (22)
North America	26 (14)	31 (16)	11 (12)	68 (15)
South America	40 (22)	38 (19)	17 (19)	95 (20)
Asia	24 (13)	25 (13)	12 (13)	61 (13)
IV Drug Use: N (%)	11 (6)	16 (8)	6 (7)	33 (7)
AIDS: N (%)	18 (10)	24 (12)	9 (10)	51 (11)
HIV RNA level (log_{10} c/mL)				
Median	4.77	4.70	4.71	4.74
CD4 cell count (cells/mm^3)				
Median	260	283	273	273

Source: AI424008 48 Week Clinical Study Report, Appendix 8.3A

[a] Includes mixed, colored and mulatto.

Table 6.1.2B: Study AI424008 Subject Disposition - Randomized Subjects

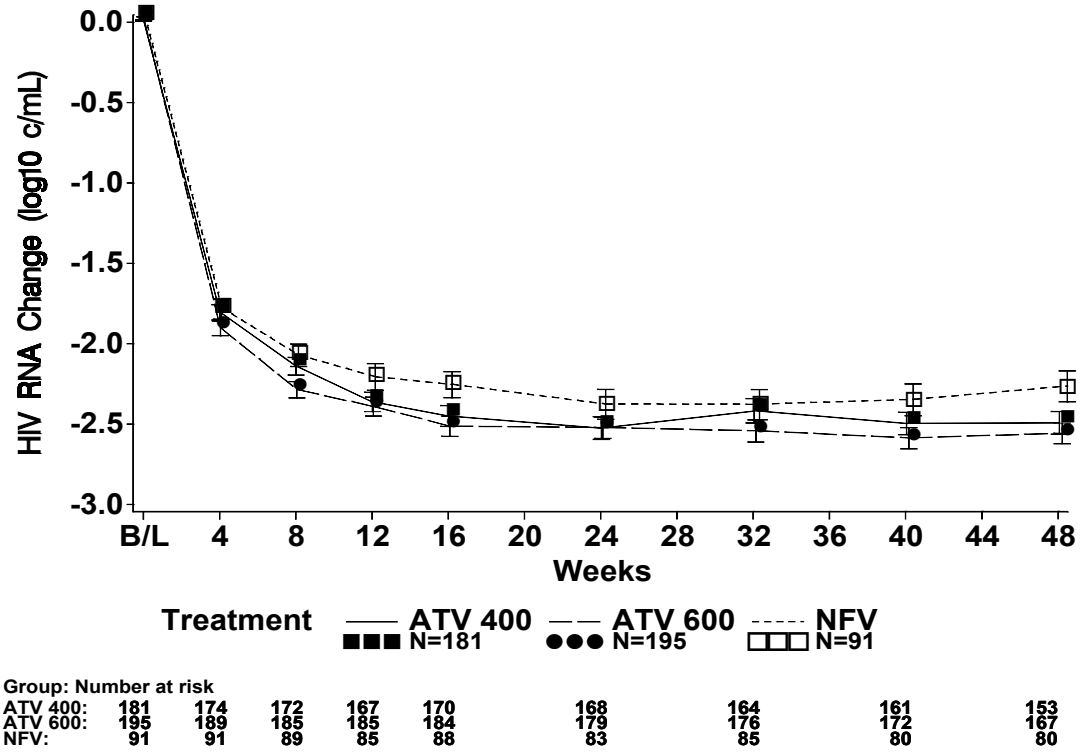
	Number of Subjects (%)							
	Treatment Regimen: d4T/3TC/PI							
	ATV (QD)				NFV (BID)		Total	
	400 mg N = 181		600 mg N = 195		1250 mg N = 91		N = 467	
Randomized	**181**	**(100)**	**195**	**(100)**	**91**	**(100)**	**467**	**(100)**
Never treated	3	(2)	--		--		3	(< 1)
Treated	**178**	**(98)**	**195**	**(100)**	**91**	**(100)**	**464**	**(99)**
Discontinued prior to Week 48	22	(12)	21	(11)	11	(12)	54	(12)
Discontinued after Week 48	7	(4)	11	(6)	6	(7)	24	(5)
Continuing on treatment beyond 48 weeks	149	(82)	162	(83)	74	(81)	385	(82)

Source: AI424008 48 Week Clinical Study Report Appendix 8.1B

6.1.2.1 Longitudinal Virologic Suppression

In Study AI424008, antiviral activity of ATV at the two doses studied (400 and 600 mg) was similar to NFV (1250 mg BID) as measured by the primary endpoint of HIV RNA change from baseline through Week 48 (Figure 6.1.2.1).

Figure 6.1.2.1: Mean Change (SE) in HIV RNA Levels from Baseline - Study AI424008 Randomized Subjects



Source: AI424008 48 Week Clinical Study Report

6.1.2.2 Proportions in Response at Week 48

The response rates for all dosing regimens in Study AI424008 are shown in Table 6.1.2.2, using the TLOVR (ITT) and VR-C (AT) proportion analyses. Using the TLOVR definition, 68% of subjects on ATV 400 mg had HIV RNA levels < 400 c/mL at Week 48 compared to 59% on NFV. In the AI424008 study, the lower boundary of the confidence intervals exceeded -10% on the TLOVR analysis demonstrating non-inferiority compared with NFV. In addition, the lower boundary of the 95% confidence limits exceeded zero for the VR-C (as treated) analysis comparing ATV with NFV.

Table 6.1.2.2: Proportions with HIV RNA Response at Week 48 (LOQ Equals 400 and 50 c/mL): Study AI424008 ARV Treatment Naive - Randomized Subjects

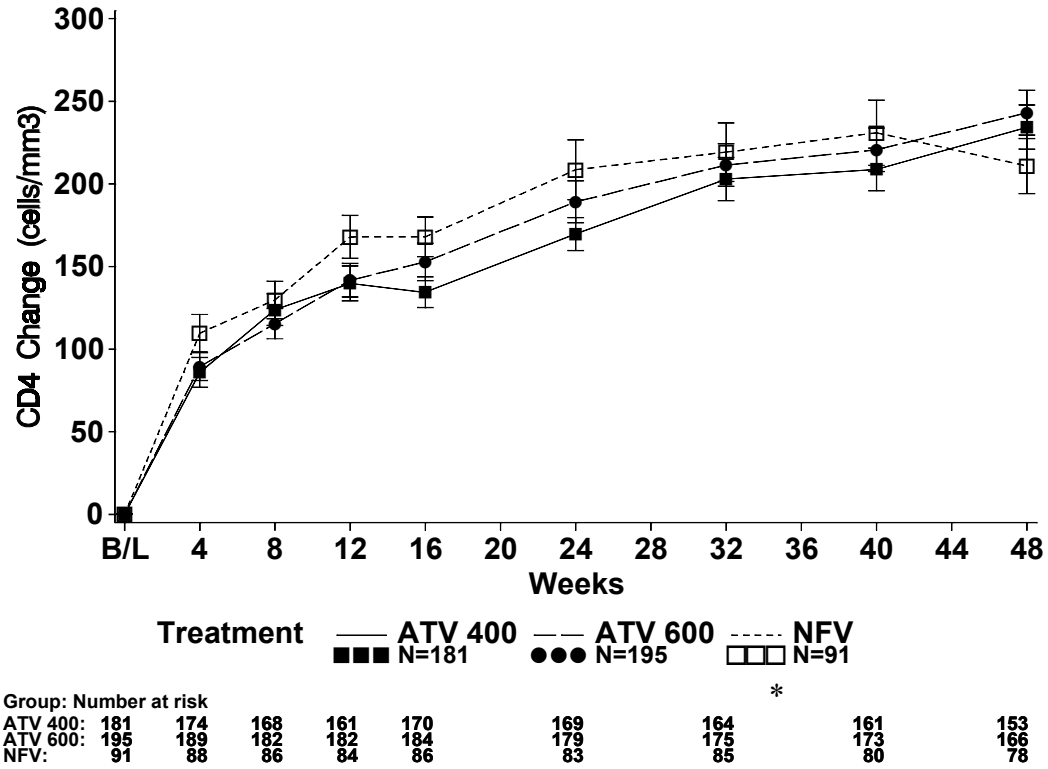
	Responders / Evaluable (%) Difference Estimate (ATV - comparator) (95% CI) Treatment		
Analysis	**400 mg N = 181**	**600 mg N = 195**	**1250 mg N = 91**
LOQ = 400 c/mL			
TLOVR (ITT)	123/181 (68)	125/195 (64)	54/91 (59)
	8.4 (-3.5, 20.3)	4.1, (-7.8, 16.0)	--
VR-C (AT)	116/156 (74)	130/174 (75)	48/80 (60)
	13.8 (1.6, 26.1)	14.0 (2.1, 25.9)	--
LOQ = 50 c/mL			
TLOVR (ITT)	60/181 (33)	72/195 (37)	35/91 (38)
	-5.6 (-17.5, 6.3)	-2.1 (-14.0, 9.8)	--
VR-C (AT)	63/156 (40)	71/174 (41)	31/80 (39)
	1.2 (-11.9, 14.3)	1.3 (-11.4, 14.0)	--

Source: AI424008 48 Week Clinical Study Report

6.1.2.3 Longitudinal Immunologic Response

As shown in Figure 6.1.2.3, immunologic response continued to increase through 48 weeks. Pairwise TAD estimates (ATV - NFV) and 95% CI for the change from baseline in CD4 cell counts demonstrated comparable immunologic response. Results were consistent when missing data were replaced with the last observation carried forward (LOCF).

Figure 6.1.2.3: Mean (SE) Change in CD4 Cell Count From Baseline - Study AI424008 Treated Subjects



Source: AI424008 48 Week Clinical Study Report

6.1.3 Efficacy Analyses in the Phase III Study AI424034

Study AI424034 was a Phase III, randomized, double-blind, double-dummy, active-controlled, multi-national, two-arm study designed to compare the antiviral efficacy and safety of ATV with zidovudine+lamivudine (ZDV+3TC) vs EFV/ZDV+3TC in HIV-infected subjects who had received no prior ARV treatment (or limited prior treatment as specified in the protocol). Treatment with ZDV+ 3TC was administered open-label as fixed-dose Combivir®. The EFV regimen was selected as the comparator regimen because it is a standard of care regimen in ARV treatment-naive subjects.

6.1.3.1 Study Population

In general, baseline characteristics for all treated subjects were comparable between the ATV and EFV treatment regimens (Table 6.1.3.1A). The study population was predominantly male (65%) and had a median age of 33 years. Non-white racial groups comprised 67% of the population. Most subjects were from South America (34%) or Europe (28%). Subjects in this trial generally were modestly immunocompromised based on CD4 cell count. The median HIV RNA level and CD4 cell count for all treated subjects were 4.88 $\log_{10}$ c/mL and 282 cells/mm^3, respectively, and were comparable between regimens. Forty-two percent of all treated subjects had baseline HIV RNA levels ≥ 100,000 c/mL.

Table 6.1.3.1A: Study AI424034 Subject Demography - Treated Subjects

CHARACTERISTIC	TREATMENT REGIMEN ATV/ZDV+3TC N = 404	EFV/ZDV+3TC N = 401	Total N = 805
Age (Years)			
MEAN (SE)	34 (0.4)	34 (0.5)	34 (0.3)
MEDIAN	33	33	33
MIN, MAX	18, 71	18, 73	18, 73
MISSING	0	0	0
Gender: N (%)			
MALE	257 (64)	265 (66)	522 (65)
FEMALE	147 (36)	136 (34)	283 (35)
Race: N (%)			
HISPANIC/LATINO	152 (38)	142 (35)	294 (37)
WHITE	136 (34)	130 (32)	266 (33)
ASIAN/PACIFIC ISLANDERS	58 (14)	69 (17)	127 (16)
BLACK	54 (13)	53 (13)	107 (13)
OTHER: ILE MAURICE	1 (<1)	0	1 (<1)
OTHER: MIXED	1 (<1)	4 (<1)	5 (<1)
OTHER: MIXED RACE	1 (<1)	1 (<1)	2 (<1)
OTHER: NATIVE AMERICAN	1 (<1)	0	1 (<1)
OTHER: COLOURED	0	1 (<1)	1 (<1)
OTHER: ETHOPIAN	0	1 (<1)	1 (<1)
Region: N (%)			
SOUTH AMERICA	142 (35)	133 (33)	275 (34)
EUROPE	111 (27)	111 (28)	222 (28)
ASIA	57 (14)	68 (17)	125 (16)
NORTH AMERICA	56 (14)	53 (13)	109 (14)
AFRICA	38 (9)	36 (9)	74 (9)
IV Drug Use: N (%)	22 (5)	23 (6)	45 (6)
AIDS: N (%)	17 (4)	24 (6)	41 (5)
HIV RNA Level (log10 c/mL)			
MEDIAN	4.87	4.91	4.88

Table 6.1.3.1A: Study AI424034 Subject Demography - Treated Subjects

CHARACTERISTIC	TREATMENT REGIMEN ATV/ZDV+3TC N = 404	EFV/ZDV+3TC N = 401	Total N = 805
CD4 Cell Count (cells/mm3)			
MEDIAN	286	280	282
HIV RNA Distribution (c/mL): N (%)			
< 30000	112 (28)	104 (26)	216 (27)
30000 - < 100000	123 (30)	126 (31)	249 (31)
>= 100000	169 (42)	171 (43)	340 (42)
Hepatitis B Surface Antigen or Hepatitis C Antibody			
POSITIVE	50 (13)	59 (15)	109 (14)
NEGATIVE	347 (87)	335 (85)	682 (86)

Source: AI424034 48 Week Clinical Study Report (Tables 8.3.1A, 8.3.1B, and S.8.3.3C)

A total of 805 subjects (99%) started therapy (404 on ATV and 401 on EFV). Of those treated, 144 subjects (18%) discontinued prior to the Week 48 visit. More subjects on the EFV regimen compared with the ATV regimen discontinued treatment before Week 48 (20% vs 16%). The disposition of subjects is presented below in Table 6.1.3.1B.

Table 6.1.3.1B: Study AI424034 Subject Disposition - Randomized Subjects

	NUMBER OF SUBJECTS (%)		
	TREATMENT REGIMEN		
	ATV/ZDV+3TC N = 405	EFV/ZDV+3TC N = 405	Total N = 810
RANDOMIZED	405	405	810
NEVER TREATED	1 (<1)	4 (<1)	5 (<1)
TREATED	404 (>99)	401 (99)	805 (99)
DISCONTINUED PRIOR TO WEEK 48 VISIT	65 (16)	79 (20)	144 (18)
ADVERSE EVENT	26 (6)	34 (8)	60 (7)
DEATH	0	2 (<1)	2 (<1)
LOST TO FOLLOW-UP	15 (4)	17 (4)	32 (4)
NEEDED CONCURRENT THERAPY	2 (<1)	0	2 (<1)
PROHIBITED BY PROTOCOL			
NON-COMPLIANCE	6 (1)	5 (1)	11 (1)
PHYSICIAN'S DECISION	0	1 (<1)	1 (<1)
PREGNANCY	1 (<1)	2 (<1)	3 (<1)
PROTOCOL VIOLATION WHILE ON STUDY	2 (<1)	3 (<1)	5 (<1)
SUBJECT WITHDREW	6 (1)	7 (2)	13 (2)
TREATMENT FAILURE/LACK OF EFFICACY	7 (2)	8 (2)	15 (2)
DISCONTINUED AFTER WEEK 48 VISIT	13 (3)	18 (4)	31 (4)
ADVERSE EVENT	2 (<1)	3 (<1)	5 (<1)
NEEDED CONCURRENT THERAPY	0	1 (<1)	1 (<1)
PROHIBITED BY PROTOCOL			
NON-COMPLIANCE	1 (<1)	0	1 (<1)
PHYSICIAN'S DECISION	1 (<1)	0	1 (<1)
PREGNANCY	1 (<1)	0	1 (<1)
SUBJECT WITHDREW	5 (1)	9 (2)	14 (2)
TREATMENT FAILURE/LACK OF EFFICACY	3 (<1)	5 (1)	8 (<1)
CONTINUING ON TREATMENT	326 (80)	304 (75)	630 (78)

Library: /wwbdm/clin/proj/av/424/034/sasds/sasds_isr_july2002
Extract Date: 15JUL02

Source: AI424034 48 Week Clinical Study Report Supplemental Table S.8.1B

6.1.3.2 Proportions in Response at Week 48

The proportion of subjects with HIV RNA response at Week 48 (LOQ = 400 c/mL) is shown in Table 6.1.3.2. The proportion of subjects who achieved and maintained HIV RNA levels < 400 c/mL and < 50 c/mL through Week 48 for Study AI424034 based on the TLOVR definition is depicted in Figure 6.1.3.2.

Using the most recent ITT analysis adopted by FDA (TLOVR), ATV/ZDV+3TC was similar to EFV/ZDV+3TC: 70% of subjects on ATV 400 mg had HIV RNA levels < 400 c/mL at Week 48 compared to 64% on EFV. The response rate for the EFV regimen was consistent with the 68% response rate observed through 48 weeks for EFV/ZDV+3TC in another large well-controlled study. Results for the proportion of subjects with HIV RNA levels < 50 c/mL were 32% on ATV vs 37% on EFV.

For all analyses, the lower limit of the 95% confidence interval of the difference was greater than the pre-specified boundary of -12%, and also greater than the more stringent and recently recommended regulatory boundary of -10%, supporting the conclusion of similarity of the two regimens. Based on the TLOVR analysis at Week 48, the difference estimate of the proportion of responders was 5.2, which favored the ATV regimen.

Differences favored EFV at Week 48 for the VR-C (as treated) definition. TLOVR is influenced by premature subject discontinuation, with such subjects considered as failures. The higher response rate on ATV is therefore consistent with the observation that through 48 weeks a greater proportion of subjects remained on the ATV regimen compared to the EFV regimen (84% vs 80%). The difference in the discontinuation rates between regimens is observed early in the study (by Week 4) and predominantly due to adverse events. Conversely, VR-C, an as treated (AT) analysis, did not include subjects who discontinued prior to the Week 48 assessment and therefore was a reflection of the treatment response among subjects who continued on their assigned treatment.

The proportions of subjects with HIV RNA < 50 c/mL at Week 48 were less than the proportions with HIV RNA < 400 c/mL at Week 48 (Table 6.1.3.2). In contrast to LOQ = 400 c/mL results, the differences in response for LOQ = 50 c/mL, although not statistically significant differences, consistently favor the EFV regimen at Week 48. In this study, response rates favored the EFV regimen for the TLOVR and VR-C analyses

compared with the ATV regimen for the same analyses, 37 - 51% compared to 32 - 44%, respectively. Based on the TLOVR analyses at Week 48, the difference estimate was -4.9% favoring EFV.

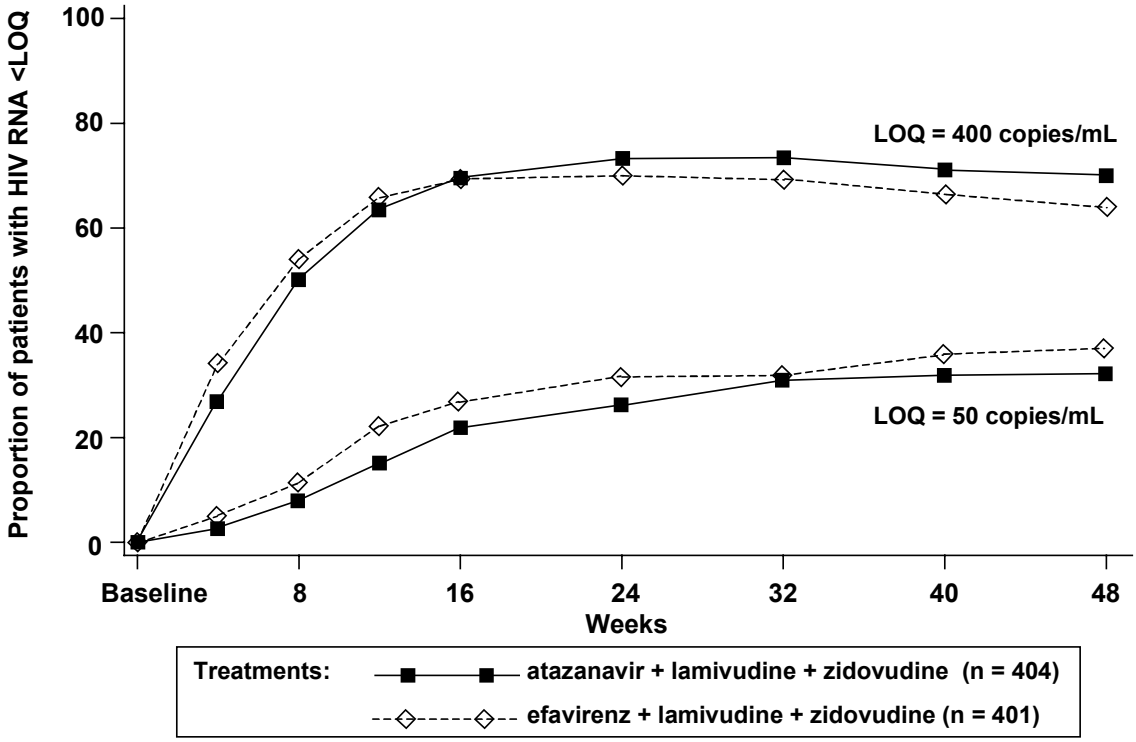
Table 6.1.3.2: Proportions with HIV RNA Response at Week 48 (LOQ Equals 400 and 50 c/mL): Study AI424034 ARV Treatment-Naive - Treated Subjects

	Responder/Evaluable (%)		
	AI424034 Treatment Regimen: ZDV/3TC/(PI or NNRTI)		
Analysis	ATV (QD) 400 mg N = 404	EFV (QD) 600 mg N = 401	Difference Estimate (ATV - Comparator) (95% CI)
LOQ = 400 c/mL			
TLOVR (ITT)	281/404 (70)	258/401 (64)	5.2 (-1.2, 11.7)
VR-C (AT)	274/339 (81)	271/322 (84)	-3.5 (-9.3, 2.3)
LOQ = 50 c/mL			
TLOVR (ITT)	131/404 (32)	150/401 (37)	-4.9 (-11.4, 1.5)
VR-C (AT)	148/339 (44)	165/322 (51)	-7.9 (-15.4, -0.3)

TLOVR = Time to Loss of Virologic Response
VR-C = Virologic Response - Completers

Source: NDA Clinical Summary of Efficacy Results (Table 4.1.4 and 4.1.8.1)

Figure 6.1.3.2: Virologic Response Through Week 48 - Study AI424034*



Source: NDA Clinical Summary of Efficacy Results (Appendices 4.1.6 and 4.1.8.3)
* Analysis uses the TLOVR response definition (ITT)

6.1.3.3 Treatment Outcome (TLOVR) and Virologic Response Through 48 Weeks

There were no notable differences between the treatment regimens with respect to reasons for failure based on the TLOVR analysis (Table 6.1.3.3). Virologic failure (confirmed viral rebound or never suppressed < LOQ) was the most frequent reason for failure (17% on both regimens). Subjects on both regimens experienced loss of virologic response at a comparable rate. Few subjects on either regimen failed to achieve viral suppression through Week 48 (5% and 6% on ATV and EFV, respectively) and virologic failure was mainly due to viral rebound (12% and 11%, respectively) rather than failure to achieve a response.

For LOQ = 50 c/mL, the rate of virologic failure was higher on the ATV regimen (54% vs 44%), primarily due to failure to achieve confirmed viral suppression.

Table 6.1.3.3: Treatment Outcomes (TLOVR) at Week 48 (LOQ Equals 400 c/mL) Study AI424034 ARV Treatment-Naive Treated Subjects

Outcome	ATV 400 mg/ZDV+3TC n=404	EFV 600 mg/ZDV+3TC n=401
Responder[a]	70%	64%
Virologic Failure[b]	17%	17%
Rebound	12%	11%
Never suppressed through Week 48	5%	6%
Death	0%	<1%
Discontinued due to adverse event	6%	9%
Discontinued for other reasons[c]	7%	9%

Source: NDA Clinical Summary of Efficacy Results (Table 4.1.5)

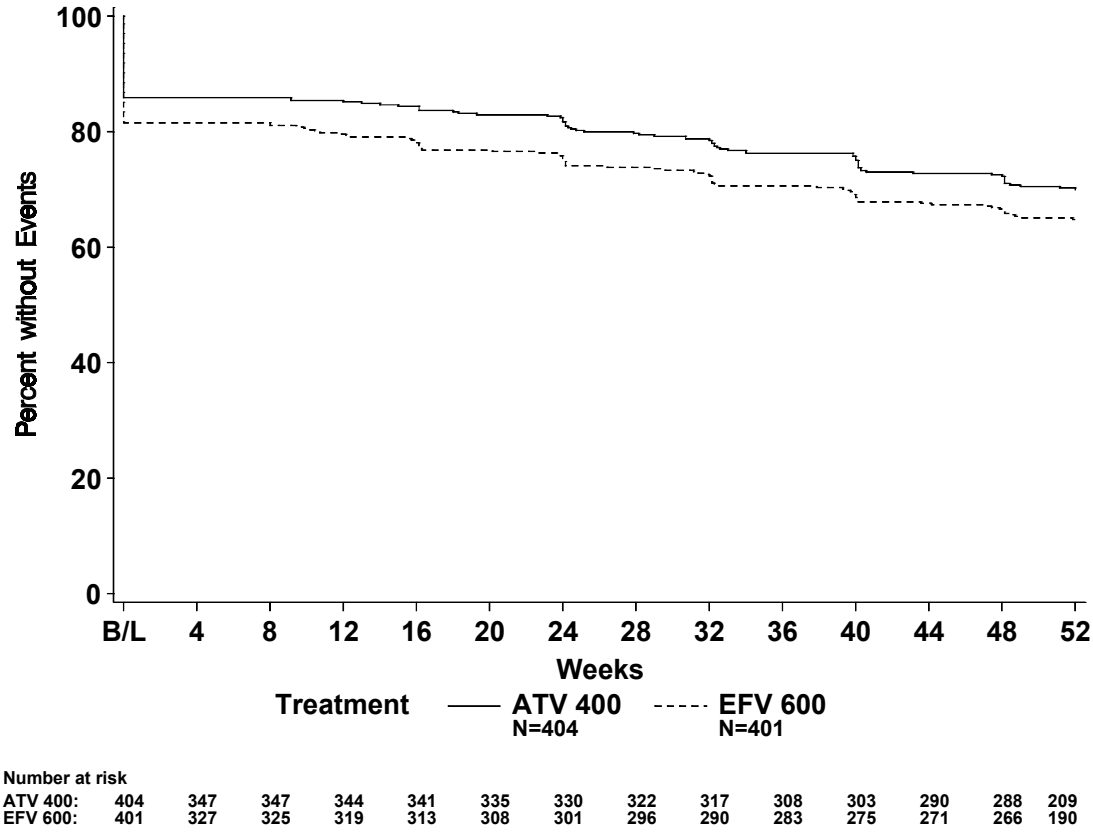
[a] Subjects achieved and maintained confirmed HIV RNA < 400 c/mL through Week 48.

[b] Included confirmed viral rebound and failure to achieve confirmed HIV RNA <400 c/mL through Week 48.

[c] Includes lost to follow up, subject's withdrawal, non-compliance, protocol violation, and other reasons.

Time to loss of virologic response was comparable on both treatment regimens (Figure 6.1.3.3). The analyses for LOQ = 400 c/mL favored ATV [hazard ratio (95% CI): 0.83 (0.65, 1.05)].

Figure 6.1.3.3: Time to Loss of Virologic Response (TLOVR, LOQ Equals 400 c/mL) - Study AI424034 ARV Treatment Naive Treated Subjects

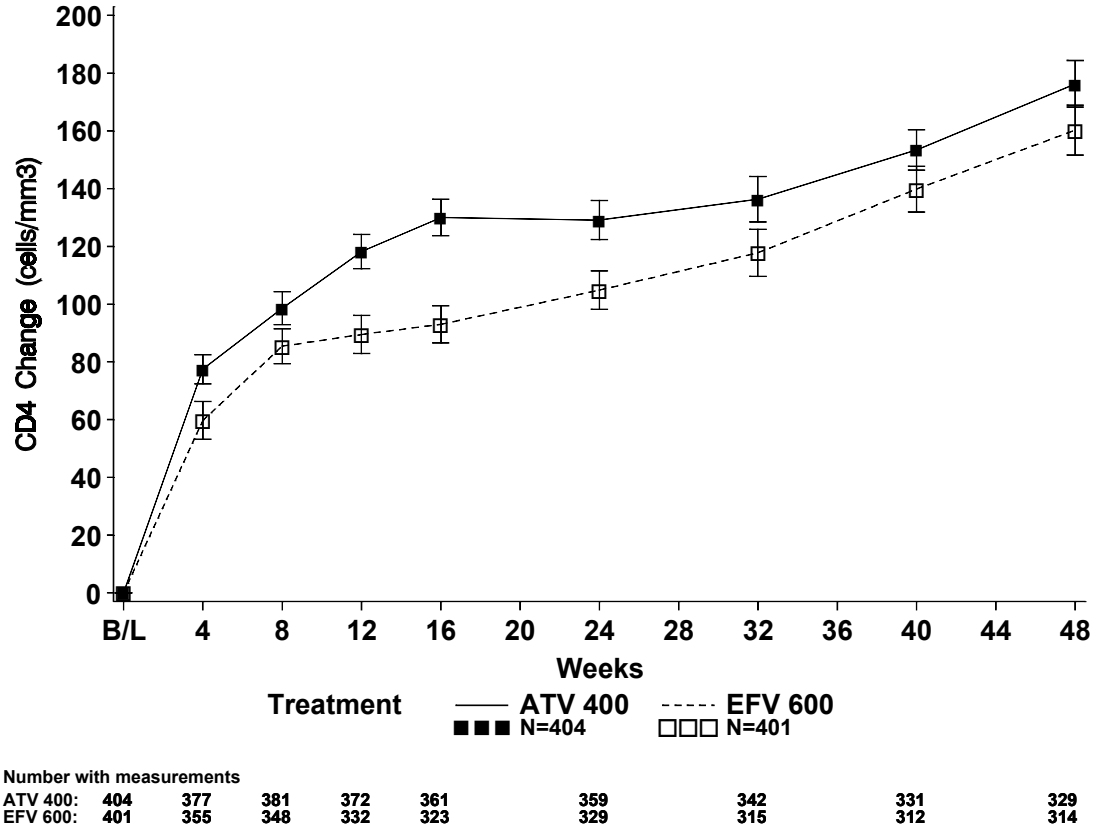


Source: AI424034 Study Report: Supplemental Table S.10.1.4

6.1.3.4 Longitudinal Immunologic Response

The mean increase in CD4 cell counts at Week 48 was 176 cells/mm^3 on ATV and 160 cells/mm^3 on EFV (Figure 6.1.3.4). The TAD estimates (ATV - comparator) and 95% CI for the change from baseline in CD4 cell count through Week 48 were 23.1 (9.7, 36.5), favoring ATV. Results were consistent when missing data were replaced with the LOCF.

Figure 6.1.3.4: Mean Change (SE) in CD4 Cell Count From Baseline - Study AI424034 Treated Subjects

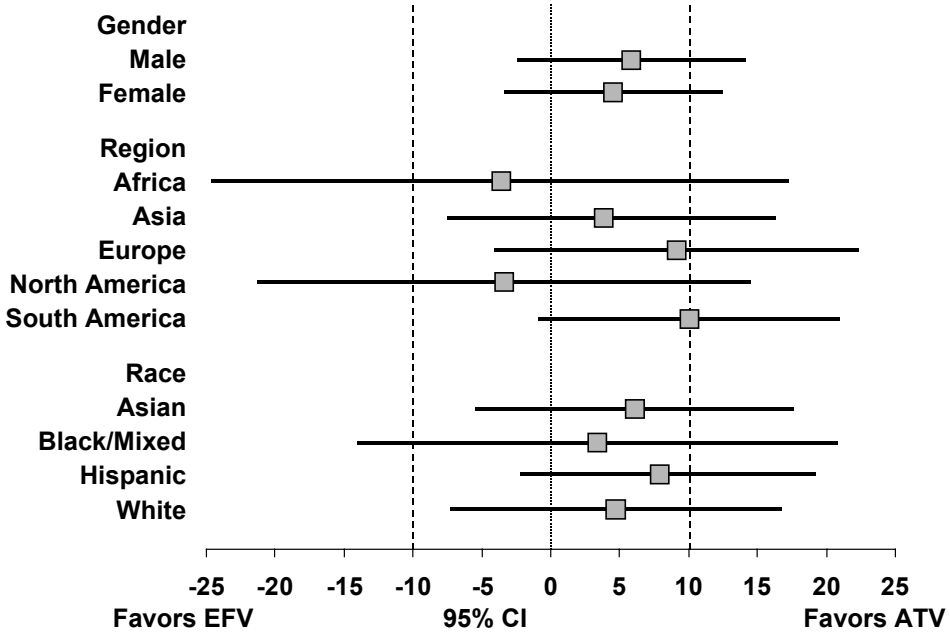


Source: AI424034 Study Report: Appendix 10.2.2

6.1.3.5 Comparison of Results in Subpopulations and Subgroups

Exploratory subpopulation analyses of the principal efficacy parameters for Study AI424034 were performed based on gender, race, region, HIV RNA level, and CD4 cell count at baseline. Age was not addressed in these analyses because there were too few subjects > 65 years of age. Figures 6.1.3.5A and 6.1.3.5B depict the results of the subpopulation and subgroup analyses that generally favor ATV.

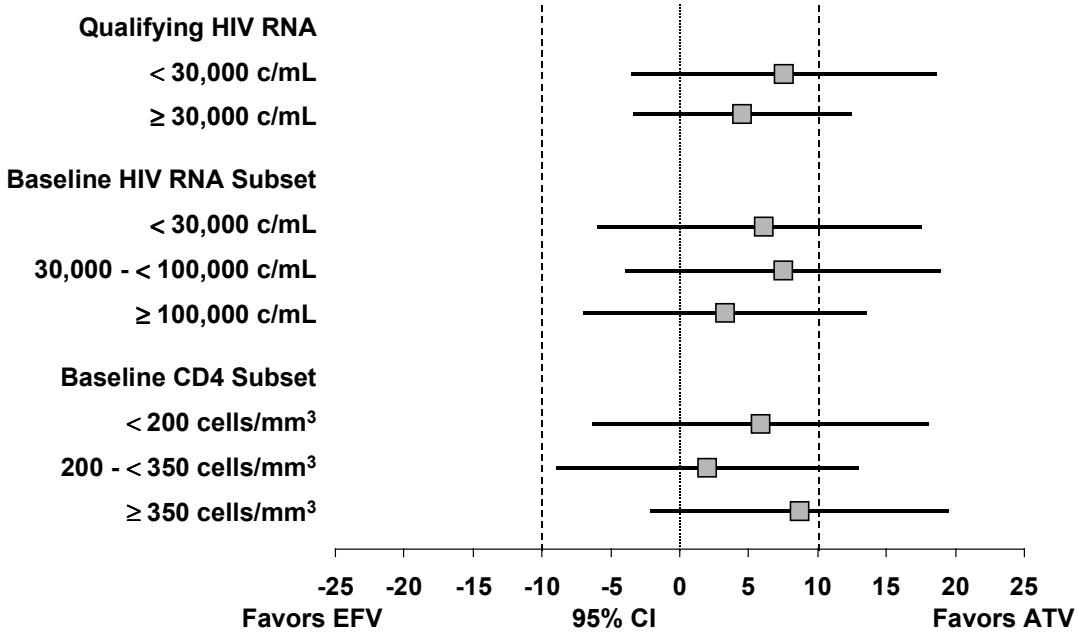
Figure 6.1.3.5A TLOVR Response at Week 48 by Gender, Region, and Race (LOQ = 400 c/mL) - Study AI424034 Treated Subjects



Source: NDA Clinical Summary of Efficacy Results

Comparisons of the treatment regimens within the subsets of baseline HIV RNA levels (< 30,000 c/mL, 30,000 - < 100,000 c/mL, ≥ 100,000 c/mL) and CD4 cell counts (< 200 cells/mm^3, 200 - < 350 cells/mm^3, ≥ 350 cells/mm^3) were also consistent between treatment regimens, slightly favoring ATV.

Figure 6.1.3.5B: TLOVR Response at Week 48 by Efficacy Subsets (LOQ = 400 c/mL) - Study AI424034 Treated Subjects



Source: NDA Clinical Summary of Efficacy Results

6.1.3.6 Development of Resistance in Study AI424034

In Study AI424034, 17% (69/404) of ATV-treated subjects were virologic failures, of whom approximately half (36/69) had samples submitted for resistance testing. Twenty-six of these had genotypable results, and 26 had phenotypable results (Table 6.1.3.6). A minority (6/26) had evidence of ATV genotypic (ie, a mutation detectable in either the protease or RT part of the viral genome) or phenotypic (decreased susceptibility vs NRTI, NNRTI, or PI) resistance. All six subjects who developed phenotypic resistance had either the I50L or I50I/L-mixed mutation. More than half of EFV-treated subjects (11/20) who had genotypable and phenotypable results had both the K103 signature mutation of EFV resistance and reduced phenotypic susceptibility to EFV. The M184V and ZDV-associated mutations occurred with comparable frequency on both the ATV and EFV treatment regimens.

Table 6.1.3.6: Resistance Profile for Virologic Failures - Study AI424034

Resistance Profile	AI424034 Treatment Regimen: ZDV/3TC/(PI or NNRTI) ATV (QD) 400 mg N = 404	AI424034 Treatment Regimen: ZDV/3TC/(PI or NNRTI) EFV (QD) 600 mg N = 401
Virologic failure through 48 weeks	69	69
Genotypic resistance testing on study	36	33
Genotypable	26	20
Genotype mutations		
I50L (ATV)	5/26 (19%)	0/20 (0%)
I50I/L (ATV)	1/26 (4%)	0/20 (0%)
K103N (EFV)	1/26 (4%)	11/20 (55%)
K103K/N (EFV)	0/26 (0%)	2/20 (10%)
41, 70, 210 or 215 (ZDV)	3/26 (12%)	2/20 (10%)
M184 (3TC)	14/26 (54%)	11/20 (55%)
Phenotypic resistance testing on study	36	33
Phenotypable	26	20
Phenotype > 2.5 x IC50 of control		
ATV	6/26 (23%)	1/20 (5%)
EFV	1/26 (4%)	13/20 (65%)

Virologic failure in protocol analysis for TLOVR.
Resistance testing required per protocol only on specimens with confirmed HIV RNA level > 1000 c/mL.
Reasons for no result include: HIV RNA level <= 1000 c/mL (n = 44), isolate non-typable (n = 23) or sample unavailable (n = 18).

Source: NDA Clinical Summary of Efficacy Results

6.1.4 Long-Term Efficacy

Study AI424041

Study AI424041 was an open-label, rollover study designed to assess the long-term safety, tolerability, and continued antiviral efficacy of ATV versus NFV in initially ARV naive subjects who completed a minimum of 48 weeks of dosing on a ATV Study AI424007. Upon entry into Study AI424041, all subjects treated with ATV in AI424007 received ATV 400 mg; subjects treated with NFV in AI424007 continued to receive NFV.

Study AI424044

Study AI424044 was an open-label (initially blinded to ATV dose), roll-over/switch study designed to assess the long-term safety, tolerability, and continued antiviral efficacy of ATV in initially ARV treatment-naive subjects who completed a minimum of 48 weeks of therapy with ATV or NFV in study AI424008. After enrollment into AI424044, ATV-treated subjects continued on their original treatment regimen and subjects treated with NFV switched to ATV 400 mg QD. Results are presented for these cohorts based on prior dosing in AI424008: ATV 400, ATV 600, and NFV⇒ATV.

6.1.4.1 Proportions with HIV RNA Less Than LOQ

In both long-term rollover studies, AI424041 and AI424044, virologic response (VR-OC) (as treated) was sustained and durable for subjects treated with ATV 400 mg for up to 108 weeks. Results for Study AI424008/44, the larger of the two rollover studies, are presented in Table 6.1.4.1 and Figure 6.1.4.1. Additionally, the response rate for ATV 400 mg was comparable to the responses observed at 500 and 600 mg.

In AI424007 (Stage II), when analyses were conducted at Week 72 prior to the ATV dosage switch in AI424041, the proportion of subjects in response with HIV RNA < 400 c/mL among subjects remaining on treatment was higher on all ATV dose groups (70%, 76% and 81% for ATV 200, 400 and 500 mg groups, respectively) compared with NFV (66%). At Week 108, the proportion of subjects in response was again higher for the ATV 400 mg regimen (89%) compared to the NFV regimen (79%).

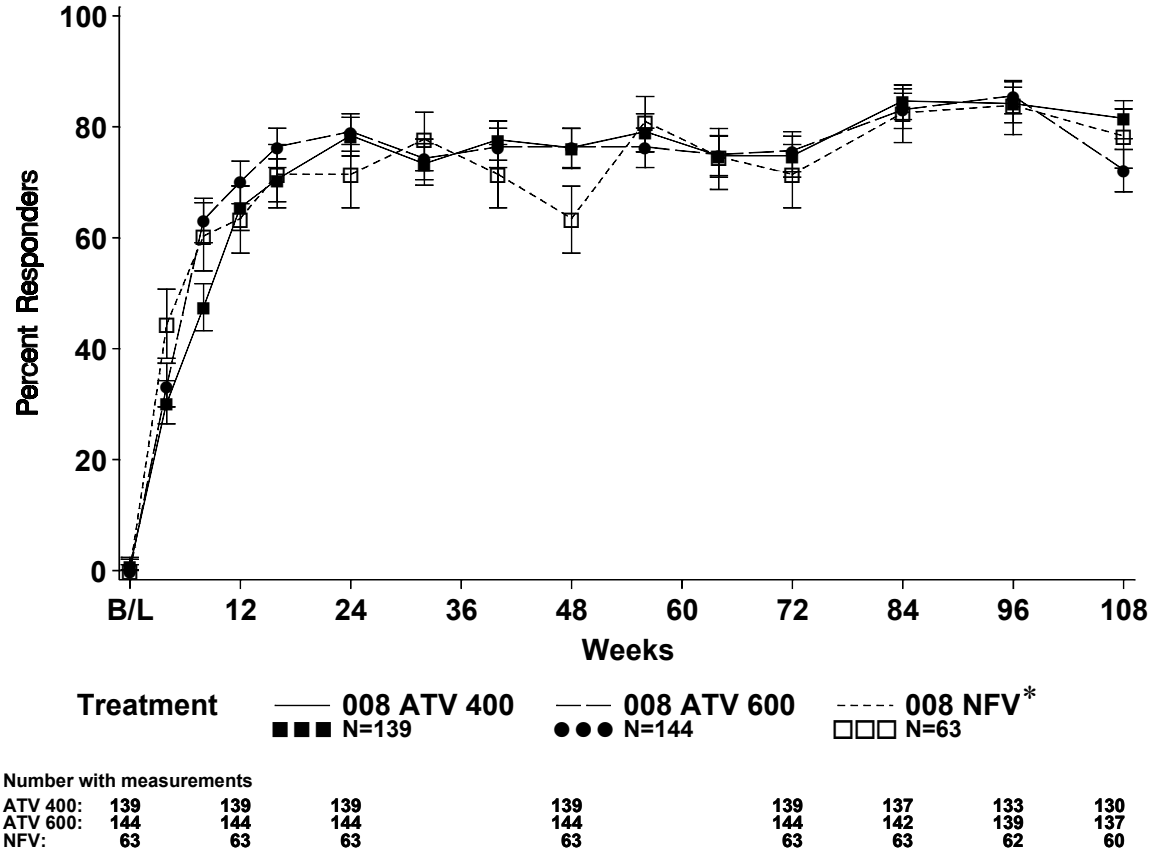
In AI424044, the proportion of subjects with virologic response, HIV RNA < 400 c/mL, was consistent among ATV dose groups (400 mg and 600 mg) and the NFV⇒ATV switch regimen until Week 96 (84% for ATV 400 mg, 86% for ATV 600 mg, and 84% for NFV⇒ATV). At Week 108, the proportion of subjects in virologic response was still comparable between the ATV 400 mg regimen and the NFV⇒ATV regimen (ATV 400, 82%; NFV⇒ATV, 78%).

Table 6.1.4.1: Virologic Response - Subjects Treated in AI424008/AI424044 Combined

	Number of Subjects (%)		
	Treatment Regimen (PI/d4T/3TC) and Cohort		
	ATV 400	**ATV 600**	**NFV⇒ATV**
Study AI424008	**(N = 181)**	**(N = 195)**	**(N = 91)**
Treated	178 (98)	195 (100)	91 (100)
Week 48			
Discontinued	22 (12)	21 (11)	11 (12)
VR-OC (AT)			
HIV RNA < 400 c/mL	116/156 (74)	130/174 (75)	48/80 (60)
HIV RNA < 50 c/mL	63/156 (40)	72/174 (41)	32/80 (40)
Discontinued after Week 48	9 (5)	21 (11)	11 (12)
Completed AI424008	147 (81)	153 (78)	69 (76)
Study AI424044	**(N = 139)**	**(N = 144)**	**(N = 63)**
Enrolled and Treated	139 (100)	144 (100)	63 (100)
VR-OC (AT) at Entry			
HIV RNA < 400 c/mL	101/129 (78)	104/134 (78)	44/60 (73)
HIV RNA < 50 c/mL	63/129 (49)	71/134 (53)	30/60 (50)
Week 24			
Discontinued	6 (4)	5 (3)	1 (2)
VR-OC (AT)			
HIV RNA < 400 c/mL	111/133 (83)	118/139 (85)	54/62 (87)
HIV RNA < 50 c/mL	80/133 (60)	78/139 (56)	37/62 (60)

Source: AI424044 Interim Study Report

Figure 6.1.4.1: Response VR-OC (AT) Through Week 108 (LOQ Equals 400 c/mL) - Studies AI424008/AI424044 Treated Subjects



Source: AI424044 Interim Study Report, Table S.10.1C

* Subjects treated with NFV in Study AI424008 were switched to ATV 400 mg upon entry into Study AI424044 (ie, NFV⇒ATV treatment group).

6.2 Efficacy in Treatment-Experienced Subjects

6.2.1 Efficacy Analyses in the Pilot Phase II Study AI424009

The pilot Phase II Study, AI424009, was a randomized, active-controlled, multi-national, three-arm study designed to provide a preliminary assessment of the activity and safety of ATV (400 mg or 600 mg) QD in combination with SQV (1200 mg) once-daily relative to

a combination of RTV (400 mg)/SQV (400 mg) BID in subjects with no more than two prior PI failures. Since AI424009 was a small Phase II pilot study, only a brief description of efficacy is provided.

Despite the small size and a high early discontinuation rate in this study, efficacy data at Week 4 (when the discontinuation rate was minimal and comparable for treatment regimens) demonstrated that the mean changes from baseline in HIV viral load were already evident and comparable to the control regimen (ATV 400 -1.38 $\log_{10}$ c/mL, ATV 600 -1.21 $\log_{10}$ c/mL, and RTV -1.20 $\log_{10}$ c/mL). This rapid drop in viral load was consistent with the activity of the other HAART regimens and provided evidence that the ATV regimens would prove useful for longer term treatment in this population. At 48 weeks the mean RNA changes from baseline decreased by 1.44 $\log_{10}$ c/mL, 1.19 $\log_{10}$ c/mL, and 1.66 $\log_{10}$ c/mL, respectively. The mean increases from baseline in CD4 cell count over 48 weeks were 109 and 149 cells/mm^3 on the ATV 400/SQV and RTV/SQV regimens, respectively, as compared to 55 cells/mm^3 on the ATV 600/SQV regimen. These data supported the selection of the ATV 400/SQV 1200 mg QD dosing regimen for further evaluation in treatment-experienced patients (Study AI424045).

6.2.2 Efficacy Analyses in Phase III Study AI424043

Phase III Study AI424043 was a randomized, open-label, active-controlled, multi-national, two-arm study to compare the antiviral activity, metabolic changes, safety, and tolerability of ATV 400 mg QD vs LPV/RTV 400 mg/100 mg BID, each in combination with two nucleosides, in HIV-infected subjects who had failed prior ARV treatment(s) that included one PI. Subjects received two NRTIs to which their screening viral isolate was sensitive. The selection of the NRTIs was based on the phenotypic susceptibility data for the subject's viral isolate obtained at the screening visit and the physician's choice at the time of randomization. If phenotypic data could not be obtained and the subject was otherwise eligible for the study, the subject was assigned to two NRTIs never taken previously. The NRTI combinations allowed were ZDV + 3TC, d4T + 3TC, ZDV + ddI, d4T + ddI, or ABC + appropriate NRTI (ddI, d4T, or 3TC). This study had two co-primary endpoints: 1) to compare the two treatment regimens with regard to serum lipid profile, as assessed by the change in LDL-cholesterol levels from baseline and 2) to compare the two treatment regimens in the magnitude of the reduction

of plasma HIV RNA from baseline. Efficacy analyses are presented for the first 229 subjects randomized (the prospective protocol-defined sample size and NDA evaluation cohort).

6.2.2.1 Study Population

In general, baseline characteristics were comparable between the ATV and LPV/RTV treatment regimens (Table 6.2.2.1A). The study population was predominately male (81%) and had a median age of 37 years. Non-white racial groups comprised 59% of the population. Most subjects were from South America (46%) or North America (46%).

Subjects entering AI424043 had on average over three years of cumulative prior HIV therapy. The mean exposure to any NRTI therapy, 3TC, d4T, or ZDV was comparable between treatment regimens. For the 229 randomized subjects who have been assessed for the primary efficacy analysis, the mean time of prior exposure to antivirals was 140 weeks for PIs, 180 weeks for NRTIs, and 85 weeks for NNRTIs. The median baseline CD4 cell count was 264 cells/mm^3 and the median baseline HIV RNA level was 4.22 $\log_{10}$ c/mL.

Table 6.2.2.1A: Study AI424043 Subject Demography - Subjects Randomized Through 02-Apr-2002

CHARACTERISTIC	TREATMENT REGIMEN ATV N = 114	LPV/RTV N = 115	Total N = 229
Age (Years)			
MEAN (SE)	38 (0.7)	39 (0.8)	38 (0.5)
MEDIAN	36	38	37
MIN, MAX	25, 61	23, 64	23, 64
MISSING	0	0	0
Gender: N (%)			
MALE	88 (77)	97 (84)	185 (81)
FEMALE	26 (23)	18 (16)	44 (19)
Race: N (%)			
HISPANIC/LATINO	60 (53)	61 (53)	121 (53)
WHITE	46 (40)	47 (41)	93 (41)
BLACK	7 (6)	7 (6)	14 (6)
ASIAN/PACIFIC ISLANDERS	1 (<1)	0	1 (<1)
Region: N (%)			
NORTH AMERICA	53 (46)	52 (45)	105 (46)
SOUTH AMERICA	52 (46)	54 (47)	106 (46)
EUROPE	9 (8)	9 (8)	18 (8)
IV Drug Use: N (%)	7 (6)	7 (6)	14 (6)
AIDS: N (%)	30 (26)	34 (30)	64 (28)
HIV RNA Level (log10 c/mL)			
MEDIAN	4.19	4.30	4.22
CD4 Cell Count (cells/mm3)			
MEDIAN	279	249	264

Table 6.2.2.1A: Study AI424043 Subject Demography - Subjects Randomized Through 02-Apr-2002

CHARACTERISTIC	TREATMENT REGIMEN ATV N = 114	LPV/RTV N = 115	Total N = 229
HIV RNA Distribution (c/mL): N (%)			
< 30000	75 (66)	66 (57)	141 (62)
30000 - < 100000	20 (18)	29 (25)	49 (21)
>= 100000	19 (17)	20 (17)	39 (17)
Hepatitis B Surface Antigen or Hepatitis C Antibody[a]			
POSITIVE	28 (20)	17 (12)	45 (16)
NEGATIVE	114 (80)	128 (88)	242 (84)

[a] Hepatitis B Surface Antigen and Hepatitis C Antibody are presented for treated subjects. n=144 for ATV 400 mg, n=146 for LPV/RTV, and n=290 for the total subjects

Source: AI424043 Interim Study Report (Tables S.8.3.1A, S.8.3.1B, and S.8.3.3B)

Sensitivity to a specific PI (≤ 2.5 x IC_{50} of control strain) ranged from 46% to 91%, with 32% of subjects highly resistant (> 10 x IC_{50} of control strain) to NFV (Table 6.2.2.1B). Of note, 74% of subjects on the ATV treatment regimen were fully susceptible to ATV, whereas 88% of subjects on the LPV/RTV treatment regimen were fully susceptible to LPV. This differential in baseline sensitivity may play some role in results observed in Study AI424043.

Table 6.2.2.1B: Study AI424043 PI and NRTI Phenotypic Sensitivity at Screening - Subjects Randomized Through 02-Apr-2002

		NUMBER OF SUBJECTS (%)		
		TREATMENT REGIMEN		
	IC50 MULTIPLE OF CONTROL	ATV N=114	LPV/RTV N=115	Total N=229
PI				
AMP	<=2.5	104 (91)	104 (90)	208 (91)
	>10	0	1 (<1)	1 (<1)
ATV	<=2.5	84 (74)	89 (77)	173 (76)
	>10	4 (4)	2 (2)	6 (3)
LPV	<=2.5	94 (82)	101 (88)	195 (85)
	>10	2 (2)	2 (2)	4 (2)
NFV	<=2.5	55 (48)	51 (44)	106 (46)
	>10	31 (27)	42 (37)	73 (32)
RTV	<=2.5	80 (70)	84 (73)	164 (72)
	>10	11 (10)	10 (9)	21 (9)
SQV	<=2.5	87 (76)	93 (81)	180 (79)
	>10	8 (7)	5 (4)	13 (6)
NRTI				
3TC	<=2.5	45 (39)	41 (36)	86 (38)
	>10	60 (53)	63 (55)	123 (54)
ABC	<=2.5	69 (61)	60 (52)	129 (56)
	>10	0	0	0
D4T	<=2.5	106 (93)	110 (96)	216 (94)
	>10	1 (<1)	0	1 (<1)
DDI	<=2.5	108 (95)	112 (97)	220 (96)
	>10	0	0	0
ZDV	<=2.5	87 (76)	82 (71)	169 (74)
	>10	13 (11)	14 (12)	27 (12)

Source: AI424043 24 Week Interim Study Report

Three hundred subjects were randomized in this study; ten randomized subjects (3%) were never treated. Two hundred ninety subjects were treated in this study (ATV, 144 subjects; LPV/RTV, 146 subjects). The disposition of subjects is presented in Table 6.2.2.1C. More subjects discontinued after the Week 24 visit on the ATV treatment regimen as compared to the LPV/RTV treatment regimen, predominantly due to treatment failure/lack of efficacy.

Table 6.2.2.1C: Study AI424043 Subject Disposition - Randomized Subjects

	NUMBER OF SUBJECTS (%)		
	TREATMENT REGIMEN		
	ATV N = 150	LPV/RTV N = 150	Total N = 300
RANDOMIZED	150	150	300
NEVER TREATED	6 (4)	4 (3)	10 (3)
TREATED	144 (96)	146 (97)	290 (97)
CONTINUING ON TREATMENT	124 (83)	135 (90)	259 (86)
DISCONTINUED PRIOR TO WEEK 24 VISIT	10 (7)	10 (7)	20 (7)
ADVERSE EVENT	1 (<1)	4 (3)	5 (2)
DEATH	1 (<1)	0	1 (<1)
LOST TO FOLLOW-UP	0	2 (1)	2 (<1)
NON-COMPLIANCE	1 (<1)	1 (<1)	2 (<1)
PROTOCOL VIOLATION WHILE ON STUDY	3 (2)	1 (<1)	4 (1)
SUBJECT WITHDREW	0	2 (1)	2 (<1)
TREATMENT FAILURE/LACK OF EFFICACY	4 (3)	0	4 (1)
DISCONTINUED AFTER WEEK 24 VISIT	10 (7)	1 (<1)	11 (4)
ADVERSE EVENT	1 (<1)	0	1 (<1)
NON-COMPLIANCE	1 (<1)	0	1 (<1)
SUBJECT WITHDREW	1 (<1)	1 (<1)	2 (<1)
TREATMENT FAILURE/LACK OF EFFICACY	7 (5)	0	7 (2)

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Run Date: 15OCT02

6.2.2.2 Longitudinal Virologic Suppression

Mean HIV RNA levels declined promptly (approximately 1.62 $\log_{10}$ c/mL by Week 4 [Figure 6.2.2.2]) on the ATV regimen. There was no interruption of ARV treatment prior to entry into the trial. Therefore, the decline observed in HIV RNA levels soon after

initiation of treatment with ATV represents the intrinsic activity of the new regimen over the prior failing regimen.

The reduction in viral load was sustained through Week 24 for both the ATV and LPV/RTV regimens. At Week 24, mean HIV RNA change from baseline was -1.73 $\log_{10}$ c/mL on the ATV regimen and -2.16 $\log_{10}$ c/mL on the LPV/RTV regimen. The TAD estimate (ATV - LPV/RTV) and 97.5% CI for the change from baseline in HIV RNA level through Week 24 were 0.31 (0.06, 0.55) (Table 6.2.2.2). A positive TAD estimate favors the LPV/RTV treatment regimen. The lower limit of the 97.5% CI was greater than zero, indicating significantly greater HIV RNA changes for the LPV/RTV treatment regimen.

Table 6.2.2.2: HIV RNA Level Change From Baseline in ARV Treatment-Experienced Randomized Subjects

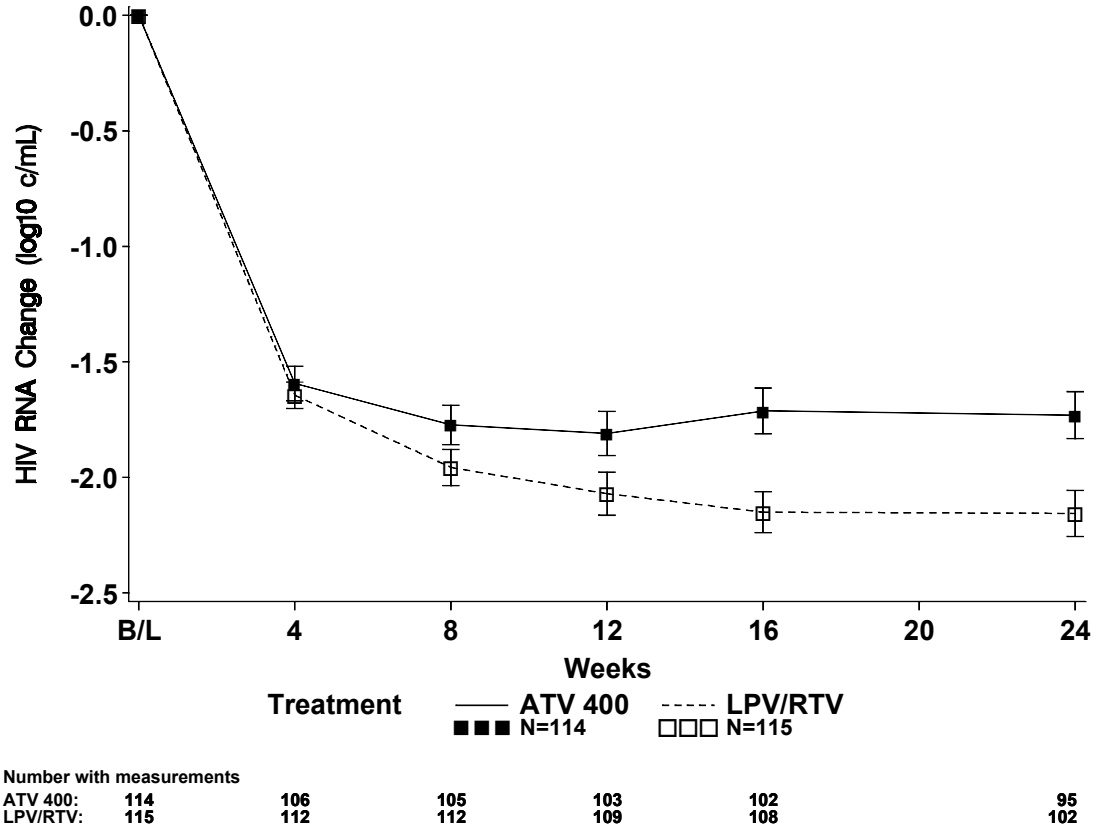
HIV RNA Level Change From Baseline (log10 c/mL)

		AI424043 Treatment Regimen: NRTI/NRTI/PI	
Week	Summary Statistics	ATV (QD) 400 mg N = 114	LPV/RTV (BID) 400/100 mg N = 115
B/L	N	114	115
	Mean (se)	4.15 (0.076)	4.19 (0.076)
	Median	4.19	4.30
24	N	95	102
	Mean (se)	-1.73 (0.102)	-2.16 (0.099)
	Median	-1.76	-2.21
TAD	(CI)	0.31 (0.06, 0.55)	

TAD = Time-Averaged Difference (ATV - Comparator) through Week 24 for AI424043.
Confidence levels are 97.5% for AI424043
Analyses for AI424043 are based on subjects randomized through 02APR2002.

Source: NDA Clinical Summary of Efficacy Results (Table 4.2.4)

Figure 6.2.2.2: Mean Change (SE) in HIV RNA Level From Baseline - Study AI424043 Randomized Subjects



Source: AI424043 ISR, Supplemental Table 10.1B

6.2.2.3 Comparison to Antiviral Activity of Dual Nucleoside Therapy in Treatment-Experienced Subjects

While the ATV regimen was less efficacious than the LPV/RTV regimen, the reduction from baseline in HIV RNA was substantial. The contribution of the ATV component of the regimen to the substantial efficacy was estimated by retrospective comparison to results from studies evaluating dual nucleoside regimens.

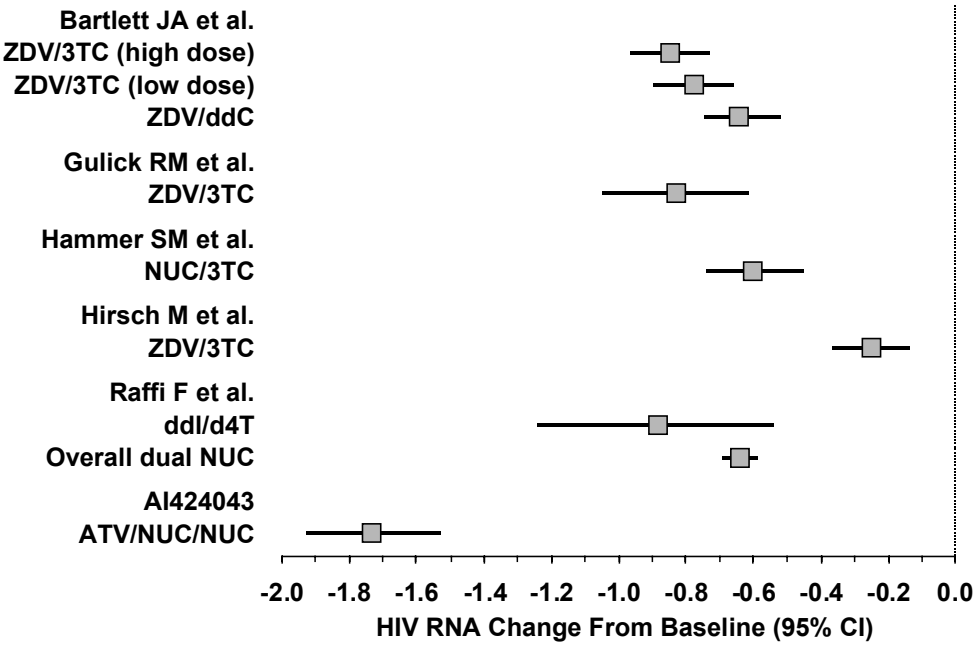
The antiviral efficacy of a dual nucleoside regimen in ARV treatment-experienced subjects was estimated from five trials identified as having been conducted in a treatment-experienced population, containing at least one treatment group with only dual

nucleoside therapy and collecting and reporting analyses of HIV RNA at baseline and Week 24. Estimates of the Week 24 HIV RNA change from baseline for dual nucleoside treatment regimens ranged from -0.25 $\log_{10}$ c/mL to -0.89 $\log_{10}$ c/mL. A combined estimate representing the dual nucleoside treatment effect (ie, the imputed placebo regimen) is -0.64 $\log_{10}$ c/mL with a 95% CI of (-0.69, -0.59).

In Study AI424043, the Week 24 mean HIV RNA change from baseline for ATV combined with dual nucleoside therapy was -1.73 $\log_{10}$ c/mL with a 95% CI of (-1.93, -1.53). All estimates with 95% CI are shown graphically in Figure 6.2.2.3 which demonstrates that the confidence interval for the ATV Week 24 mean HIV RNA change from baseline does not overlap the confidence interval for the individual or combined estimates for dual nucleoside treatment. In fact, the 95% CI for the difference estimate (ATV-'placebo': -1.09 $\log_{10}$ c/mL; 95%CI: (-1.30, -0.88)) excludes zero, indicating a significantly greater Week 24 decrease from baseline in HIV RNA for the ATV regimen as compared with the dual nucleoside therapy alone.

Despite limitations associated with historical and cross-study comparisons, the difference observed between ATV with two nucleosides and two nucleosides alone is large enough to overcome many of these limitations. These analyses support the conclusion that the combination of ATV with two nucleosides provides significantly greater antiviral suppression than would be expected with dual nucleosides alone in the treatment-experienced patient population and therefore ATV contributes to the efficacy seen in Study AI424043.

Figure 6.2.2.3: Meta-analysis: ATV+Dual Nucleoside vs Dual Nucleoside Week 24 HIV RNA Change from Baseline



Source:
Bartlett JA et al. NUCA 3002. Ann Intern Med. 1996; 125:161-172.
Gulick RM et al. Merck 035. N Engl J Med. 1997;337:734-739.
Hammer SM et al. ACTG 320. N Engl J Med. 1997; 337:725-733.
Hirsch M et al. MSD Protocol 039. J Infect Dis. 1999;180:659-665.
Raffi F et al. AIDS. 1998;12:1999- 2005.

6.2.2.4 Proportions in Response at Week 24

The proportion of subjects with HIV RNA < 400 c/mL at Week 24 using the TLOVR definition was 61% on the ATV regimen and 81% on the LPV/RTV treatment regimen. The difference estimate (ATV - LPV/RTV) and 95% CI were -19.0 (-30.7, -7.3), favoring the LPV/RTV treatment regimen (Table 6.2.2.4). The proportion of subjects on the ATV regimen compared to the LPV/RTV regimen with HIV RNA < 50 c/mL was 41% vs 52%. The results of all other efficacy analyses of viral response were consistent with the TLOVR analysis.

Table 6.2.2.4: Proportions with HIV RNA Response at Week 24 (LOQ Equals 400 and 50 c/mL): Study AI424043 ARV Treatment-Experienced Randomized Subjects

	Responder/Evaluable (%)		
	AI424043 Treatment Regimen: NRTI/NRTI/PI		
Analysis	ATV (QD) 400 mg N = 114	LPV/RTV (BID) 400/100 mg N = 115	Difference Estimate (ATV - Comparator) (95% CI)
LOQ = 400 c/mL			
TLOVR (ITT)	69/114 (61)	93/115 (81)	-19.0 (-30.7, -7.3)
VR-OC (AT)	61/100 (61)	86/107 (80)	-18.8 (-31.1, -6.5)
LOQ = 50 c/mL			
TLOVR (ITT)	47/114 (41)	60/115 (52)	-10.0 (-23.1, 3.1)
VR-OC (AT)	42/100 (42)	65/107 (61)	-18.3 (-31.9, -4.6)

TLOVR = Time to Loss of Virologic Response
VR-C = Virologic Response - Completers
Analyses for AI424043 are presented at Week 24 for subjects randomized through 02APR2002.

Source: NDA Clinical Summary of Efficacy Results (Table 4.2.5)

6.2.2.5 Treatment Outcomes (TLOVR) at Week 24

Virologic failure was the most frequent reason for failure on both regimens (28% and 13% for ATV and LPV/RTV, respectively) due mainly to failure to achieve confirmed HIV RNA below 400 c/mL (21% vs 10%) rather than viral rebound (7% vs 3%) (Table 6.2.2.5).

Table 6.2.2.5: Treatment Outcomes (TLOVR) at Week 24 (LOQ Equals 400 c/mL) - Study AI424043 ARV Treatment Experienced Randomized Subjects

	Number of Subjects (%)	
	Treatment Regimen: NRTI/NRTI/PI	
Analysis	ATV (QD) 400 mg N = 114	LPV/RTV (BID) 400/100 mg N = 115
Responder	69 (61)	93 (81)
Virologic failure	32 (28)	15 (13)
Never suppressed through Week 24 and on study at Week 24	24 (21)	12 (10)
Rebound	8 (7)	3 (3)
Discontinued due to adverse events	1 (<1)	2 (2)
Discontinued due to other reasons*	6 (5)	4 (3)
Death	1 (<1)	0
Never treated	5 (4)	1 (<1)

Responders achieved and maintained to Week 48 at least two consecutive HIV RNA levels < 400 c/mL.
* Includes insufficient viral load response, lost to follow-up, non-compliance, pregnancy, protocol violation and withdrawal.

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Run Date: 17OCT02

6.2.2.6 Exploratory Efficacy Analyses for Study AI424043

To better understand the efficacy findings in Study AI424043, several post-hoc exploratory analyses were performed (Table 6.2.2.6). None of the exploratory analyses provide a strong rationale for the observed difference between ATV and LPV/RTV.

Table 6.2.2.6: Study AI424043 - Summary of Exploratory Efficacy Analyses

	Treatment Regimen			
	ATV N = 114		LPV/RTV N = 115	
Baseline Characteristic	**Mean Change in HIV RNA (log_{10} c/mL)**	**TLOVR (LOQ = 400 c/mL)**	**Mean Change in HIV RNA (log_{10} c/mL)**	**TLOVR (LOQ = 400 c/mL)**
PI Sensitive ($\leq$ 2.5 x IC_{50} of control)	-1.84	57/84 (68)	-2.19	83/101 (82)
PI Resistant ($>$ 2.5 x IC_{50} of control)	-1.60	11/26 (42)	-2.00	9/12 (75)
One Prior PI	-1.85	58/85 (68)	-2.13	67/83 (81)
$\geq$ Two Prior PIs	-1.38	11/28 (39)	-2.24	26/31 (84)
No Baseline NRTI Mutations	-2.06	19/32 (59)	-1.96	18/26 (69)
$\geq$ One Baseline NRTI Mutations	-1.61	50/82 (61)	-2.20	75/89 (84)

Source: Study AI424043 24-Week Interim Study Report

NOTE: Number of subjects (N) is based on subjects randomized through 02-Apr-2002. Denominator N differed for each subgroup analysis.

These exploratory analyses demonstrate:

- Subjects with virus demonstrating reduced sensitivity to their assigned PI treatment showed lower response rates; this was observed on both treatment regimens.
- The HIV RNA change from baseline and virologic responses between treatment regimens tended to be closer for subjects who had a treatment history of only one PI than for subjects who had been exposed to more than one PI where substantial differences in efficacy were seen. However, treatment comparisons within these subgroups were consistent with the primary analyses.
- In general, consistent results in HIV RNA change from baseline and response rates were observed for subjects with no NRTI mutations and subjects with at least one NRTI mutation. On the ATV treatment regimen, subjects with no identified NRTI mutations had slightly greater decreases in HIV RNA and slightly higher response rates than subjects with at least one NRTI mutation. In contrast on the LPV/RTV treatment regimen, subjects with no NRTI mutations had lower response rates than subjects with at least one NRTI mutation.

Exploratory subpopulation analyses of the principal efficacy parameters for Study AI424043 were performed based on gender, race, region, HIV RNA level, and CD4 cell count at baseline. Age was not addressed in the subpopulation analyses because there were no subjects > 65 years of age in this study. Overall, the population was small, making comparisons difficult for some subpopulations. Consistent response rates were observed in the gender, race, and region subpopulations.

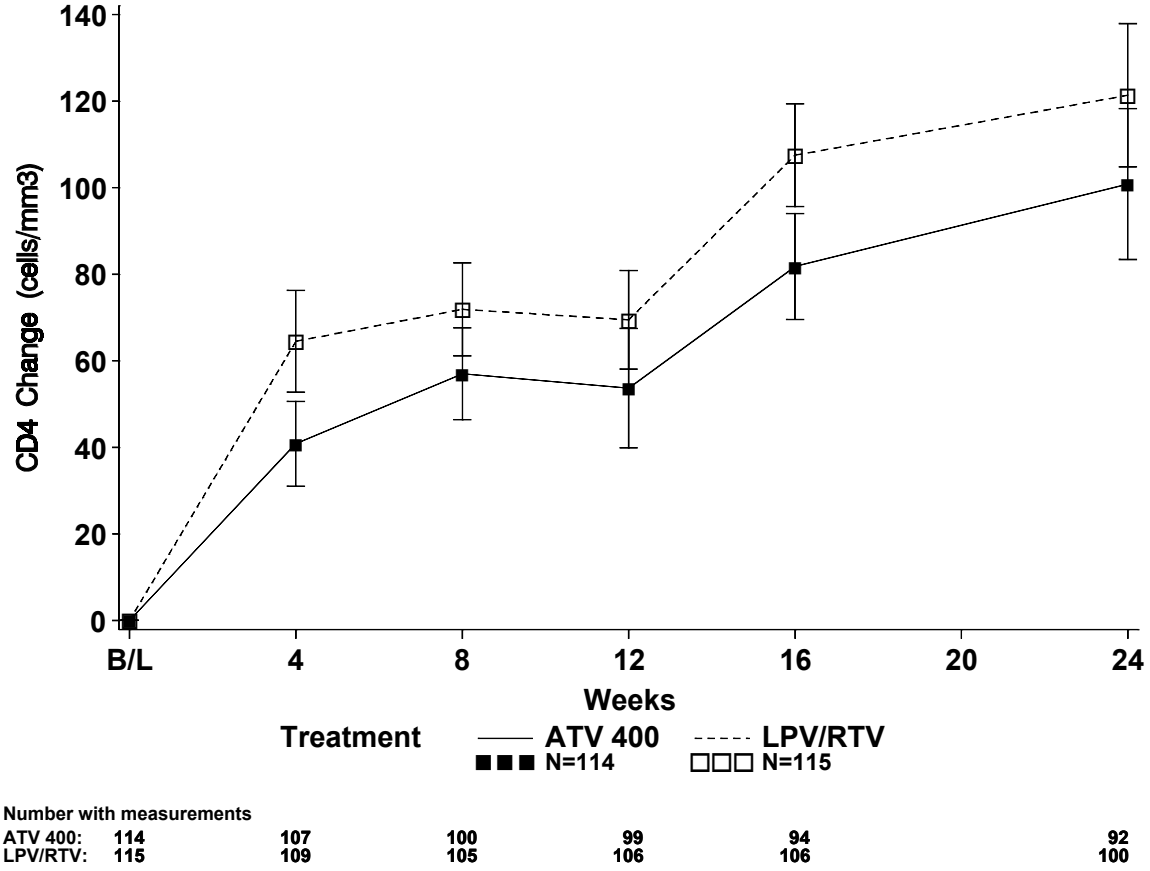
By the TLOVR definition (LOQ = 400 c/mL), the response rate for subjects with HIV RNA < 100,000 c/mL treated with ATV 400 mg was about twice that of subjects with HIV RNA ≥ 100,000 c/mL (66% vs 32%) treated with ATV 400 mg. Response rates were lower for subjects with baseline CD4 cell counts < 200 cells/mm^3 compared with subjects with baseline CD4 cell counts ≥ 200 cells/mm^3 (55% vs 63%).

6.2.2.7 Longitudinal Immunologic Response

There was a rapid increase in mean CD4 cell count. Mean CD4 cell count reached approximately 430 cells/mm^3 by Week 24; the mean increase from baseline at Week 24 was 101 cells/mm^3 on the ATV regimen and 121 cells/mm^3 on the LPV/RTV regimen

(Figure 6.2.2.7). The TAD estimate (ATV - LPV/RTV) and 95% CI for the change from baseline in CD4 cell count through Week 24 were -25.3 (-49.8, -0.8), which favored the LPV/RTV regimen.

Figure 6.2.2.7: Mean Change (SE) in CD4 Cell Count From Baseline - Study AI424043 Randomized Subjects



Source: AI424043 ISR, Supplemental Table S.10.3B

6.2.2.8 Independent Safety Monitoring Review

An independent safety monitoring board reviewed these Week 24 interim results. Their recommendations were implemented and are as follows:

1) Subjects on ATV 400 mg QD co-administered with two nucleosides could remain on study if they are receiving benefit through virologic suppression;

2) If the subject is not benefiting from treatment, then implement a regimen of ATV (300 mg) combined with RTV or initiate dosing with LPV/RTV.

6.2.2.9 Conclusion

Study AI424043 demonstrated the efficacy of ATV in ARV treatment-experienced subjects. Although inferior to LPV/RTV in the analyses of virologic suppression and proportions below LOQ, there was clear evidence that ATV was superior to a dual nucleoside regimen based on historical analysis.

6.2.3 Efficacy Analyses in Phase III Study AI424045

The Phase III study AI424045 is an ongoing multi-national, open-label, randomized, three-arm study designed to determine the antiviral activity and tolerability of ATV (300 mg)/RTV (100 mg), ATV (400 mg)/SQV (1200 mg), and LPV/RTV, each in combination with TFV and an NRTI (after two weeks), through 48 weeks. The study targeted subjects who were highly treatment-experienced, having failed at least two prior HAART regimens that included members of each of the three classes of approved HIV treatments (ie, highly treatment experienced [HTE]).

An interim analysis of efficacy and safety for the first 106 randomized subjects was included with the ATV NDA. That analysis suggested the ATV/RTV "boosted" regimen was providing efficacy comparable to LPV/RTV, while the combination of ATV 400/SQV appeared to be less effective. Only preliminary inferences were possible from this interim analysis. All randomized subjects in this study were subsequently analyzed after the entire cohort reached Week 16, and these data are detailed in this section. While this analysis was submitted to the NDA with the Updated Summary of Clinical Safety, the efficacy analysis has not been reviewed by FDA and therefore inferences from these data are also preliminary. Additionally, data on all randomized subjects through Week 24 have recently become available; however, they have not been submitted to the NDA nor formally reviewed by the FDA.

6.2.3.1 Study Population

The study population was predominately male (78%) and had a mean age of 41 years. Non-white racial groups comprised 40% of the population. Most subjects were from South America (46%) or North America (35%). Additional baseline characteristics are described in Table 6.2.3.1A.

The majority of randomized subjects had recently taken a NRTI (96%) or NNRTI (60%), whereas only 34% had taken a PI. The most common ARV agents taken within 90 days of study entry were d4T (63%), 3TC (54%), and EFV (38%). For randomized subjects, the mean exposure to any PI, NRTI, or NNRTI therapy was 138, 280, and 85 weeks, respectively.

Table 6.2.3.1A: Study AI424045 Subject Demography - Randomized Subjects

CHARACTERISTIC	TREATMENT REGIMEN ATV 300/RTV N = 120	ATV 400/SQV N = 115	LPV/RTV N = 123	Total N = 358
Age (Years)				
MEAN (SE)	41 (0.8)	42 (0.8)	40 (0.7)	41 (0.5)
MEDIAN	39	41	39	40
MIN, MAX	24, 71	26, 74	25, 72	24, 74
MISSING	0	0	0	0
Gender: N (%)				
MALE	96 (80)	89 (77)	96 (78)	281 (78)
FEMALE	24 (20)	26 (23)	27 (22)	77 (22)
Race: N (%)				
WHITE	75 (63)	70 (61)	71 (58)	216 (60)
HISPANIC/LATINO	27 (23)	26 (23)	27 (22)	80 (22)
BLACK	18 (15)	16 (14)	21 (17)	55 (15)
OTHER: COLORED	0	1 (<1)	0	1 (<1)
OTHER: HAITIAN	0	0	1 (<1)	1 (<1)
OTHER: MAPUCHE (NATIVE)	0	0	1 (<1)	1 (<1)
OTHER: MULATTO	0	1 (<1)	2 (2)	3 (<1)
OTHER: MULLATO	0	1 (<1)	0	1 (<1)
Region: N (%)				
SOUTH AMERICA	56 (47)	55 (48)	54 (44)	165 (46)
NORTH AMERICA	39 (33)	38 (33)	47 (38)	124 (35)
EUROPE	25 (21)	22 (19)	22 (18)	69 (19)
IV Drug Use: N (%)	8 (7)	7 (6)	8 (7)	23 (6)
AIDS: N (%)	33 (28)	32 (28)	36 (29)	101 (28)
HIV RNA Level (log10 c/mL)				
MEDIAN	4.44	4.42	4.47	4.45
HIV RNA Distribution (c/mL): N (%)				
< 30000	64 (53)	60 (52)	62 (50)	186 (52)
30000 - < 100000	28 (23)	24 (21)	33 (27)	85 (24)
>= 100000	28 (23)	31 (27)	28 (23)	87 (24)

Table 6.2.3.1A: Study AI424045 Subject Demography - Randomized Subjects

CHARACTERISTIC	TREATMENT REGIMEN ATV 300/RTV N = 120	ATV 400/SQV N = 115	LPV/RTV N = 123	Total N = 358
CD4 Cell Count (cells/mm3)				
MEDIAN	317	286	282	297
Hepatitis B Surface Antigen or Hepatitis C Antibody[a]				
POSITIVE	20 (17)	20 (19)	18 (16)	58 (17)
NEGATIVE	96 (83)	87 (81)	93 (84)	276 (83)

[a] Hepatitis B Surface Antigen and Hepatitis C Antibody are presented for treated subjects. n=119 for ATV 300/RTV, n=110 for ATV 400/SQV, n=118 for LPV/RTV, and n=347 for the total subjects

Source: AI424045 Interim Study Report Week 16 (Tables S.8.3.1B, S.8.3.1E, and S.8.3.3B)

Sensitivity to a specific PI (≤ 2.5 x IC_{50} of control strain) ranged from 56% to 83%, with 23% of the treated subjects highly resistant (> 10 x IC_{50} of control strain) to NFV and 21% of the subjects highly resistant to RTV (Table 6.2.3.1B). Seventy-four percent (74%) and 75% of subjects were susceptible to ATV and LPV, respectively. Susceptibility to ATV or LPV was comparable across the treatment regimens.

Table 6.2.3.1B: Study AI424045 PI and NRTI Phenotypic Sensitivity at Screening - Randomized Subjects

		NUMBER OF SUBJECTS (%)			
		TREATMENT REGIMEN			
	IC50 MULTIPLE OF CONTROL	ATV 300/RTV N=120	ATV 400/SQV N=115	LPV/RTV N=123	Total N=358
PI					
AMP	<=2.5	100 (83)	99 (86)	99 (80)	298 (83)
	>10	9 (8)	3 (3)	11 (9)	23 (6)
ATV	<=2.5	88 (73)	83 (72)	94 (76)	265 (74)
	>10	12 (10)	8 (7)	13 (11)	33 (9)
LPV	<=2.5	91 (76)	89 (77)	88 (72)	268 (75)
	>10	17 (14)	9 (8)	15 (12)	41 (11)
NFV	<=2.5	66 (55)	66 (57)	68 (55)	200 (56)
	>10	32 (27)	23 (20)	29 (24)	84 (23)
RTV	<=2.5	80 (67)	76 (66)	77 (63)	233 (65)
	>10	26 (22)	19 (17)	29 (24)	74 (21)
SQV	<=2.5	98 (82)	97 (84)	102 (83)	297 (83)
	>10	13 (11)	6 (5)	10 (8)	29 (8)
NRTI					
3TC	<=2.5	33 (28)	32 (28)	34 (28)	99 (28)
	>10	72 (60)	63 (55)	57 (46)	192 (54)
ABC	<=2.5	48 (40)	48 (42)	47 (38)	143 (40)
	>10	5 (4)	2 (2)	2 (2)	9 (3)
D4T	<=2.5	96 (80)	100 (87)	89 (72)	285 (80)
	>10	2 (2)	0	2 (2)	4 (1)
DDI	<=2.5	111 (93)	110 (96)	111 (90)	332 (93)
	>10	2 (2)	0	1 (<1)	3 (<1)
ZDV	<=2.5	56 (47)	48 (42)	45 (37)	149 (42)
	>10	51 (43)	37 (32)	62 (50)	150 (42)

Source: AI424045 Second Interim Study Report

An important caveat regarding interruption of baseline PI susceptibility data is that only 34% of randomized subjects were taking a PI at study entry. This would lead to PI susceptibility measurements that are overstated (ie, resistance, therefore, being understated).

A total of 347 subjects (97%) started therapy. Of those treated, 20 subjects (6%) discontinued prior to the Week 16 visit. A total of 312 subjects (87%) continued on study therapy, 91% on ATV 300/RTV, 83% on ATV 400/SQV, and 87% on LPV/RTV (Table 6.2.3.1C).

Table 6.2.3.1C: Study AI424045 Subject Disposition - Randomized Subjects

	NUMBER OF SUBJECTS (%)			
	TREATMENT REGIMEN			
	ATV 300/RTV N = 120	ATV 400/SQV N = 115	LPV/RTV N = 123	Total N = 358
RANDOMIZED	120	115	123	358
NEVER TREATED	1 (<1)	5 (4)	5 (4)	11 (3)
TREATED	119 (99)	110 (96)	118 (96)	347 (97)
COMPLETED TREATMENT	0	0	1 (<1)	1 (<1)
CONTINUING ON TREATMENT	109 (91)	96 (83)	107 (87)	312 (87)
DISCONTINUED PRIOR TO WEEK 16 VISIT	5 (4)	11 (10)	4 (3)	20 (6)
ADVERSE EVENT	4 (3)	5 (4)	1 (<1)	10 (3)
LOST TO FOLLOW-UP	0	2 (2)	0	2 (<1)
NON-COMPLIANCE	0	1 (<1)	2 (2)	3 (<1)
PROTOCOL VIOLATION WHILE ON STUDY	0	1 (<1)	1 (<1)	2 (<1)
SUBJECT WITHDREW	1 (<1)	2 (2)	0	3 (<1)
DISCONTINUED AFTER WEEK 16 VISIT	5 (4)	3 (3)	6 (5)	14 (4)
ADVERSE EVENT	0	0	3 (2)	3 (<1)
NON-COMPLIANCE	0	1 (<1)	0	1 (<1)
PROTOCOL VIOLATION WHILE ON STUDY	0	0	1 (<1)	1 (<1)
SUBJECT WITHDREW	0	1 (<1)	0	1 (<1)
TREATMENT FAILURE/LACK OF EFFICACY	5 (4)	1 (<1)	2 (2)	8 (2)

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6.2.3.2 Efficacy Results Through Week 16 for the First 106 Randomized Subjects

Comparable antiviral efficacy of ATV regimens to LPV/RTV was suggested for the primary efficacy endpoint (TAD), as well as supported by secondary endpoints, although the ATV 400/SQV regimen appeared less effective based on the mean change from baseline in HIV RNA (Table 6.2.3.2).

Table 6.2.3.2 Efficacy Results - AI424045 Treated Subjects Randomized Through 03MAY2002

	Treatment Regimen: TFV and an NRTI				
	ATV 300 mg/RTV N = 37	**ATV 400 mg/SQV N = 34**	**LPV/RTV N = 35**	**ATV 300 mg/RTV - LPV/RTV**	**ATV 400 mg/SQV - LPV/RTV**
Longitudinal Endpoint	**Week 16 Mean Change from Baseline (SE)**			**Time-Averaged Difference (97.5% CI) through Week 16**	
HIV RNA (log_{10} c/mL)	-1.74 (0.21)	-1.70 (0.19)	-1.87 (0.20)	0.13 (-0.32, 0.57)	0.13 (-0.30, 0.56)
Proportions of subjects responding	**Week 16 Responders/Evaluable (%)**			**Difference Estimate (95% CI)**	
LOQ = 400 c/mL					
TLOVR (ITT)	21/37 (57)	17/34 (50)	21/35 (60)	-3.2 (-26.0, 19.5)	-10.0 (-33.5, 13.5)
VR-OC (AT)	21/34 (62)	18/28 (64)	19/32 (59)	2.4 (-21.2, 26.0)	4.9 (-19.7, 29.6)
LOQ = 50 c/mL					
TLOVR (ITT)	14/37 (38)	10/34 (29)	7/35 (20)	17.8 (-3.2, 38.8)	9.4 (-10.9, 29.7)
VR-OC (AT)	17/34 (50)	11/28 (39)	9/32 (28)	21.9 (-1.7, 45.5)	11.2 (-12.7, 35.1)

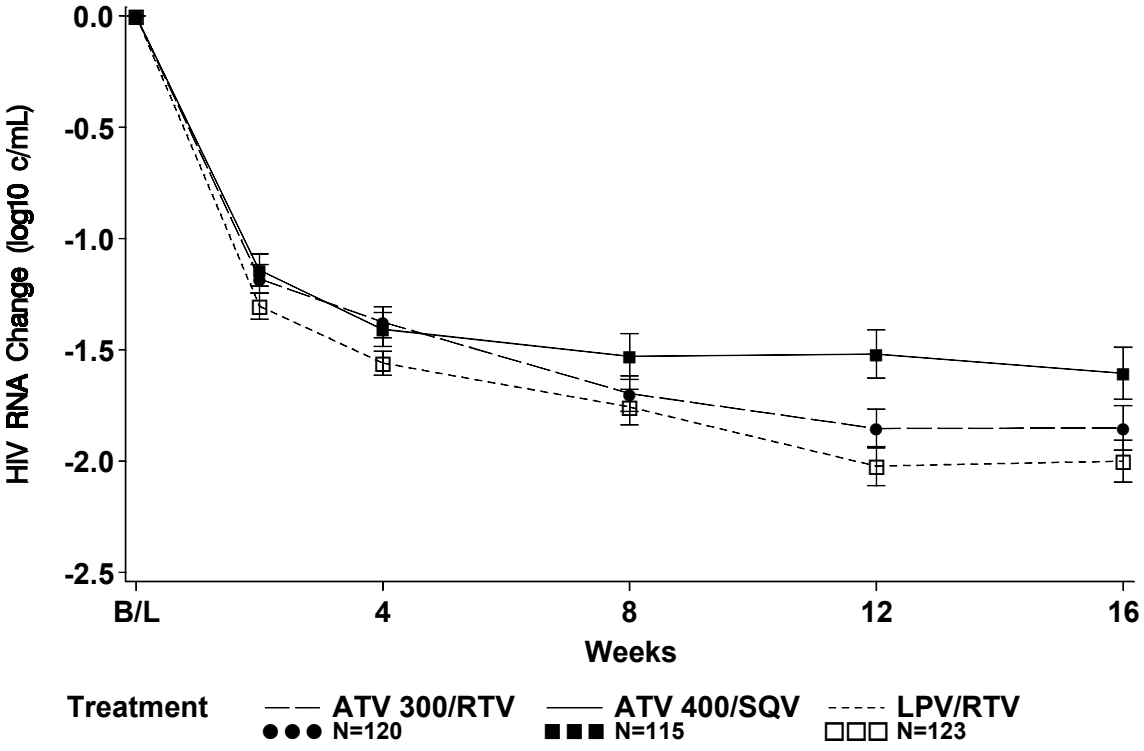
Source: AI424045 Interim Study Report

6.2.3.3 Longitudinal Virologic Suppression Through Week 16 - All Randomized Subjects

Comparable antiviral efficacy of the ATV 300/RTV regimen to the LPV/RTV regimen as suggested was the primary efficacy endpoint through Week 16 (TAD [97.5% CI] for ATV 300/RTV - LPV/RTV was 0.15 [-0.06, 0.37]). In contrast, the antiviral efficacy of the ATV 400/SQV regimen was less than that of the LPV/RTV regimen (ATV 400/SQV - LPV/RTV was 0.29 [0.06, 0.52]) (Table 6.2.3.3; Figure 6.2.3.3).

The intrinsic antiviral activity of ATV 300/RTV, ATV 400/SQV, and LPV/RTV was demonstrated during the first two weeks of the study where replacement of only the PI or NNRTI component of the HAART regimen was implemented, leaving the existing NRTI backbone unchanged. During the first two weeks, HIV RNA levels declined by 1.18 $\log_{10}$ c/mL for ATV 300/RTV, 1.14 $\log_{10}$ c/mL for ATV 400/SQV, and 1.30 $\log_{10}$ c/mL for LPV/RTV and appear comparable across treatment regimens (mean difference 95% CI in HIV RNA changes for ATV 300/RTV - LPV/RTV was 0.12 [-0.05, 0.29], and for ATV 400/SQV - LPV/RTV was 0.16 [-0.02, 0.34]).

Figure 6.2.3.3: Mean (SE) Change in HIV RNA Level From Baseline Through Week 16 - Study AI424045 All Randomized Subjects



Number with measurements

ATV 300:	120	119	117	114	111	113
ATV 400:	115	107	105	100	99	98
LPV/RTV	123	117	115	115	114	114

Source: AI424045 ISR02, Table S.10.1B

Table 6.2.3.3: Virologic Suppression Through Week 16 - Study AI424045 All Randomized Subjects

	HIV RNA Level Change From Baseline (log10 c/mL)	
	Time-Averaged Difference (TAD) Estimate (97.5% CI)	
	ATV 300/RTV - LPV/RTV	ATV 400/SQV - LPV/RTV
Overall	0.15 (-0.06, 0.37)	0.29 (0.06, 0.52)
Last observation carried forward	0.11 (-0.11, 0.32)	0.31 (0.08, 0.54)
Overall adjusted by region	0.16 (-0.06, 0.38)	0.29 (0.06, 0.52)

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6.2.3.4 Proportions in Response at Week 16 - All Randomized Subjects

The comparability of ATV 300/RTV regimen relative to LPV/RTV was supported by the analyses of proportions in response. The proportion of subjects in response was comparable between ATV 300/RTV and LPV/RTV (TLOVR [LOQ = 400 c/mL]: 63% vs 65%; TLOVR [LOQ = 50 c/mL]: 30% vs 33%). Week 16 TLOVR response rates for ATV/SQV were lower than those for the LPV/RTV regimen (46% vs 65% for LOQ = 400 c/mL) (Table 6.2.3.4).

Table 6.2.3.4: Proportions in Response at Week 16 - Study AI424045 (LOQ Equals 400 c/mL and LOQ Equals 50 c/mL) Randomized Subjects

	Proportions in Response at Week 16 (LOQ = 400 c/mL)				
	Responder/Evaluable (%)				
	Treatment Regimen			Difference Estimate (95% CI)	
Analysis	ATV 300/RTV N = 120	ATV 400/SQV N = 115	LPV/RTV N = 123	ATV 300/RTV - LPV/RTV	ATV 400/SQV - LPV/RTV
LOQ = 400 c/mL					
TLOVR (ITT)	76/120 (63)	53/115 (46)	80/123 (65)	-1.7 (-13.8, 10.3)	-19.0 (-31.6, -6.3)
VR-OC (AT)	77/114 (68)	55/99 (56)	80/114 (70)	-2.6 (-14.7, 9.4)	-14.6 (-27.6, -1.6)
LOQ = 50 c/mL					
TLOVR (ITT)	36/120 (30)	27/115 (23)	41/123 (33)	-3.3 (-15.0, 8.4)	-9.9 (-21.3, 1.6)
VR-OC (AT)	45/114 (39)	31/99 (31)	53/114 (46)	-7.0 (-19.9, 5.8)	-15.2 (-28.3, -2.0)

TLOVR: Time To Loss of Virologic Response
VR-OC: Virologic Response - Observed Cases

Source: AI424045 ISR02, Tables 10.2.1A and 10.2.5A and Appendix 10.2

6.2.3.5 Treatment Outcomes (TLOVR) at Week 16 - All Randomized Subjects

The table of treatment outcomes at Week 16 (for all randomized subjects) is based on the TLOVR definition and provides a classification of failure reasons (Tables 6.2.3.5). At Week 16, the virologic failure rate was 32% on ATV 300/RTV, 40% on ATV 400/SQV, and 28% on LPV/RTV. The most common reason for virologic failure was lack of confirmed response.

Table 6.2.3.5: Treatment Outcomes (TLOVR) at Week 16 (LOQ Equals 400 c/mL) - Study AI424045 All Randomized Subjects

	Treatment Outcomes at Week 16 (LOQ = 400 c/mL)		
	Number of Subjects (%)		
	Treatment Regimen		
Outcome	ATV 300/RTV N = 120	ATV 400/SQV N = 115	LPV/RTV N = 123
Responder	76 (63)	53 (46)	80 (65)
Virologic failure	38 (32)	46 (40)	34 (28)
Never suppressed through Week 16 and on study at Week 16	35 (29)	41 (36)	30 (24)
Rebound	2 (2)	5 (4)	4 (3)
Discontinued due to insufficient viral load response	1 (<1)	0	0
Discontinued before achieving confirmed suppression	4 (3)	11 (10)	4 (3)
Adverse event	3 (3)	5 (4)	1 (<1)
Lost to follow-up	0	2 (2)	0
Non-compliance	0	1 (<1)	2 (2)
Protocol violation while on study	0	1 (<1)	1 (<1)
Subject withdrew	1 (<1)	2 (2)	0
Discontinued while suppressed	1 (<1)	0	0
Adverse event	1 (<1)	0	0
Never treated	1 (<1)	5 (4)	5 (4)

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6.2.3.6 Longitudinal Immunologic Response - All Randomized Subjects

The ATV 300/RTV and LPV/RTV regimens were associated with mean CD4 cell counts > 400 cells/mm^3 at Week 16 with median values of 389 and 366 cells/mm^3, respectively. The mean change from baseline at Week 16 was highest on the LPV/RTV regimen (84 cells/mm^3 on ATV 300/RTV, 55 cells/mm^3 on ATV 400/SQV, and 110 cells/mm^3 on LPV/RTV). These increases are substantial for a highly treatment experienced population and have reached levels that have been shown to confer clinical benefit. The TAD estimate for ATV 300/RTV - LPV/RTV and the 95% CI for the change from baseline in CD4 cell count through Week 16 were -20.3 (-45.7, 5.1), while Week 16 CD4 changes were lower for the ATV 400/SQV regimen than for the LPV/RTV regimen (TAD estimate for ATV 400/SQV - LPV/RTV and 95% CI were -45.6 [-74.9, -16.3]). Results were consistent when using the LOCF.

6.2.3.7 Efficacy Results Through Week 24 - All Randomized Subjects

Data on all randomized subjects through Week 24 have also recently become available. Likewise, these data have not been reviewed by the FDA. Efficacy results through Week 24 appeared consistent with both the initial interim analysis of the first 106 randomized subjects and the subsequent Week 16 analysis of all randomized subjects, in that, ATV 300 mg in combination with RTV 100 mg dosed once daily appears similar to an accepted standard-of-care (LPV/RTV) (Table 6.2.3.7). This finding was consistent across all primary and key secondary efficacy analyses, and again suggested that ATV 400/SQV was less efficacious than LPV/RTV in this population.

Table 6.2.3.7: Study AI424045 Efficacy Results Through Week 24 - All Randomized Subjects

	Treatment Regimen:				
	ATV 300 mg/RTV N = 120	ATV 400 mg/SQV N = 115	LPV/RTV N = 123	ATV 300 mg/RTV - LPV/RTV	ATV 400 mg/SQV - LPV/RTV
Longitudinal Endpoint	**Week 24 Mean Change from Baseline (SE)**			**Time-Averaged Difference (97.5% CI) through Week 24**	
HIV RNA (log_{10} c/mL)	-1.86 (0.11)	-1.52 (0.13)	-1.89 (0.11)	0.14 (-0.09, 0.37)	0.31 (0.07, 0.55)
Proportions Responding	**Week 24 Responders/Evaluable (%)**			**Difference Estimate (95% CI)**	
LOQ = 400 c/mL					
TLOVR (ITT)	77/120 (64)	51/115 (44)	76/123 (62)	2.4 (-9.8, 14.5)	-17.4 (-30.1, -4.8)
VR-OC (AT)	76/112 (68)	51/96 (53)	76/112 (68)	0.0 (-12.2, 12.2)	-14.7 (28.0, -1.4)
LOQ = 50 c/mL					
TLOVR (ITT)	47/120 (39)	26/115 (23)	52/123 (42)	-3.1 (-15.5, 9.2)	-19.7 (-31.6, -7.7)
VR-OC (AT)	53/112 (47)	28/96 (29)	57/112 (51)	-3.6 (-16.7, 9.5)	-21.7 (-35.1, -8.3)

Source: AI424045 Executive Summary for All Randomized Subjects at Week 24

6.2.3.8 Conclusion

A series of analyses with increasing numbers of subjects and over long treatment periods suggest that the ATV 300/RTV regimen was equivalent to LPV/RTV. These data strongly support the activity of ATV combinations in ARV treatment-experienced patients.

6.3 Overall Efficacy Conclusions

The efficacy of ATV has been established across a broad clinical spectrum of HIV disease, including ARV treatment-naive, moderately experienced, and highly experienced patients.

At 48 weeks in the ARV treatment-naive population, the proportion of subjects in treatment response was similar between ATV and the standard of care EFV. The mean decreases from baseline in HIV RNA levels were similar for both regimens. The mean increases from baseline in CD4 cell counts were significantly greater on ATV.

At 24 weeks in the ARV treatment-experienced population, ATV 400 mg, while providing antiviral activity that is greater than dual nucleosides, was less efficacious than the standard of care LPV/RTV.

Preliminary data suggest that the efficacy of ATV 300 mg pharmacologically enhanced with RTV 100 mg is comparable to the same standard of care.

Therefore, the efficacy of ATV has been adequately characterized to support its use for treatment of HIV infection as part of a HAART regimen in ARV treatment-naive and treatment-experienced subjects.

7 LIPID AND METABOLIC PROFILE OF ATAZANAVIR

Hyperlipidemia and the risk of attendant cardiovascular disease have emerged as important side effects that limit the usefulness of PI-containing HAART regimens. Current treatment guidelines for the general population and for those treated for HIV emphasize the importance of cardiovascular (CV) risk reduction though aggressive management of hyperlipidemia and hypertriglyceridemia. In the general population, a large body of evidence has established that cardiovascular risk is associated with hyperlipidemia (in particular LDL-cholesterol) and has established that CV risk and significant clinical events (eg, death, myocardial infarction) are reduced with lipid and triglyceride reduction. The evolving body of evidence indicates that individuals treated for HIV are not protected from the morbidity and mortality associated with hyperlipidemia. Although there are conflicting data, biologic and epidemiological evidence suggest that HAART therapies are associated with an increase in cardiac events. Although therapeutic interventions are used with increasing frequency for treating the hyperlipidemia and hypertriglyceridemia that complicates most PI-containing HAART regimens, dietary interventions and lipid lowering therapies are only partially successful and significantly complicate HAART regimens by introducing additional pill burden, drug-drug interactions and toxicity. A PI that does not result in hyperlipidemia and hypertriglyceridemia would offer substantial benefit by reducing the need for poly-pharmacy while addressing the potential for increased cardiovascular morbidity and mortality. Because CV risk reduction in the general population is achieved with reduction in serum lipids, a similar benefit is expected among subjects receiving ATV over a longer, but yet undefined period of time.

The results of five Phase II/III comparative studies conducted across ARV treatment-naive and treatment-experienced individuals consistently demonstrated that ATV treatment, as part of a HAART regimen, resulted in significantly less hyperlipidemia and hypertriglyceridemia as compared with other PIs (eg, NFV, LPV/RTV) and as compared with the NNRTI, EFV. The favorable lipid and triglyceride profile for ATV was consistently demonstrated when ATV was combined with a variety of NRTI backbones (ZDV, d4T, ddI, 3TC, TDF). One study (AI424043) met the co-primary objective to demonstrate superior lipid parameters for ATV compared with the PI LPV/RTV as assessed by low density lipoprotein (LDL-cholesterol)

measurements. Another study (AI424008/44) confirmed the long term durability of achieving lower lipid concentrations with ATV treatment through 108 weeks and demonstrated a regression in hyperlipidemia and hypertriglyceridemia when NFV was switched to ATV. In addition, ATV demonstrated no clinically important effect on insulin/glucose metabolism.

The magnitude of the difference between LDL-cholesterol concentrations observed for the population of subjects treated with ATV relative to comparator PIs and to the NNRTI EFV is clinically relevant based upon NCEP criteria described in Table 7. In the short-term, fewer ATV-treated patients meet requirements for lipid lowering interventions. The long-term benefits of avoiding hyperlipidemia have been established in the general population, and current clinical practice for HAART-treated patients presumes a similar association between hyperlipidemia and CV risk. For example, 18 - 30% of patients treated with PIs have a co-morbidity condition of hyperlipidemia, and 8% of patients initiate lipid lowering therapy.

Table 7: Grading of Serum Lipids for ATV Trials Adopted from NCEP Categorization

Total Cholesterol (mg/dL)	Range:	< 200	200 - 239	240 - 299	> 300
	Category:	Desirable	Borderline High	High	Very High
LDL-Cholesterol (mg/dL)	Range:	< 130	130 - 159	160 - 189[a]	> 190
	Category:	Optimal or Near Optimal	Borderline High	High	Very High
HDL-Cholesterol (mg/dL)	Range:	< 40	40 - 59	> 60	
	Category:	Low	Average	High	

Source: NCEP Adult Treatment Panel Guidelines

[a] LDL-cholesterol > 160 mg/dL is notable in that treatment with cholesterol lowering drugs and/or dietary intervention is recommended even in the absence of underlying cardiovascular risk factors.

7.1 Lipid Metabolism in Treatment-Naive Subjects

Results from three Phase II/III studies conducted in ARV treatment-naive HIV-infected subjects consistently demonstrated an improved lipid profile for ATV-treated subjects

compared to NFV and EFV treated subjects as assessed by total cholesterol, fasting LDL-cholesterol, and fasting triglycerides changes from baseline.

7.1.1 Lipid Metabolism in Phase II Studies AI424007 and AI424008

Studies AI424007 and AI424008 were randomized studies comparing ATV regimens to NFV regimens in ARV treatment-naive subjects that are more fully described in Section 6 (Efficacy). Differences between ATV and comparator regimens were observed by Week 4 and continued throughout the treatment period. Analysis of mean percent changes from baseline indicated that subjects on the NFV treatment regimens had substantial increases in LDL-cholesterol by Week 12 and that these increases were sustained through 72 weeks. ATV-treated subjects experienced little or not increases in LDL-cholesterol. Based on NCEP, 80 - 87% of subjects had baseline LDL-cholesterol in the optimal or near optimal range (< 130 mg/dL). However, at Week 72 the proportion of subjects who achieved LDL-cholesterol concentrations that were classified as high or very high (≥ 160 mg/dL) was greater on NFV compared with ATV (17% vs 5%).

7.1.2 Lipid Metabolism in Phase III Study AI424034

Study AI424034 was randomized blinded Phase III study comparing ATV with EFV, each in combination with fixed dose ZDV. Through 48 weeks of treatment, ATV did not result in increases from baseline in fasting LDL-cholesterol, total cholesterol, or insulin, and resulted in a statistically significant decrease of 9% in fasting triglycerides and a statistically significant increase of 13% in HDL-cholesterol $p < 0.05$ for comparisons to baseline (Table 7.1.2). Baseline LDL-cholesterol values assessed by NCEP categories were comparable for ATV and EFV regimens. At 48 weeks, the proportion of ATV-treated fasting LDL-cholesterol concentrations outside the NCEP-defined desirable range was unchanged from baseline. Among ATV-treated subjects, LDL-cholesterol was ≥ 130 mg/dL in 13% of subjects at baseline and 13% at Week 48. LDL-cholesterol was ≥ 160 mg/dL in 2% and 3% of ATV-treated subjects at baseline and Week 48, respectively. In comparison, the proportion of EFV-treated subjects with LDL-cholesterol ≥ 130 or ≥ 160 mg/dL increased from baseline. Nineteen subjects (2%) were administered lipid reduction pharmacological therapy while on-study, five (1%) on ATV and 14 (3%) on EFV.

Table 7.1.2: Lipid, Insulin, and Glucose Mean Values From Study AI424034

	ATV			EFV		
	Baseline (mg/dL) (n = 383)[a]	Week 48		Baseline (mg/dL) (n = 378)[a]	Week 48	
		mg/dL (n = 283)[a]	Change (n = 272)[a]		mg/dL (n = 264)[a]	Change (n = 253)[a]
LDL-Cholesterol (fasting)	98	98	+1%[b]	98	114	+18%
HDL-Cholesterol	39	43	+13%[b]	38	46	+24%
Total-Cholesterol	164	168	+2%[b]	162	195	+21%
Triglycerides (fasting)	138	124	-9%[b]	129	168	+23%
Insulin (fasting)	11.3	12.3	+1.3 µU/mL[c]	9.9	11.5	+1.4 µU/mL
Glucose (fasting)	90	93	+3 mg/dL[c]	90	94	+6 mg/dL

Source: 48 Week Clinical Study Report for AI424034

[a] Number of patients with fasting LDL-cholesterol.

[b] $p < 0.0001$ for comparisons of ATV to EFV.

[c] p = not significant for comparisons of ATV to EFV.

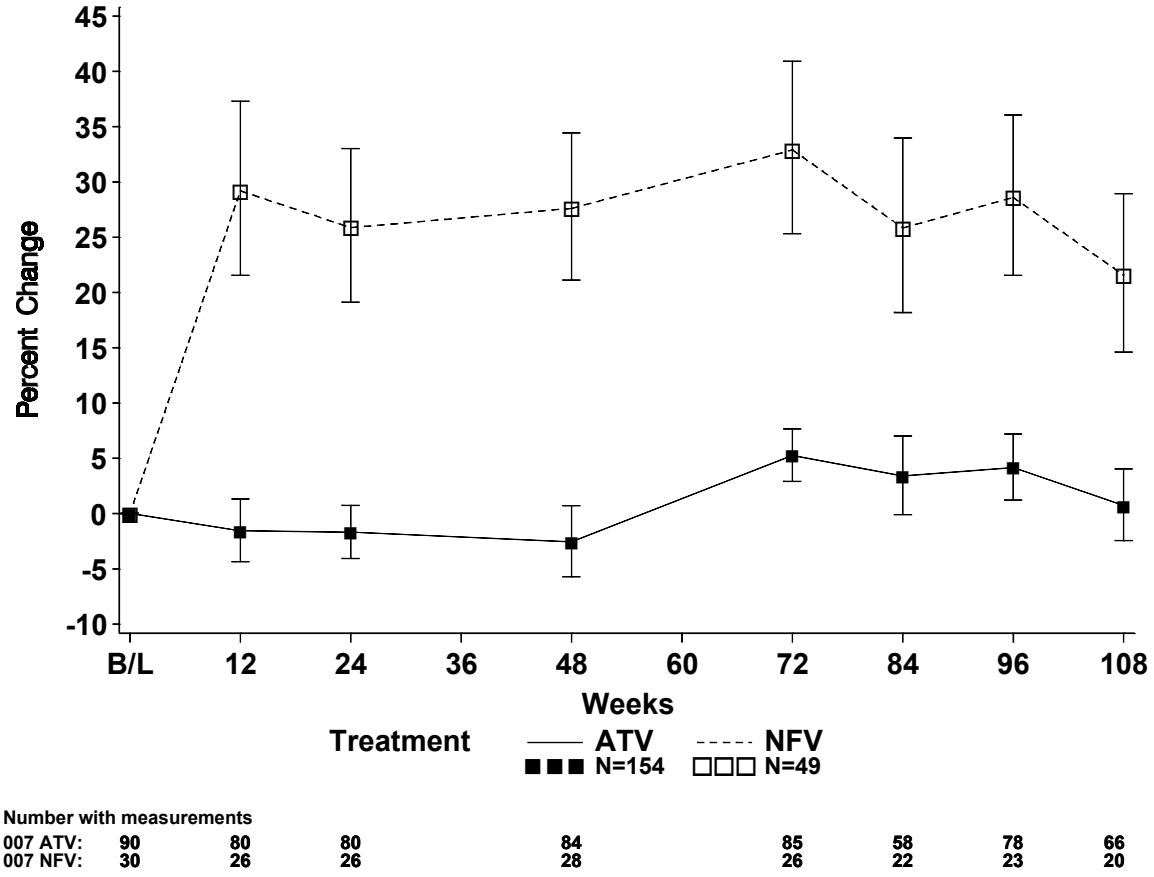
7.1.3 Long-term Lipid Metabolism

Long-term lipid benefits were maintained through Week 108 for those subjects who enrolled into Studies AI424041 and AI424044. The following fasting LDL-cholesterol analyses were conducted on the cohort of subjects who were treated on the extended dosing studies that followed completion of Studies AI424007 and AI424008.

7.1.3.1 AI424007/41

AI424007/041 provided long term lipid data for subjects treated with ATV+ddI+d4T versus a NFV comparator. Through Week 108, subjects treated with the NFV regimen show substantially higher mean fasting LDL-cholesterol levels compared to ATV-treated subjects, who show no substantial mean increase from baseline. The ATV regimen was associated with a minimal mean percent increase from baseline in fasting LDL-cholesterol of 1% whereas, the NFV regimen was associated with a 22% increase from baseline (Figure 7.1.3.1).

Figure 7.1.3.1: Mean (SE) Percent Change in Fasting LDL-Cholesterol From Baseline - Subjects Treated in Study AI424041 (ATV Doses Pooled)



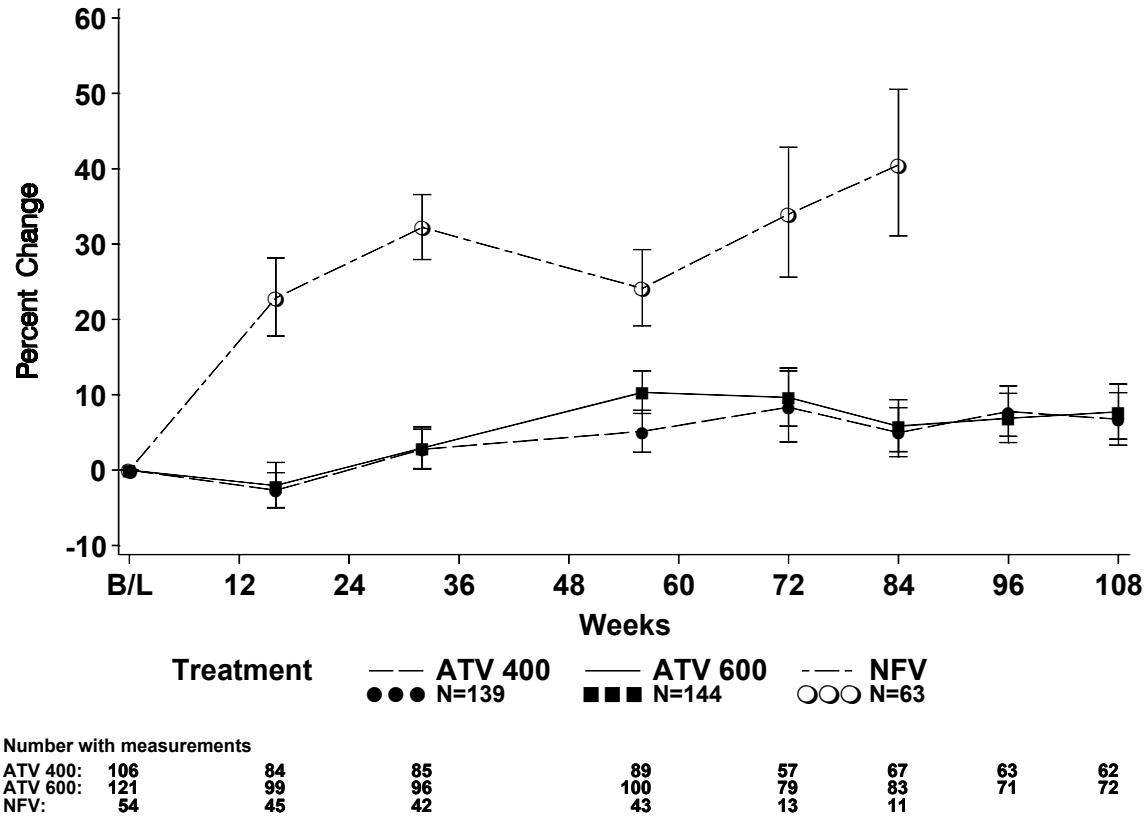
Source: February 14, 2003 FDA Response, Table 1D

7.1.3.2 AI424008/44

AI424008/44 provided long term lipid data (108 weeks) for subjects continuing on treatment with ATV +d4T+3TC and demonstrated that after prolonged therapy (median 76 weeks) with another PI (NFV), reduction in serum lipid and triglyceride concentrations to pre-ARV levels was achieved within four weeks of the switch to ATV and sustained for 24 weeks following the switch.

Subjects who enrolled into AI424044 and were initially treated with NFV maintained an increase from baseline in fasting LDL-cholesterol of approximately 30% through the time they rolled over. Changes from baseline for the corresponding subjects treated with ATV were minimal through Week 108 (ATV 400, 7%; ATV 600, 8%) (Figure 7.1.3.2).

Figure 7.1.3.2: Mean (SE) Percent Change in Fasting LDL-Cholesterol From Baseline - Subjects Treated in Studies AI424008/044



Source: Study Reports for AI424008 (48 Week) and AI424044

Note: NFV group switched to ATV 400 mg upon entry. Therefore, no NFV data are available after Week 84.

7.1.4 Lipid Metabolism in Subjects Who Switched From Nelfinavir to Atazanavir

Study AI424044 had a specific objective to assess changes in serum lipid concentrations associated with a switch from NFV⇒ATV. The sample size had sufficient statistical power to detect a mean decrease of 15% or greater in total cholesterol after 12 weeks of therapy. The 12-week endpoint was selected based on data from previous Phase II studies (AI424007 and AI424008) that showed ARV associated dyslipidemia can be detected as early as Week 4 after the start of HAART therapy. The mean time on NFV prior to a switch to ATV was 76 weeks. The mean time on ATV in Study AI424044 was 38 weeks among the 63 subjects switching from NFV⇒ATV. The aggregate time on ATV for those subjects continuing ATV from AI424008 was approximately 108 weeks.

At the Week 12 endpoint, significant differences were observed for the mean percent change from entry in total cholesterol (-16%), HDL-cholesterol (+5%), fasting LDL-cholesterol (-21%), and fasting triglycerides (-28%) (Table 7.1.4). For all lipid parameters except HDL-cholesterol, these statistically significant differences were maintained through Week 24. Median Week 12 levels of total cholesterol (165 mg/dL), fasting LDL-cholesterol (94 mg/dL), and fasting triglycerides (86 mg/dL) in this cohort were comparable to median baseline levels in Study AI424008 (168 mg/dL, 91 mg/dL, and 93 mg/dL, respectively).

Additionally, more than half of subjects in the NFV⇒ATV cohort who entered AI424044 with borderline high or high LDL-cholesterol no longer met these criteria by Week 12 (LDL-cholesterol ≥ 130 mg/dL in 55% at entry vs 22% at Week 12; LDL-cholesterol ≥ 160 mg/dL in 27% at entry vs 10% at Week 12).

Table 7.1.4: Lipid, Insulin, and Glucose Mean Values From Study AI424044 - Treated Subjects who Switched from Nelfinavir to Atazanavir

		NFV ⇒ ATV			
		Week 12		Week 24	
	Entry (mg/dL) (n = 33)[a]	mg/dL (n = 41)[a]	Change (n = 29)[a]	mg/dL (n = 40)[a]	Change (n = 29)[a]
LDL-Cholesterol (fasting)	138	104	-21%	106	-20%
Total-Cholesterol	214	175	-16%	178	-16%
HDL-Cholesterol	46	48	+5%[b]	47	+5%[c]
Triglycerides (fasting)	157	108	-28%	129	-25%
Insulin (fasting)	9.8	9.3	ND	8.2	ND
Glucose (fasting)	86	88	ND	88	ND

Source: Clinical Study Report for AI424044

ND = Not Done

$p < 0.0001$ unless otherwise noted.

[a] Number of patients with fasting LDL-cholesterol measured. For change scores, n = number of patients with fasting LDL-cholesterol measured at entry and at timepoint assessed.

[b] $p < 0.05$

[c] p = not significant

7.2 Lipid Metabolism in Treatment-Experienced Subjects

Results in treatment-experienced HIV-infected subjects demonstrated a favorable lipid profile for ATV-treated subjects compared to RTV/SQV and LPV/RTV-treated subjects, as assessed by changes in total cholesterol, LDL-cholesterol, and fasting triglycerides.

7.2.1 Lipid Metabolism in Phase II Study AI424009

Study AI424009 was a pilot study conducted in 85 ARV treatment-experienced subjects. At Week 72 on Study AI424009, the mean change in LDL-cholesterol for RTV/SQV treated subjects was 8% compared to a mean decrease of 2% for ATV 400/SQV and 30% for ATV 600/SQV-treated subjects. While the mean change in serum triglycerides for

RTV/SQV-treated subjects was 95% compared to 27% for ATV 400/SQV-treated subjects and a decrease of 15% for ATV 600/SQV-treated subjects.

7.2.2 Lipid Metabolism in Phase III Study AI424043

Study AI424043 was a randomized, open-label, study in ARV treatment-experienced subjects comparing ATV with LPV/RTV, each in combination with two nucleosides selected on the basis of resistance testing. In Study AI424043, the co-primary objective was to compare the magnitude of change in LDL-cholesterol at Week 24. The magnitude of changes in total cholesterol, HDL-cholesterol, glucose, and fasting triglycerides through Week 24 were analyzed as secondary study objectives.

The ATV-containing treatment regimen was associated with a decrease from baseline in fasting LDL-cholesterol (6%), whereas LPV/RTV was associated with an increase from baseline (8%) at Week 24 (Table 7.2.2; Figure 7.2.2). The superior fasting LDL-cholesterol levels for ATV compared with LPV/RTV were demonstrated by comparing the mean percent change from baseline in fasting LDL-cholesterol (-14.2%, 97.5% CI: -23.0%, -5.4%, nominal $p < 0.0001$).

Table 7.2.2: Lipid, Insulin, and Glucose Mean Values From Study AI424043

	ATV			LPV/RTV		
	Baseline (mg/dL) (n = 109)[a]	Week 24		Baseline (mg/dL) (n = 114)[a]	Week 24	
		mg/dL (n = 91)[a]	Change (n = 91)[a]		mg/dL (n = 83)[a]	Change (n = 82)[a]
LDL-Cholesterol (fasting)	104	92	-6%[b]	100	106	+8%
HDL-Cholesterol	37	41	+15%	37	45	+17%
Total-Cholesterol	179	169	-2%[b]	172	199	+18%
Triglycerides (fasting)	207	207	-2%[b]	196	260	+57%
Insulin (fasting)	10.8	11.4	+0.3 μU/mL[c]	9.9	10.2	+0.2 μU/mL
Glucose (fasting)	89	91	+2 mg/dL[c]	90	90	-1 mg/dL

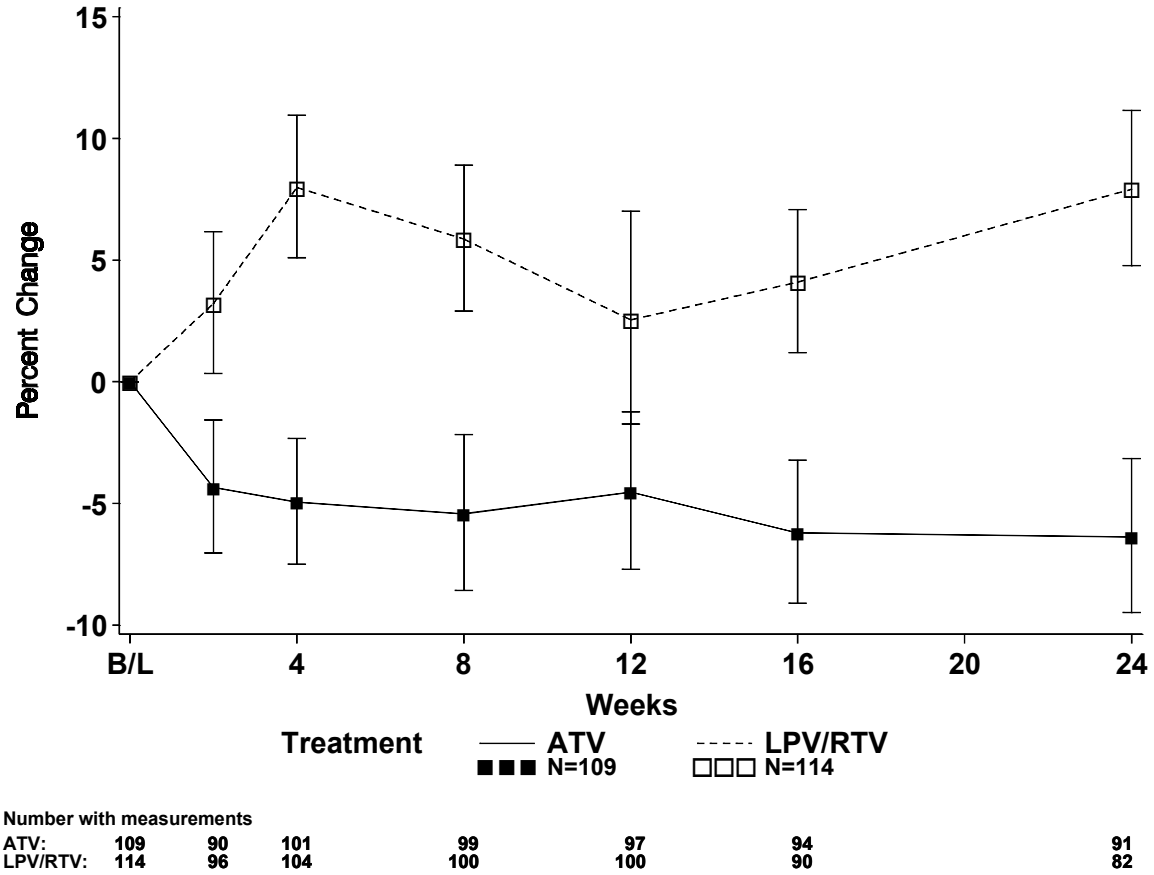
Source: Clinical Study Report for AI424043

[a] Number of subjects with fasting LDL-cholesterol.

[b] $p < 0.0001$ for comparisons of ATV to LPV/RTV.

[c] p = not significant for comparisons of ATV to LPV/RTV.

Figure 7.2.2: Mean (SE) Percent Change in Fasting LDL-Cholesterol From Baseline - Study AI424043 Treated Subjects Randomized Through 02-Apr-2002



Source: AI424043 24-Week Interim Clinical Study Report, Table S.12.7A

Atazanavir treatment was also associated with small decreases from baseline in total cholesterol (2%) and fasting triglycerides (2%) through 24 weeks. In contrast, at 24 weeks LPV/RTV was associated with substantial increases from baseline in total cholesterol (18%) and fasting triglycerides (57%). Mean percent changes from baseline were statistically superior for ATV for total cholesterol (-18.1%, 95% CI: -23.4%, -12.9%; $p < 0.0001$) and fasting triglycerides (-36.1%, 95% CI: -46.7%, -25.5%, $p < 0.0001$). The differences in LDL-cholesterol, total cholesterol, and fasting triglyceride levels were observed for ATV-treated subjects within four weeks of

beginning therapy and persisted through Week 24. HDL-cholesterol increased for both treatment regimens, with slightly greater increases on the LPV/RTV treatment regimen. As a result, the use of serum lipid reducing agents was less common on the ATV treatment regimen (5%) than on the LPV/RTV treatment regimen (18%).

7.2.3 Lipid Metabolism in Phase III Study AI424045

In the highly treatment-experienced population (AI424045), both ATV-containing regimens were associated with superior lipid parameters compared to LPV/RTV, as assessed by the mean percent change from baseline at Week 16 in total cholesterol (ATV/RTV: -7%; ATV/SQV: -10%; LPV/RTV: +5%) and fasting triglycerides (ATV/RTV: 2%; ATV/SQV: -15%; LPV/RTV: +34%). Mean percent changes from baseline in fasting LDL-cholesterol at Week 16 for ATV 400/SQV were superior compared to LPV/RTV (ATV/SQV: -10%; LPV/RTV: +1%). At Week 16, fasting LDL-cholesterol concentrations outside the desirable range (values ≥ 130 mg/dL) were comparable across the three treatment regimens (Table 7.2.3).

Thirty-eight subjects (11%) took serum lipid reduction therapy while on study, 7% on ATV 300/RTV, 12% on ATV 400/SQV, and 14% on LPV/RTV. More importantly, 3% of subjects each on ATV 300/RTV and ATV 400/SQV and 8% of subjects on LPV/RTV initiated serum lipid reduction therapy while on study.

Table 7.2.3: Lipid, Insulin, and Glucose Mean Values From Study AI424045 - Treated Subjects

	ATV 300/RTV			ATV 400/SQV			LPV/RTV		
		Week 16			Week 16			Week 16	
	Baseline (mg/dL) (n = 112)[a]	mg/dL (n = 100)[a]	% Change (n = 99)[a]	Baseline (mg/dL) (n = 101)[a]	mg/dL (n = 84)[a]	% Change (n = 84)[a]	Baseline (mg/dL) (n = 108)[a]	mg/dL (n = 88)[a]	% Change (n = 86)[a]
LDL-Cholesterol (fasting)	109	98	-8	97	88	-10	104	102	1
HDL-Cholesterol	40	38	-6	39	39	-5	39	40	0
Total-Cholesterol	188	172	-7	175	154	-10	181	187	5
Triglycerides (fasting)	215	198	2	253	156	-15	197	247	34
Glucose (fasting)	95	95	-1	94	90	-4	90	91	3

Source: AI424045 Interim Study Report at Week 16

[a] N = number of subjects with fasting LDL-cholesterol at specified timepoint. Percent change results were calculated only for subjects who had both a baseline result and an on-study result at Week 16. Data from subjects who initiated lipid-lowering therapy were censored from these analyses.

7.3 Preclinical Assessments of Metabolic Attributes

In support of the clinical findings, a substantial amount of work has been done to provide a biologic explanation for the lipid, triglyceride, and glucose metabolic attributes of ATV.

Preclinical findings showed that ATV exhibited markedly less interference with lipid metabolism in cell culture models of hepatocytes and adipocytes compared with other PIs. Several PIs were shown to augment lipid (cholesterol and triglyceride) synthesis in hepatocytes and to suppress lipid (triglyceride) formation in adipocytes, while ATV exhibited lesser effects and with higher concentration-dependency. An underlying mechanism for the PI disturbance of lipid metabolism, involving inhibition of proteasome function leading to dysregulation of lipogenic enzyme pathways in liver and adipose, has been proposed. ATV exhibited lesser effects on expression of lipogenic genes in hepatocyte and adipocyte models compared to other PIs studied. Direct assays of human 20S proteasome *in vitro* showed that ATV is a weak inhibitor of proteasome activity with IC_{50} values several times higher than typical plasma C_{max}, while several other PIs inhibited proteasome activity with IC_{50}s below reported plasma C_{max} values.

The pathogenesis of PI-associated insulin resistance is incompletely understood. However, *in vitro* data suggest that several PIs inhibit the activity of the insulin-sensitive glucose transporter GLUT-4 and a related transporter GLUT-1 in a selective, rapid manner. These glucose transporters are critical for glucose uptake in fat and muscle tissues. Data from *in vitro* studies demonstrated that ATV has little or no effect on GLUT-4 or GLUT-1 glucose transporters in cell culture models of adipocytes and myocytes. Because of the role of glucose metabolism in lipid biosynthesis and its regulation, the lack of inhibition of GLUT-4 or GLUT-1 activity by ATV is expected to contribute to its neutral lipid profile in the clinic. These findings for ATV are consistent with the clinical profile and suggest a lower potential for lipodystrophy associated with its use relative to other PIs.

7.4 Lipid Metabolism and Lipodystrophy

Objective assessments of changes in fat distribution are ongoing in Study AI424043 and substudies of AI424034; these datasets have not yet been reviewed by FDA. Dual Energy X-ray Absorptiometery (DEXA) and/or cross section computerized tomography (CT) are to be performed at baseline and at the completion of 48 weeks of study therapy.

Preliminary results from the metabolic substudy of AI424034 provide a comparative assessment of body fat redistribution for ATV and EFV-containing regimens using measurements from DEXA and cross sectional CT scans at baseline and Week 48. All subjects received fixed dose ZDV + 3TC as nucleoside therapy. One hundred and eleven ATV and 100 EFV-treated subjects participated in the substudy; 77 and 63 subjects receiving ATV and EFV, respectively, had evaluable DEXA scans at baseline and at Week 48 while 57 and 44 subjects receiving ATV and EFV, respectively, had evaluable CT scans at baseline and Week 48.

These results indicated that there were small increases in total body fat, and small but proportional increases in appendicular fat and truncal fat in subjects on both regimens. The pattern of fat increase observed with EFV and ATV in Study AI424034 is consistent with weight gain and not with the profile described for central adiposity (disproportional increase in truncal fat) or lipoatrophy (loss of appendicular fat). Recent prospective data assessing truncal fat using DEXA scans identified median increases of less than 5% for EFV and median increases up to 15% for NFV-treated subjects at 48 weeks. Historical data on subjects who received the PI IDV reported increases in truncal fat that were far greater than those recently reported in the ACTG study 5005.

The results of cross-sectional CT scans of visceral adipose tissue (VAT), total adipose tissue (TAT), and subcutaneous adipose tissue (SAT) were consistent with the results on the DEXA data. Importantly, over 48 weeks, there was no increase in the VAT-to-TAT ratio on either the ATV or EFV regimen. An increase in the VAT-to-TAT ratio is a hallmark of lipodystrophy (central adiposity) associated with PI therapy. In summary, the available data indicate little evidence of lipodystrophy on ATV and EFV-containing regimens through 48 weeks in Study AI424034.

Preliminary results of AI424034 metabolic substudy:

- Demographic and baseline information including HIV RNA level, CD4 count and age were consistent between substudy participants (n = 211) and the overall study population (n = 805).
- DEXA scans performed at baseline and Week 48 for treated subjects enrolled in the metabolic substudy identified the following:
  - Mean increases from baseline at Week 48 were small and comparable between regimens in appendicular fat (3% ATV, 3% EFV), truncal fat (5% ATV, 8% EFV), and total body fat (5% ATV, 5% EFV).
  - No changes from baseline in the ratios of appendicular-to-total fat and truncal-to-total fat were observed on either regimen.
- Cross sectional CT scans performed at baseline and Week 48 identified the following:
  - Mean increases from baseline at Week 48 were comparable between regimens in VAT (40% ATV, 29% EFV), SAT (19% ATV, 5% EFV), and TAT (23% ATV, 11% EFV). Modest increases in VAT and TAT were observed on both regimens.
  - No change from baseline in the ratio of VAT-to-TAT (which remained at 0.3) was observed on either regimen.

In addition to the objective measurements of fat redistribution provided in Study AI424034, the general safety database for ATV provides estimates of the incidence of lipodystrophy events. It is recognized that passive collection of lipodystrophy events on case report forms without standardized criteria or a case definition does not provide a rigorous assessment of ATV's effect on body fat. Lipodystrophy-related AEs are included in this section for the purposes of completeness. Through approximately two years of treatment with ATV in combination with d4T and/or ddI, the frequency of lipodystrophy was 16 - 18% for subjects receiving 400 mg of ATV, which was comparable to the rates observed in long-term Studies AI424007/41 and AI424008/44 with other doses of ATV and with NFV (Tables 7.4A and 7.4B).

Table 7.4A: Lipodystrophy-Related Clinical Adverse Events - Subjects Treated in Studies AI424007/AI424041 Combined (95 Weeks Mean Follow-up)

	Number of Subjects (%)							
	ATV 200 ddI+d4T N = 102		ATV 400 ddI+d4T N = 101		ATV 500 ddI+d4T N = 107		NFV 750 ddI+d4T N = 100	
Any Event	**13**	**(13)**	**18**	**(18)**	**17**	**(16)**	**11**	**(11)**
Lipodystrophy	10	(10)	13	(13)	12	(11)	8	(8)
Buffalo Hump	0		0		0		1	(1)
Gynecomastia	3	(3)	5	(5)	5	(5)	2	(2)

Source: Appendix 12.1.1 from the AI424041 Interim Study Report.

Table 7.4B: Lipodystrophy-Related Clinical Adverse Events - Subjects Treated in Studies AI424008/AI424044 Combined (94 Weeks Mean Follow-up)

	Number of Subjects (%)			
	ATV 400 d4T+3TC N = 178		ATV 600 d4T+3TC N = 195	
Any Event	**28**	**(16)**	**36**	**(18)**
Lipodystrophy	26	(16)	30	(15)
Buffalo Hump	1	(1)	1	(1)
Lipoatrophy	1	(1)	1	(1)
Gynecomastia	2	(1)	7	(4)

Source: Appendix 12.5.9.B from the AI424044 Interim Study Report.

7.5 Summary of Lipid Metabolism

In summary, clinical studies have demonstrated lower lipid and triglyceride concentrations for subjects treated with ATV-containing regimens as compared with a variety of ARV agents. These lipid effects are substantial, durable for periods exceeding two years and have been consistently observed across a range of patient populations

(ARV treatment-naive through heavily treatment-experienced, including subjects who switched from NFV to ATV) and in combinations with a variety of companion NRTIs and PIs. An immediate and quantifiable metabolic benefit of ATV-containing regimens is a reduced need for less lipid lowering interventions. ATV-containing regimens consistently resulted in fewer patients meeting or exceeding NCEP guidelines for lipid lowering therapy than those treated with comparator ARV agents. This was reflected in a notably greater usage of lipid lowering agents on comparator regimens in contrast to ATV-containing regimens (Table 7.5).

Table 7.5: Selected Baseline and On-Treatment LDL-Cholesterol NCEP Categories for Atazanavir and Comparators

	% of Subjects with LDL-C ≥ 130 mg/dL		% of Subjects with LDL-C ≥ 160 mg/dL	
	Baseline	On-Treatment	Baseline	On-Treatment
ARV Treatment-Naive				
ATV 400 (AI424034 48 Week)	13%	13%	2%	3%
NFV (AI424008 48 Week)	17%	37%	5%	15%
EFV (AI424034 48 Week)	14%	28%	4%	8%
ARV Treatment-Experienced				
Prior Therapy⇒ATV 400 (AI424043 24 Week)	23%	7%	6%	0%
Prior Therapy⇒LPV/RTV (AI424043 24 Week)	20%	28%	6%	7%
Prior Therapy⇒ATV/RTV (AI424045 16 Week)	28%	17%	11%	9%
NFV⇒ATV[a] (AI424044 24 Week)	55%	30%	27%	10%

Source: Clinical Study Reports for AI424034, AI424008, AI424043, AI424045

[a] NFV⇒ATV comprises subjects who received NFV on Study AI424008 and switched to ATV upon entry into Study AI424044.

8 SAFETY

The sections below present safety information from Phase II/III studies in ARV treatment-naive adults (AI424007/041, AI424008/044, AI424034), ARV treatment-experienced adults (AI424043, AI424045), and pediatric subjects (AI424020). Data from these patient populations are presented separately in Sections 8.1, 8.2, and 8.3, respectively. Safety in other ongoing research programs are presented in Section 8.4. Topics of special interest are discussed in Section 8.5.

The proposed doses of ATV are 400 mg QD for ARV treatment-naive patients and ATV 300 mg in combination with RTV 100 mg for ARV treatment-experienced patients given in combination with other ARV agents. As safety data are presented separately for ARV treatment-naive and treatment-experienced subjects, the number of subjects treated and the duration of treatment exposure are reported separately for these patient populations in Sections 8.1.2 and 8.2.2, respectively.

ATV-containing regimens were generally safe, well-tolerated, and comparable to several standard of care regimens with respect to key safety parameters. Among ATV-treated subjects, the most common AEs of any grade, irrespective of relatedness to study therapy, were infection and nausea, which were comparable in frequency to comparator regimens. The most common Grade 2 - 4 (ie, moderate to very severe) treatment-related AEs reported in at least 2% of ATV-treated subjects were nausea, jaundice, lipodystrophy, rash, headache, vomiting, abdominal pain, and peripheral neurologic symptoms. Jaundice and scleral icterus were the only treatment-related Grade 2 - 4 AEs that were reported at a higher incidence on ATV than on comparator regimens. Discontinuation of study therapy due to AEs was infrequent.

8.1 Safety in ARV Treatment-Naive Subjects

8.1.1 Study Population

A total of 1087 ARV treatment-naive subjects received at least one dose of ATV in combination with other ARV therapies, and 592 subjects received a comparator treatment in combination with other ARV therapies (Table 8.1.1). Of the subjects treated with ATV, 683 subjects received ATV 400 mg.

Table 8.1.1: Number of ARV Treatment-Naive Treated Subjects in Safety Analyses in Phase II/III Clinical Studies of ATV

	ATV-Containing Regimens							
Dose	**200 mg**	**400 mg**	**500 mg**	**600 mg**	**Any ATV Dose**	**NFV**	**EFV**	**All Regimens**
N	102	683	107	195	1087	191	401	1679

Source: Updated Summary of Clinical Safety (Table 5.3.1A)

8.1.2 Exposure

ARV treatment-naive subjects treated with at least one dose of ATV had a mean time on therapy of 87 weeks (1814 patient years exposure) (Table 8.1.2). A total of 683 subjects were treated with ATV 400 mg. Of these, 85% received ATV for at least 48 weeks and 57% received ATV for at least 72 weeks. The mean time on therapy for treatment-naive subjects treated with ATV 400 mg was of 78 weeks (1019 patient years exposure).

Table 8.1.2: Treatment Exposure in ARV Treatment-Naive Treated Subjects

	Any ATV Dose	**ATV 400 mg**	**EFV**	**NFV**
Number of Subjects Treated	1087	683	401	191
Mean Time on Therapy (weeks)	87	78	57	83
Range (weeks)	(< 1, 177)	(< 1, 176)	(< 1, 79)	(1, 185)
Exposure (patient years)	1814	1019	441	305

Source: Updated Summary of Clinical Safety (Table 5.3.1B, Appendix 5.3.1B, Appendix 5.3.1C)

8.1.3 Clinical Adverse Events

8.1.3.1 Adverse Events of Any Grade Regardless of Relationship to Study Therapy

In ARV treatment-naive subjects, at least 94% of subjects on the ATV and comparator treatment regimens reported one or more clinical AE of any grade, regardless of relationship to study therapy. The most common clinical AEs, infection, headache, and nausea, occurred with comparable frequencies for both ATV and comparator regimens.

There were few differences in the incidence of clinical AEs between the ATV and comparator regimens with the exception of a higher incidence of jaundice and scleral icterus in ATV-treated subjects, dizziness and rash in EFV-treated subjects, and diarrhea in NFV-treated subjects.

8.1.3.2 Treatment-Related Grade 2 - 4 Adverse Events

Treatment-related (possible, probable, certain, and unknown) Grade 2 - 4 (ie, moderate, severe, and very severe) clinical AEs are shown in Table 8.1.3.2. As observed for clinical AEs of all grades, there were few differences in the incidence of clinical AEs between the ATV and comparator regimens with the exception of a higher incidence of jaundice in ATV-treated subjects, dizziness, rash, and vomiting in EFV-treated subjects, and diarrhea in NFV-treated subjects.

Table 8.1.3.2: Treatment-Related Adverse Events of Grade 2 - 4 (Moderate to Severe) Intensity Reported in Greater than or Equal to 2% of Adult Treatment-Naive Treated Subjects

Clinical Complaints Developing On-Study
Occurring Up To 30 Days After Last Dose of Drug

	NUMBER OF SUBJECTS (%)			
COSTART BODY SYSTEM COSTART PREFERRED TERM	34 ATV 400 (N= 404)	34 EFV 600 (N= 401)	7-41,8-44 ATV 400 (N= 279)	7-41,8 NFV (N= 191)
ANY ADVERSE EXPERIENCE	170(42)	184(46)	100(36)	57(30)
Body as a whole	47(12)	45(11)	11(4)	14(7)
ASTHENIA	7(2)	5(1)	3(1)	4(2)
HEADACHE	24(6)	26(6)	3(1)	3(2)
Digestive system	108(27)	88(22)	57(20)	39(20)
ANOREXIA	3(< 1)	12(3)	3(1)	1(< 1)
DIARRHEA	6(1)	10(2)	8(3)	31(16)
DYSPEPSIA	9(2)	9(2)	1(< 1)	1(< 1)
ICTERUS EYE	7(2)	0	6(2)	0
JAUNDICE	22(5)	0	15(5)	0
NAUSEA	56(14)	49(12)	16(6)	7(4)
PAIN ABDOMEN	16(4)	16(4)	10(4)	4(2)
VOMITING	17(4)	27(7)	9(3)	5(3)

NOTE: PRIMARY TERMS ARE DISPLAYED ONLY IF THE TOTAL INCIDENCE IN COLUMNS 1 OR 2 OR 3 OR 4 WAS AT LEAST 2%

Subjects may have had more than one adverse event.

Library: /wwbdm/clin/proj/av/424/iss01/sasds/sasds_nov2002_safety
Program Source: /wwbdm/clin/proj/av/424/iss01/val/cpp/sfty_aetab.sas

Extract Date: 02DEC02
Run Date: 07JAN03

Table 8.1.3.2: Treatment-Related Adverse Events of Grade 2 - 4 (Moderate to Severe) Intensity Reported in Greater than or Equal to 2% of Adult Treatment-Naive Treated Subjects

Clinical Complaints Developing On-Study
Occurring Up To 30 Days After Last Dose of Drug

	NUMBER OF SUBJECTS (%)			
COSTART BODY SYSTEM COSTART PREFERRED TERM	34 ATV 400 (N= 404)	34 EFV 600 (N= 401)	7-41,8-44 ATV 400 (N= 279)	7-41,8 NFV (N= 191)
Metabolic/nutritional system	9(2)	9(2)	22(8)	9(5)
LIPODYSTROPHY	5(1)	5(1)	19(7)	5(3)
Musculoskeletal system	1(< 1)	6(1)	9(3)	4(2)
Nervous system	36(9)	73(18)	15(5)	6(3)
DEPRESSION	2(< 1)	9(2)	2(< 1)	0
DIZZINESS	9(2)	28(7)	2(< 1)	0
INSOMNIA	12(3)	14(3)	1(< 1)	0
PERIPHERAL NEUROLOGIC SYMPTOM	2(< 1)	5(1)	10(4)	5(3)
Skin/appendages	34(8)	50(12)	18(6)	2(1)
RASH	27(7)	41(10)	14(5)	2(1)
Special senses	3(< 1)	7(2)	1(< 1)	0
Urogenital system	10(2)	8(2)	5(2)	2(1)

NOTE: PRIMARY TERMS ARE DISPLAYED ONLY IF THE TOTAL INCIDENCE IN COLUMNS 1 OR 2 OR 3 OR 4 WAS AT LEAST 2%

Subjects may have had more than one adverse event.

Library: /wwbdm/clin/proj/av/424/iss01/sasds/sasds_nov2002_safety
Program Source: /wwbdm/clin/proj/av/424/iss01/val/cpp/sfty_aetab.sas

Extract Date: 02DEC02
Run Date: 07JAN03

8.1.4 Deaths

A total of 17 deaths were reported in ARV treatment-naive subjects: 13 deaths (1.2%, 7.2 deaths per 1000 patient years) in subjects treated with ATV; three deaths (0.8%, 6.8 deaths per 1000 patient years) in subjects treated with EFV; and one death (0.5%, 3.3 deaths per 1000 patient years) in subjects treated with NFV (Table 8.1.4). The majority of deaths were due to events that were considered by the investigators to be unrelated or not likely related to ATV or its comparators. Deaths were due to a variety of causes that were not unexpected in an HIV population and, with the exception of lactic acidosis (discussed below), no pattern of events was apparent.

Five of the deaths were associated with lactic acidosis syndrome (four on ATV [0.4%], one on NFV [0.5%]); this included a subject who had fatty liver deposit which was judged by the BMS medical monitor to be lactic acidosis. All deaths due to lactic acidosis were in female subjects, one of whom was pregnant at the time of symptom onset. In all but one case (AI424007-45-237), the lactic acidosis was judged to be related to ARV therapy (ie, NRTI), but unrelated or not likely related to ATV or NFV.

Table 8.1.4: Deaths in ARV Treatment-Naive Enrolled Subjects

Subject ID	Study Regimen	Gender/ Age	Study Days to Death	Cause of Death
AI424007-1-338	ATV 200	M/48	60	Liver failure: Kaposi's sarcoma
AI424007-45-223	ATV 200	M/26	550	Gunshot wound
AI424007-46-283	ATV 200	M/31	802	Unknown[a]
AI424007-10-525	ATV 500	M/40	430	Multifocal Kaposi's sarcoma of the lungs, liver and lymph nodes
AI424007-41-497	ATV 500	F/48	379	Sepsis: lactic acidosis, liver failure
AI424007-45-237	ATV 500	F/22	336	Upper gastrointestinal bleed: fatty liver deposit, lactic acidosis
AI424007-41-90	NFV 750	F/28	445	Acute pancreatitis, renal failure, liver: lactic acidosis
AI424008-39-254	ATV 400	M/50	77	Suicide
AI424008-40-154	ATV 600	F/21	347	Myocarditis, hepatic steatosis, lactic acidosis
AI424008-51-355	ATV 600	F/41	276	Lactic acidosis
AI424044-73-311	ATV 600	M/38	Unknown[b]	Unknown[b]
AI424034-39-396	ATV 400	F/27	120	Tuberculosis meningoencephalitis
AI424034-51-831	ATV 400	M/25	415	Pneumonia; brain edema
AI424034-84-87	ATV 400	M/39	292	CNS Lymphoma
AI424034-66-863	EFV 600	F/27	110	Pulmonary tuberculosis
AI424034-82-675	EFV 600	M/63	209	Non-small cell lung CA; post-obstructive pneumonia
AI424034-91-162	EFV 600	M/27	265	Homicide (gun shot wound)

Source: Updated Summary of Clinical Safety (Table 5.3.4)

[a] Death reported after data-cut for the Updated Summary of Clinical Safety; subject died at local hospital and discharge records are pending.

[b] Subject had AEs of infection (chest), abdominal pain, and vomiting at time of death.

8.1.5 Serious Adverse Events

Among ARV treatment-naive subjects, no differences in the overall incidence of serious adverse events (SAEs) between ATV 400 mg treatment regimens and comparator

regimens were observed (AI424034: 12% and 11%, respectively; AI424007/41 and AI424008/44 combined: 16% and 16%, respectively). Table 8.1.5 presents SAEs occurring in at least two subjects in any treatment group. The majority of SAEs were judged to be not likely or unrelated to ATV or the comparator by the investigators of the studies.

Table 8.1.5: Serious Adverse Events Reported in Two or More Subjects in Any Treatment Group - ARV Treatment-Naive Treated Subjects

	NUMBER OF SUBJECTS (%)			
COSTART BODY SYSTEM COSTART PREFERRED TERM	34 ATV 400 (N= 404)	34 EFV 600 (N= 401)	7-41,8-44 ATV 400 (N= 279)	7-41,8 NFV (N= 191)
ANY ADVERSE EXPERIENCE	49(12)	43(11)	46(16)	31(16)
Body as a whole	18(4)	15(4)	15(5)	5(3)
ACCIDENTAL INJURY	2(< 1)	2(< 1)	1(< 1)	1(< 1)
CYST	2(< 1)	0	0	0
FEVER	3(< 1)	3(< 1)	4(1)	1(< 1)
HEADACHE	2(< 1)	2(< 1)	0	0
INFECTION	5(1)	2(< 1)	2(< 1)	3(2)
NEOPLASM	2(< 1)	3(< 1)	0	0
OVERDOSE	0	1(< 1)	2(< 1)	0
Cardiovascular system	1(< 1)	4(< 1)	1(< 1)	2(1)
SYNCOPE	0	2(< 1)	1(< 1)	0
Digestive system	10(2)	10(2)	20(7)	10(5)
APPENDICITIS	3(< 1)	2(< 1)	3(1)	1(< 1)
DISORDER RECTAL	0	2(< 1)	1(< 1)	1(< 1)
HEPATITIS	0	0	2(< 1)	1(< 1)
JAUNDICE	2(< 1)	0	0	0
NAUSEA	2(< 1)	0	1(< 1)	0
PAIN ABDOMEN	3(< 1)	3(< 1)	4(1)	2(1)
PANCREATITIS	0	0	4(1)	2(1)
VOMITING	1(< 1)	1(< 1)	3(1)	1(< 1)
Hemic/lymphatic system	12(3)	5(1)	1(< 1)	1(< 1)
ANEMIA	9(2)	4(< 1)	1(< 1)	1(< 1)

Source: Updated Summary of Clinical Safety (Table 5.3.5)
Subjects may have had more than one adverse event.

Table 8.1.5: Serious Adverse Events Reported in Two or More Subjects in Any Treatment Group - ARV Treatment-Naive Treated Subjects

	NUMBER OF SUBJECTS (%)			
COSTART BODY SYSTEM COSTART PREFERRED TERM	34 ATV 400 (N= 404)	34 EFV 600 (N= 401)	7-41,8-44 ATV 400 (N= 279)	7-41,8 NFV (N= 191)
Metabolic/nutritional system	5(1)	4(< 1)	7(3)	5(3)
ACIDOSIS LACTIC	0	1(< 1)	4(1)	1(< 1)
DEHYDRATION	0	1(< 1)	1(< 1)	2(1)
WEIGHT DECREASED	2(< 1)	1(< 1)	0	0
Musculoskeletal system	0	1(< 1)	1(< 1)	2(1)
Nervous system	9(2)	7(2)	8(3)	4(2)
CONVULSION	2(< 1)	0	0	0
DEPRESSION	0	2(< 1)	2(< 1)	2(1)
DISORDER PERSONALITY	0	2(< 1)	0	0
DRUG DEPENDENCE	0	0	3(1)	0
SUICIDE ATTEMPT	0	1(< 1)	3(1)	0
Respiratory system	3(< 1)	1(< 1)	3(1)	4(2)
DISORDER PLEURAL	0	0	2(< 1)	0
PNEUMONIA	2(< 1)	1(< 1)	1(< 1)	2(1)
Skin/appendages	0	5(1)	4(1)	1(< 1)
CELLULITIS	0	2(< 1)	2(< 1)	0
RASH	0	2(< 1)	1(< 1)	0
Urogenital system	7(2)	7(2)	7(3)	5(3)
ABORTION	2(< 1)	0	0	1(< 1)
DISORDER CERVIX	1(< 1)	2(< 1)	1(< 1)	0
DISORDER URINARY TRACT	0	0	2(< 1)	0
PYELONEPHRITIS	0	2(< 1)	0	0
WART GENITAL	3(< 1)	1(< 1)	1(< 1)	2(1)

Source: Updated Summary of Clinical Safety (Table 5.3.5)
Subjects may have had more than one adverse event.

8.1.6 Adverse Events Leading to Discontinuation of Treatment

The incidence of ARV treatment-naive subjects who discontinued treatment due to one or more AEs was comparable across studies and treatment regimens (AI424034: 7% and 9%, respectively; AI424007/41 and AI424008/44 combined: 8% and 8%, respectively). Table 8.1.6 presents AEs leading to discontinuation of treatment in at least two subjects in any treatment group. Among subjects treated with ATV 400 mg, discontinuations due to lactic acidosis syndrome (3 subjects) and lipodystrophy (2 subjects) occurred only in the Phase II studies (AI424007/41 and AI424008/44), which included d4T and/or ddI in the backbone regimen.

Table 8.1.6: Adverse Events Leading to Discontinuation of Study Therapy in Two or More Subjects in Any Treatment Group - ARV Treatment-Naive Treated Subjects

	NUMBER OF SUBJECTS (%)			
COSTART BODY SYSTEM COSTART PREFERRED TERM	34 ATV 400 (N= 404)	34 EFV 600 (N= 401)	7-41,8-44 ATV 400 (N= 279)	7-41,8 NFV (N= 191)
ANY ADVERSE EXPERIENCE	29(7)	38(9)	21(8)	16(8)
Body as a whole	4(< 1)	7(2)	4(1)	2(1)
ALLERGIC REACTION	0	2(< 1)	0	1(< 1)
FATIGUE	3(< 1)	1(< 1)	1(< 1)	0
FEVER	0	4(< 1)	1(< 1)	0
HEADACHE	0	3(< 1)	0	0
Cardiovascular system	0	5(1)	0	0
Digestive system	12(3)	10(2)	7(3)	6(3)
DIARRHEA	0	1(< 1)	0	4(2)
HEPATITIS	1(< 1)	0	5(2)	2(1)
ICTERUS EYE	2(< 1)	0	0	0
JAUNDICE	2(< 1)	0	1(< 1)	0
NAUSEA	6(1)	6(1)	2(< 1)	1(< 1)
PAIN ABDOMEN	3(< 1)	2(< 1)	2(< 1)	1(< 1)
VOMITING	6(1)	4(< 1)	1(< 1)	0
Hemic/lymphatic system	9(2)	6(1)	1(< 1)	2(1)
ANEMIA	8(2)	4(< 1)	1(< 1)	1(< 1)

Source: Updated Summary of Clinical Safety
Subjects may have had more than one adverse event.

Table 8.1.6: Adverse Events Leading to Discontinuation of Study Therapy in Two or More Subjects in Any Treatment Group - ARV Treatment-Naive Treated Subjects

	NUMBER OF SUBJECTS (%)			
COSTART BODY SYSTEM COSTART PREFERRED TERM	34 ATV 400 (N= 404)	34 EFV 600 (N= 401)	7-41,8-44 ATV 400 (N= 279)	7-41,8 NFV (N= 191)
Metabolic/nutritional system	4(< 1)	3(< 1)	7(3)	7(4)
ACIDOSIS LACTIC	0	1(< 1)	2(< 1)	0
ALT INCREASED	0	1(< 1)	1(< 1)	2(1)
AST INCREASED	0	0	0	2(1)
GGT INCREASED	0	0	0	3(2)
HYPERBILIRUBINEMIA	2(< 1)	0	0	0
LIPODYSTROPHY	0	0	3(1)	2(1)
Nervous system	5(1)	8(2)	3(1)	2(1)
ABNORMAL DREAM	2(< 1)	0	0	0
DIZZINESS	1(< 1)	2(< 1)	0	0
INSOMNIA	1(< 1)	2(< 1)	1(< 1)	0
PERIPHERAL NEUROLOGIC SYMPTOM	0	0	1(< 1)	2(1)
Skin/appendages	3(< 1)	10(2)	1(< 1)	0
RASH	3(< 1)	9(2)	1(< 1)	0

Source: Updated Summary of Clinical Safety
Subjects may have had more than one adverse event.

8.1.7 Laboratory Evaluations

Laboratory data were collected before treatment and at scheduled and unscheduled visits while on study. The resulting data were assessed, and abnormal values were classified according to modified WHO criteria as Grades 1 - 4. These grades reference multiples of the upper limit of normal (ULN). Since this varied for each test, where appropriate the multiple above normal is specified.

8.1.7.1 Hematology

In studies in ARV treatment-naive subjects, the majority of on-study hematologic abnormalities were Grade 1 - 2, and were generally comparable between regimens (Table 8.1.7.1). Leukopenia and neutropenia were the most common hematologic abnormalities across all studies. There were few platelet abnormalities observed.

Table 8.1.7.1: Hematologic Abnormalities - ARV Treatment-Naive Treated Subjects

	NUMBER OF SUBJECTS / NUMBER AT RISK (%)			
	ATV 400 mg and Comparator Cohort			
LABORATORY TEST	34 ATV 400 N = 404	34 EFV 600 N = 401	7-41,8-44 ATV 400 N = 279	7-41,8 NFV N = 191
HEMOGLOBIN				
GRADE 1 - 4	98/ 402 (24)	75/ 394 (19)	40/ 276 (14)	30/ 191 (16)
GRADE 3 - 4	19/ 402 (5)	11/ 394 (3)	1/ 276 (<1)	7/ 191 (4)
WBC				
GRADE 1 - 4	255/ 402 (63)	240/ 394 (61)	92/ 276 (33)	77/ 191 (40)
GRADE 3 - 4	0/ 402 (0)	1/ 394 (<1)	1/ 276 (<1)	0/ 191 (0)
NEUTROPHILS				
GRADE 1 - 4	161/ 402 (40)	144/ 394 (37)	69/ 276 (25)	61/ 191 (32)
GRADE 3 - 4	27/ 402 (7)	36/ 394 (9)	9/ 276 (3)	14/ 191 (7)
PLATELETS				
GRADE 1 - 4	12/ 401 (3)	10/ 394 (3)	7/ 276 (3)	10/ 191 (5)
GRADE 3 - 4	2/ 401 (<1)	3/ 394 (<1)	1/ 276 (<1)	2/ 191 (1)

Source: Updated Summary of Clinical Safety (Table 5.3.7.1 and Appendix 5.3.7.1A)

8.1.7.2 Hepatic Transaminases and Bilirubin

Elevation in total bilirubin (indirect, unconjugated) was the most frequent abnormality observed on ATV-containing regimens. A detailed discussion of hyperbilirubinemia is presented in Section 8.5.

Among ARV treatment-naive subjects, the majority of liver function test abnormalities were Grade 1 - 2 (Table 8.1.7.2). Grade 3 - 4 elevations in liver transaminases (ie, > 5 x ULN) were infrequent on all treatment regimens.

Table 8.1.7.2: Liver Function Abnormalities - ARV Treatment-Naive Treated Subjects

	NUMBER OF SUBJECTS / NUMBER AT RISK (%)			
	ATV 400 mg and Comparator Cohort			
LABORATORY TEST	34 ATV 400 N = 404	34 EFV 600 N = 401	7-41,8-44 ATV 400 N = 279	7-41,8 NFV N = 191
ALT/SGPT				
GRADE 1 - 4	102/ 402 (25)	126/ 395 (32)	157/ 277 (57)	75/ 191 (39)
GRADE 3 - 4	16/ 402 (4)	10/ 395 (3)	26/ 277 (9)	14/ 191 (7)
AST/SGOT				
GRADE 1 - 4	78/ 402 (19)	87/ 395 (22)	146/ 277 (53)	77/ 191 (40)
GRADE 3 - 4	8/ 402 (2)	8/ 395 (2)	20/ 277 (7)	10/ 191 (5)
TOTAL BILIRUBIN				
GRADE 1 - 4	346/ 402 (86)	13/ 395 (3)	252/ 277 (91)	23/ 191 (12)
GRADE 3 - 4	140/ 402 (35)	2/ 395 (<1)	131/ 277 (47)	5/ 191 (3)
ALKALINE PHOSPHATASE				
GRADE 1 - 4	34/ 402 (8)	50/ 395 (13)	36/ 277 (13)	15/ 191 (8)
GRADE 3 - 4	0/ 402 (0)	0/ 395 (0)	0/ 277 (0)	1/ 191 (<1)

Source: Updated Summary of Clinical Safety (Table 5.3.7.2 and Appendix 5.3.7.2A)
Note: Grade 1 - 4: > 1.25 x ULN; Grade 3 - 4: > 5 x ULN

8.1.7.3 Serum Chemistry

In studies in ARV treatment-naive subjects, the majority of on-study serum chemistry abnormalities were Grade 1 - 2, and were generally comparable between regimens (Table 8.1.7.3).

Table 8.1.7.3: Serum Chemistry Abnormalities - ARV Treatment-Naive Treated Subjects

	NUMBER OF SUBJECTS / NUMBER AT RISK (%)			
	ATV 400 mg and Comparator Cohort			
LABORATORY TEST	34 ATV 400 N = 404	34 EFV 600 N = 401	7-41,8-44 ATV 400 N = 279	7-41,8 NFV N = 191
CK				
GRADE 1 - 4	78/ 401 (19)	75/ 395 (19)	104/ 277 (38)	47/ 191 (25)
GRADE 3 - 4	25/ 401 (6)	23/ 395 (6)	30/ 277 (11)	18/ 191 (9)
BUN				
GRADE 1 - 4	1/ 401 (<1)	3/ 395 (<1)	6/ 161 (4)	2/ 97 (2)
GRADE 3 - 4	0/ 401 (0)	0/ 395 (0)	1/ 161 (<1)	0/ 97 (0)
CREATININE				
GRADE 1 - 4	9/ 401 (2)	11/ 395 (3)	18/ 277 (6)	8/ 191 (4)
GRADE 3 - 4	0/ 401 (0)	0/ 395 (0)	2/ 277 (<1)	1/ 191 (<1)
AMYLASE				
GRADE 1 - 4	1/ 3 (33)	0/ 0	53/ 138 (38)	57/ 124 (46)
GRADE 3 - 4	0/ 3 (0)	0/ 0	19/ 138 (14)	12/ 124 (10)
LIPASE				
GRADE 1 - 4	21/ 401 (5)	22/ 395 (6)	53/ 277 (19)	32/ 191 (17)
GRADE 3 - 4	4/ 401 (<1)	5/ 395 (1)	12/ 277 (4)	10/ 191 (5)
SERUM URIC ACID				
GRADE 1 - 4	12/ 401 (3)	6/ 395 (2)	33/ 277 (12)	22/ 191 (12)
GRADE 3 - 4	0/ 401 (0)	0/ 395 (0)	8/ 277 (3)	5/ 191 (3)
HYPERCARBIA				
GRADE 1 - 4	5/ 394 (1)	4/ 379 (1)	8/ 225 (4)	7/ 138 (5)
GRADE 3 - 4	0/ 394 (0)	0/ 379 (0)	1/ 225 (<1)	0/ 138 (0)
HYPOCARBIA				
GRADE 1 - 4	73/ 394 (19)	75/ 379 (20)	65/ 225 (29)	34/ 138 (25)
GRADE 3 - 4	0/ 394 (0)	1/ 379 (<1)	1/ 225 (<1)	2/ 138 (1)

Source: Updated Summary of Clinical Safety (Table 5.3.7.3 and Appendix 5.3.7.3A)

In the Phase II studies, an imbalance in the incidence of lactic acidosis syndrome/symptomatic hyperlactatemia (LAS/SHL) was observed between ATV (2.2%) and the comparator NFV (1.0%) regimens; however, in largest Phase III Study AI424034, the overall incidence of LAS/SHL was low and comparable between the ATV (0.2%) and EFV (0.2%) treatment regimens. Among all ARV treatment-naive subjects, the rate of LAS/SHL in subjects treated with ATV was low (1.5% [range 0 - 2.6%]) and

consistent with rates cited in the literature (1.2 - 2%) and the recently reported DAD study (1.4%).

8.2 Safety in ARV Treatment-Experienced Subjects

8.2.1 Study Population

A total of 510 ARV treatment-experienced subjects received at least one dose of ATV in combination with other ARV therapies, and 301 subjects received a comparator treatment in combination with other ARV therapies (Table 8.2.1). Of the subjects treated with ATV, 222 subjects received ATV 400 mg, 142 subjects received ATV 400 mg/SQV, and 119 subjects received ATV 300 mg pharmacologically enhanced with RTV 100 mg (Table 8.2.1).

Table 8.2.1: Number of ARV Treatment-Experienced Treated Subjects in Safety Analyses in Phase II/III Clinical Studies of ATV

	ATV-Containing Regimens								
Dose	**400 mg**	**400 mg/ SQV**	**300 mg/ RTV**	**600 mg/ SQV**	**Any ATV Dose**	**LPV/ RTV**	**NFV**	**RTV/ SQV**	**All Regimens**
N	222[a]	142	119	27	510	264	14	23	811

Source: Updated Summary of Clinical Safety (Table 5.4.1A)

[a] Includes 63 subjects treated first with NFV in AI424008 and then with ATV 400 mg in AI424044.

8.2.2 Exposure

ARV treatment-experienced subjects treated with at least one dose of ATV had a mean time on therapy of 17 weeks (164 patient years exposure) (Table 8.2.2). The mean time on therapy for treatment-experienced subjects treated with ATV 400 mg or ATV 300 mg/RTV 100 mg was 32 weeks (135 patient years exposure) and 21 weeks (48 patient years exposure), respectively.

Table 8.2.2: Treatment Exposure in ARV Treatment-Experienced Treated Subjects

	Any ATV Dose	ATV 400 mg	ATV 400/ SQV	ATV 300/ RTV	LPV/RTV
Number of Subjects Treated	510	222	142	119	264
Mean Time on Therapy (weeks)	17	32	30	21	24
Range (weeks)	(< 1, 128)	(2, 61)	(< 1, 128)	(1, 48)	(2, 48)
Exposure (patient years)	164	135	82	48	124

Source: Updated Summary of Clinical Safety (Table 5.4.1B)

8.2.3 Clinical Adverse Events

8.2.3.1 Adverse Events of Any Grade Regardless of Relationship to Study Therapy

In ARV treatment-experienced subjects treated in Study AI424043, 69% of subjects treated with ATV and 79% of subjects treated with LPV/RTV reported one or more clinical AE of any grade, regardless of relationship to study therapy. The most common clinical AEs, infection, headache, and nausea, occurred with comparable frequency for both ATV and the comparator regimen, LPV/RTV.

In Study AI424045, 64% of subjects treated with ATV 300/RTV, 73% of subjects treated with ATV 400/SQV, and 75% of subjects treated with LPV/RTV reported one or more clinical AE of any grade. The most common clinical AEs, infection, headache, and nausea, occurred with comparable frequency in all three regimens. There were few differences in the incidence of clinical AEs between the three regimens with the exception of a higher incidence of jaundice and scleral icterus on ATV 300/RTV regimen and diarrhea in LPV/RTV-treated subjects.

8.2.3.2 Treatment-Related Grade 2 - 4 Adverse Events

Treatment-related Grade 2 - 4 clinical AEs reported in Study AI424043 are shown in Table 8.2.3.2A. There were few differences in the incidence of clinical AEs between the ATV and LPV/RTV regimens with the exception of higher incidences of jaundice in

ATV-treated subjects and allergic reaction, diarrhea, and gastritis in LPV/RTV-treated subjects.

Table 8.2.3.2A: Treatment-Related Adverse Events of Grade 2 - 4 (Moderate to Severe) Intensity Reported in Greater than or Equal to 2% of Adult Treatment-Experienced Treated Subjects in Study AI424043

Clinical Complaints Developing On-Study
Occurring Up To 30 Days After Last Dose of Drug

	NUMBER OF SUBJECTS (%)	
COSTART BODY SYSTEM COSTART PREFERRED TERM	43 ATV 400 (N= 144)	43 LPV/RTV (N= 146)
ANY ADVERSE EXPERIENCE	25(17)	33(23)
Body as a whole	9(6)	11(8)
ALLERGIC REACTION	0	3(2)
ASTHENIA	2(1)	1(< 1)
FATIGUE	1(< 1)	2(1)
FEVER	0	0
HEADACHE	6(4)	5(3)
Digestive system	13(9)	18(12)
ANOREXIA	1(< 1)	1(< 1)
DIARRHEA	2(1)	5(3)
DISORDER GASTROINTESTINAL	0	1(< 1)
DYSPEPSIA	1(< 1)	2(1)
GASTRITIS	0	4(3)
JAUNDICE	5(3)	0
NAUSEA	1(< 1)	4(3)
PAIN ABDOMEN	1(< 1)	3(2)
VOMITING	1(< 1)	1(< 1)
Metabolic/nutritional system	6(4)	2(1)
LIPODYSTROPHY	4(3)	2(1)
Musculoskeletal system	1(< 1)	1(< 1)
Nervous system	3(2)	9(6)
INSOMNIA	0	1(< 1)
NERVOUSNESS	1(< 1)	0
REFLEXES INCREASED	1(< 1)	3(2)
SOMNOLENCE	0	1(< 1)
Skin/appendages	3(2)	3(2)
RASH	3(2)	1(< 1)
Urogenital system	1(< 1)	0

Source: Updated Summary of Clinical Safety, Table 5.4.3.3A
Note: Primary terms are displayed only if the total incidence in either treatment regimen was at least 2%.
Subjects may have had more than one adverse event.

Treatment-related Grade 2 - 4 clinical AEs reported in Study AI424045 are shown in Table 8.2.3.2B. Except as noted, the incidence and patterns of treatment-related Grade 2 - 4 clinical AEs were comparable between the ATV 300/RTV and LPV/RTV treatment regimens and higher on the ATV 400/SQV treatment regimen. Among ATV-treated subjects, a higher incidence of scleral icterus, jaundice, and myalgia were observed in the ATV 300/RTV regimen, and a higher incidence of nausea, vomiting, and rash were observed in the ATV 400/SQV regimen. A higher incidence of diarrhea was observed among LPV/RTV-treated subjects.

Table 8.2.3.2B: Treatment-Related Adverse Events of Grade 2 - 4 (Moderate to Severe) Intensity Reported in Greater than or Equal to 2% of Adult Treatment-Experienced Treated Subjects in Study AI424045

Clinical Complaints Developing On-Study
Occurring Up To 30 Days After Last Dose of Drug

	NUMBER OF SUBJECTS (%)		
COSTART BODY SYSTEM COSTART PREFERRED TERM	45 ATV 300/RTV (N= 119)	45 ATV 400/SQV (N= 110)	45 LPV/RTV (N= 118)
ANY ADVERSE EXPERIENCE	24(20)	28(25)	22(19)
Body as a whole	4(3)	7(6)	2(2)
FATIGUE	1(< 1)	3(3)	1(< 1)
Digestive system	17(14)	14(13)	17(14)
DIARRHEA	3(3)	4(4)	12(10)
ICTERUS EYE	4(3)	0	0
JAUNDICE	7(6)	2(2)	0
NAUSEA	2(2)	8(7)	2(2)
VOMITING	0	4(4)	1(< 1)
Metabolic/nutritional system	3(3)	4(4)	3(3)
LIPODYSTROPHY	3(3)	4(4)	2(2)
Musculoskeletal system	3(3)	1(< 1)	0
MYALGIA	3(3)	0	0
Nervous system	5(4)	4(4)	5(4)
Skin/appendages	1(< 1)	4(4)	2(2)
RASH	0	3(3)	1(< 1)

Source: AI424045 ISR02, Appendix 12.1D
Note: Primary terms are displayed only if the total incidence in any treatment regimen was at least 2%. Subjects may have had more than one adverse event.

8.2.4 Deaths

A total of three deaths were reported in ARV treatment-experienced subjects: two deaths (2/510, 0.4%) in subjects treated with ATV, and one death (1/264, 0.4%) in subjects treated with LPV/RTV (Table 8.2.4). None of the deaths were due to events that were considered by the Investigators to be related to ATV or LPV/RTV.

Table 8.2.4: Deaths in ARV Treatment-Experienced Enrolled Subjects

Subject ID	Study Regimen	Gender/ Age	Study Days to Death	Cause of Death
AI424044-35-107[a]	NFV⇒ATV	M/69	298	Congestive heart failure
AI424043-95-124	ATV 400	F/34	16	Homicide (Traumatic cardiac arrest)
AI424045-45-203	LPV/RTV	M/36	56	Aneurysm, subdural hematoma, and renal failure

Source: Updated Summary of Clinical Safety

[a] Death occurred in subject who had switched from NFV to ATV; the subject is considered ARV treatment-experienced due to the prior NFV.

8.2.5 Serious Adverse Events

Among ARV treatment-experienced subjects, SAEs were infrequent and evenly distributed among the ATV and the LPV/RTV comparator treatment regimens of AI424043 and AI424045. Serious adverse events occurring in at least two subjects in any treatment group are presented in Tables 8.2.5A and 8.2.5B for Studies AI424043 and AI424045, respectively. The majority of SAEs were judged by the Investigators to be unrelated to ATV or LPV/RTV.

Table 8.2.5A: Serious Adverse Events Reported in Two or More Subjects in Any Treatment Group - ARV Treatment-Experienced Treated Subjects in Study AI424043

COSTART BODY SYSTEM COSTART PREFERRED TERM	NUMBER OF SUBJECTS (%) 43 ATV 400 (N= 144)	 43 LPV/RTV (N= 146)
ANY ADVERSE EXPERIENCE	9(6)	7(5)
Body as a whole	4(3)	1(< 1)
HERNIA	2(1)	0
Digestive system	3(2)	2(1)
Hemic/lymphatic system	0	2(1)
Metabolic/nutritional system	2(1)	0
Nervous system	0	2(1)

Source: Updated Summary of Clinical Safety
Subjects may have had more than one adverse event.

Table 8.2.5B: Serious Adverse Events Reported in Two or More Subjects in Any Treatment Group - Treated Subjects in Study AI424045

COSTART BODY SYSTEM COSTART PREFERRED TERM	NUMBER OF SUBJECTS (%) 45 ATV 300/RTV (N= 119)	 45 ATV 400/SQV (N= 110)	 45 LPV/RTV (N= 118)
ANY ADVERSE EXPERIENCE	6(5)	8(7)	4(3)
Body as a whole	3(3)	2(2)	3(3)
FEVER	0	2(2)	1(< 1)
OVERDOSE	1(< 1)	0	2(2)
Digestive system	2(2)	3(3)	0
Metabolic/nutritional system	1(< 1)	2(2)	0

Source: Updated Summary of Clinical Safety
Subjects may have had more than one adverse event.

8.2.6 Adverse Events Leading to Discontinuation of Treatment

The number of ARV treatment-experienced subjects who discontinued treatment due to one or more AEs was infrequent and evenly distributed among the ATV and the

LPV/RTV comparator treatment regimens of Studies AI424043 and AI424045. Adverse events leading to discontinuation of treatment in at least two subjects in any treatment group are presented in Tables 8.2.6A and 8.2.6B for Studies AI424043 and AI424045, respectively.

Table 8.2.6A: Adverse Events Leading to Discontinuation of Study Therapy in Two or More Subjects in Any Treatment Group - ARV Treatment-Experienced Treated Subjects in Study AI424043

	NUMBER OF SUBJECTS (%)	
COSTART BODY SYSTEM COSTART PREFERRED TERM	43 ATV 400 (N= 144)	43 LPV/RTV (N= 146)
ANY ADVERSE EXPERIENCE	2(1)	4(3)
Digestive system	1(< 1)	3(2)
Metabolic/nutritional system	2(1)	0

Source: Updated Summary of Clinical Safety
Subjects may have had more than one adverse event.

Table 8.2.6B: Adverse Events Leading to Discontinuation of Study Therapy in Two or More Subjects in Any Treatment Group in Study AI424045

	NUMBER OF SUBJECTS (%)		
COSTART BODY SYSTEM COSTART PREFERRED TERM	45 ATV 300/RTV (N= 119)	45 ATV 400/SQV (N= 110)	45 LPV/RTV (N= 118)
ANY ADVERSE EXPERIENCE	3(3)	5(5)	3(3)
Digestive system	1(< 1)	2(2)	1(< 1)
NAUSEA	0	2(2)	0
VOMITING	0	2(2)	0
Metabolic/nutritional system	0	1(< 1)	2(2)
Nervous system	2(2)	0	2(2)

Source: Updated Summary of Clinical Safety
Subjects may have had more than one adverse event.

8.2.7 Laboratory Evaluations

8.2.7.1 Hematology

In Studies AI424043, the majority of on-study hematologic abnormalities were Grade 1 - 2, and were generally comparable between regimens (Table 8.2.7.1A). In Study AI424045, Grade 1 - 4 neutropenia and leukopenia were more frequent on the ATV 400/SQV treatment regimen; however, the Grade 3 - 4 incidence of these abnormalities was comparable across the treatment regimens (Table 8.2.7.1B). Leukopenia and neutropenia were the most common hematologic abnormalities in both studies.

Table 8.2.7.1A: Hematologic Abnormalities - ARV Treatment-Experienced Treated Subjects in Study AI424043

	NUMBER OF SUBJECTS / NUMBER AT RISK (%)	
LABORATORY TEST	43 ATV 400 N = 144	43 LPV/RTV N = 146
HEMOGLOBIN		
GRADE 1 - 4	10/ 143 (7)	9/ 145 (6)
GRADE 3 - 4	2/ 143 (1)	1/ 145 (<1)
WBC		
GRADE 1 - 4	53/ 143 (37)	50/ 145 (34)
GRADE 3 - 4	0/ 143 (0)	0/ 145 (0)
NEUTROPHILS		
GRADE 1 - 4	36/ 143 (25)	28/ 145 (19)
GRADE 3 - 4	7/ 143 (5)	5/ 145 (3)
PLATELETS		
GRADE 1 - 4	5/ 143 (3)	8/ 145 (6)
GRADE 3 - 4	0/ 143 (0)	0/ 145 (0)

Source: Updated Summary of Clinical Safety (Table 5.4.7.1A and Appendix 5.4.7.1A)

Table 8.2.7.1B: Hematologic Abnormalities - ARV Treatment-Experienced Treated Subjects in Study AI424045

	NUMBER OF SUBJECTS / NUMBER AT RISK (%)		
	TREATMENT REGIMEN		
LABORATORY TEST	ATV 300/RTV N = 119	ATV 400/SQV N = 110	LPV/RTV N = 118
HEMOGLOBIN			
GRADE 1 - 4	3/ 119 (3)	9/ 108 (8)	6/ 118 (5)
GRADE 3 - 4	0/ 119 (0)	0/ 108 (0)	0/ 118 (0)
WBC			
GRADE 1 - 4	34/ 119 (29)	42/ 108 (39)	34/ 118 (29)
GRADE 3 - 4	0/ 119 (0)	0/ 108 (0)	0/ 118 (0)
NEUTROPHILS			
GRADE 1 - 4	18/ 119 (15)	23/ 108 (21)	14/ 118 (12)
GRADE 3 - 4	5/ 119 (4)	5/ 108 (5)	5/ 118 (4)
PLATELETS			
GRADE 1 - 4	6/ 119 (5)	7/ 108 (6)	10/ 118 (8)
GRADE 3 - 4	1/ 119 (<1)	4/ 108 (4)	1/ 118 (<1)

Source: AI424045 ISR02 (Tables 12.6.2A and 12.6.2B)

8.2.7.2 Hepatic Transaminases and Bilirubin

Elevation in total bilirubin (indirect, unconjugated) was the most frequent abnormality observed on ATV-containing regimens. A detailed discussion of hyperbilirubinemia is presented in Section 8.5.

In Study AI424043, no differences were observed for Grade 1 - 4 ALT and AST elevations between the treatment regimens (Table 8.2.7.2A). Grade 3 - 4 elevations in ALT and AST were observed in 6% and 3% of ATV-treated subjects, respectively vs 1% each for LPV/RTV-treated subjects (Table 8.2.7.2A). There was a slightly higher incidence of hepatitis B and/or C co-infection at baseline among subjects treated with ATV (20%) compared with LPV/RTV (12%); this did not account for the observed differences.

Table 8.2.7.2A: Liver Function Abnormalities - ARV Treatment-Experienced Treated Subjects in Study AI424043

LABORATORY TEST	43 ATV 400 N = 144	43 LPV/RTV N = 146
	NUMBER OF SUBJECTS / NUMBER AT RISK (%)	
ALT/SGPT		
GRADE 1 - 4	51/ 143 (36)	47/ 145 (32)
GRADE 3 - 4	8/ 143 (6)	2/ 145 (1)
AST/SGOT		
GRADE 1 - 4	52/ 143 (36)	46/ 145 (32)
GRADE 3 - 4	4/ 143 (3)	2/ 145 (1)
TOTAL BILIRUBIN		
GRADE 1 - 4	108/ 143 (76)	16/ 145 (11)
GRADE 3 - 4	31/ 143 (22)	0/ 145 (0)
ALKALINE PHOSPHATASE		
GRADE 1 - 4	4/ 143 (3)	7/ 145 (5)
GRADE 3 - 4	0/ 143 (0)	1/ 145 (<1)

Source: Updated Summary of Clinical Safety (Table 5.4.7.2A and Appendix 5.4.7.2A)
Note: Grade 1 - 4: > 1.25 x ULN; Grade 3 - 4: > 5 x ULN

In Study AI424045, a slightly higher incidence of Grade 1 - 4 ALT elevation was observed on the ATV-containing regimens compared with the LPV/RTV regimen (ATV 300/RTV, 44%; ATV 400/SQV 49%; LPV/RTV 31%) (Table 8.2.7.2B); Grade 3 - 4 elevations in liver transaminases were infrequent (< 1% - 3%) on all regimens.

Table 8.2.7.2B: Liver Function Abnormalities - ARV Treatment-Experienced Treated Subjects in Study AI424045

	NUMBER OF SUBJECTS / NUMBER AT RISK (%)		
	TREATMENT REGIMEN		
LABORATORY TEST	ATV 300/RTV N = 119	ATV 400/SQV N = 110	LPV/RTV N = 118
ALT/SGPT			
GRADE 1 - 4	52/ 119 (44)	53/ 108 (49)	36/ 118 (31)
GRADE 3 - 4	3/ 119 (3)	3/ 108 (3)	3/ 118 (3)
AST/SGOT			
GRADE 1 - 4	39/ 119 (33)	37/ 108 (34)	37/ 118 (31)
GRADE 3 - 4	2/ 119 (2)	2/ 108 (2)	1/ 118 (<1)
TOTAL BILIRUBIN			
GRADE 1 - 4	105/ 119 (88)	73/ 108 (68)	10/ 118 (8)
GRADE 3 - 4	53/ 119 (45)	18/ 108 (17)	1/ 118 (<1)
ALKALINE PHOSPHATASE			
GRADE 1 - 4	7/ 119 (6)	4/ 108 (4)	7/ 118 (6)
GRADE 3 - 4	0/ 119 (0)	0/ 108 (0)	0/ 118 (0)

Source: AI424045 ISR02 (Tables 12.6.3A and 12.6.3B)

8.2.7.3 Serum Chemistry

In Studies AI424043 and AI424045, the majority of on-study serum chemistry abnormalities were Grade 1 - 2, and were generally comparable between regimens (Tables 8.2.7.3A and 8.2.7.3B). In Study AI424045, the incidence of Grade 1 - 4 CK elevations was higher on the ATV 300/RTV treatment regimen (29%) compared with ATV 400/SQV (15%) and LPV/RTV (18%).

Table 8.2.7.3A: Serum Chemistry Abnormalities - ARV Treatment-Experienced Treated Subjects in Study AI424043

LABORATORY TEST	43 ATV 400 N = 144	43 LPV/RTV N = 146
	NUMBER OF SUBJECTS / NUMBER AT RISK (%)	
CK		
GRADE 1 - 4	21/ 143 (15)	23/ 145 (16)
GRADE 3 - 4	11/ 143 (8)	7/ 145 (5)
BUN		
GRADE 1 - 4	0/ 142 (0)	1/ 145 (<1)
GRADE 3 - 4	0/ 142 (0)	0/ 145 (0)
CREATININE		
GRADE 1 - 4	2/ 143 (1)	2/ 145 (1)
GRADE 3 - 4	0/ 143 (0)	0/ 145 (0)
AMYLASE		
GRADE 1 - 4	0/ 3 (0)	0/ 1 (0)
GRADE 3 - 4	0/ 3 (0)	0/ 1 (0)
LIPASE		
GRADE 1 - 4	26/ 143 (18)	26/ 145 (18)
GRADE 3 - 4	6/ 143 (4)	4/ 145 (3)
SERUM URIC ACID		
GRADE 1 - 4	11/ 143 (8)	13/ 145 (9)
GRADE 3 - 4	1/ 143 (<1)	1/ 145 (<1)
HYPERCARBIA		
GRADE 1 - 4	6/ 144 (4)	3/ 145 (2)
GRADE 3 - 4	0/ 144 (0)	0/ 145 (0)
HYPOCARBIA		
GRADE 1 - 4	33/ 144 (23)	45/ 145 (31)
GRADE 3 - 4	2/ 144 (1)	1/ 145 (<1)

Source: Updated Summary of Clinical Safety (Table 5.4.7.3A and Appendix 5.4.7.3A)

Table 8.2.7.3B: Serum Chemistry Abnormalities - ARV Treatment-Experienced Treated Subjects in Study AI424045

	NUMBER OF SUBJECTS / NUMBER AT RISK (%)		
	TREATMENT REGIMEN		
LABORATORY TEST	ATV 300/RTV N = 119	ATV 400/SQV N = 110	LPV/RTV N = 118
CK			
GRADE 1 - 4	34/ 119 (29)	16/ 108 (15)	21/ 118 (18)
GRADE 3 - 4	10/ 119 (8)	3/ 108 (3)	6/ 118 (5)
BUN			
GRADE 1 - 4	0/ 119 (0)	1/ 108 (<1)	0/ 118 (0)
GRADE 3 - 4	0/ 119 (0)	0/ 108 (0)	0/ 118 (0)
CREATININE			
GRADE 1 - 4	3/ 119 (3)	3/ 108 (3)	0/ 118 (0)
GRADE 3 - 4	0/ 119 (0)	0/ 108 (0)	0/ 118 (0)
LIPASE			
GRADE 1 - 4	29/ 119 (24)	22/ 108 (20)	22/ 118 (19)
GRADE 3 - 4	6/ 119 (5)	2/ 108 (2)	7/ 118 (6)
SERUM URIC ACID			
GRADE 1 - 4	8/ 119 (7)	10/ 108 (9)	4/ 118 (3)
GRADE 3 - 4	0/ 119 (0)	0/ 108 (0)	1/ 118 (<1)
HYPERCARBIA			
GRADE 1 - 4	4/ 119 (3)	5/ 108 (5)	2/ 118 (2)
GRADE 3 - 4	0/ 119 (0)	1/ 108 (<1)	1/ 118 (<1)
HYPOCARBIA			
GRADE 1 - 4	37/ 119 (31)	34/ 108 (31)	35/ 118 (30)
GRADE 3 - 4	2/ 119 (2)	0/ 108 (0)	0/ 118 (0)

Source: AI424045 ISR02 (Tables 12.6.4A and 12.6.4B)

The rate of LAS/SHL in ARV treatment-experienced subjects treated with ATV was low (0.7% [range 0 - 1.4%]) and consistent with rates cited in the literature (1.2 - 2%) and the recently reported DAD study (1.4%).

8.3 Safety in Pediatric Subjects

In Study AI424020, no novel safety findings have been identified in the HIV-infected pediatric population relative to those seen in HIV-infected adult population (Table 8.3). Atazanavir is not recommended in pediatric patients below 3 months of age because of the enhanced propensity for increased bilirubin elevations due to immature hepatic

metabolism. Since this study is still in the dose ranging phase, the data are insufficient to recommend a dose in children 3 months to 16 years of age.

Table 8.3: Summary of Safety from Pediatric Study AI424020

Study No.	N[a]	Study Population	Deaths N (%)	AE/SAEs[b] N (%)	Disc. due to AEs N (%)	Grade 3 - 4 Laboratory Abnormalities: Bilirubin N (%)	ALT N (%)	AST N (%)
AI424020	48	Pediatric subjects between 3 months and 21 years of age	**Total:** 2 (4%) Events: CHF: 1 (2%) ARDS: 1 (2%)	**Total:** 22 (46%) Events: Bradycardia: 7 (15%) Jaundice: 1 (2%) Lipodystrophy: 1 (2%) Prolonged PR: 11 (23%) Prolonged QT_cB: 2 (4%) Prolonged QT: 2 (4%) Prolonged QRS: 1 (2%) Scleral icterus: 3 (6%) Vomiting: 2 (4%)	**Total:** 8 (17%) Events: Bilirubin ↑: 2 (4%) Emesis: 2 (4%) Heart Block: 2 (4%) Pancreatitis: 1 (2%) Cardiomyopathy: 1 (2%)	16 (33%)	0	1 (2%)

Source: Study report for AI424020 (DCN 930003301)

[a] Number of ATV-treated subjects as of November 21, 2002 data cut-off.

[b] Seriousness not differentiated for this program. Events of any severity grade are included.

8.4 Safety in Collaborative and EAP Studies

The safety and tolerability of ATV has been assessed in the four ongoing collaborative research studies in a variety of research settings ranging from acute infection to salvage therapy. Additionally, preliminary safety data are available from the early access program (EAP) Study AI424900, an open-label, multi-center, non-comparative program to make ATV available to high-need HIV-infected subjects who are unable to construct an alternative effective treatment regimen. In addition to Study AI424900, this program is concurrently open in France under the French Authorization for Temporary Utilization (ATU) Nominative program. At the time of the Updated Summary of Clinical Safety, approximately 400 subjects had received ATV. Safety data from these trials are consistent with the findings of the Bristol-Myers Squibb registrational trials.

8.5 Topics of Special Interest

8.5.1 Hyperbilirubinemia and Hepatic Function

Elevation in bilirubin is the most frequent laboratory abnormality observed in Phase II and III clinical studies. The majority of elevations in total bilirubin were isolated (ie, not associated with liver function test elevations) and reversible upon discontinuation or interruption of ATV. Greater than 500 HIV infected patients have received ATV for at least two years (range up to 3.5 years) and no long-term consequences of elevated total bilirubin have been identified. The elevations are primarily composed of indirect (unconjugated) bilirubin.

Importantly, a thorough assessment of the mechanism by which ATV results in hyperbilirubinemia has been completed and has confirmed that ATV competitively inhibits uridine diphosphate-glucuronosyl; transferase 1A1 (UGT 1A1), the enzyme responsible for bilirubin glucuronidation/conjugation. UGT 1A1 inhibition is also the mechanism identified for IDV-associated hyperbilirubinemia and reduced UGT activity is the metabolic basis for the benign inherited condition known as Gilbert’s syndrome.

8.5.1.1 Mechanism for Bilirubin Elevation

A number of *in vitro* and other studies have elucidated the mechanism of hyperbilirubinemia associated with ATV dosing and contribute to the understanding of its benign nature. Competitive inhibition of the UGT 1A1 enzyme, the mechanism by which ATV results in hyperbilirubinemia, was demonstrated through a series of studies described below. These studies confirm ATV's effect on UGT 1A1 and importantly demonstrated lack of effect on other steps in bilirubin production and metabolism.

Increased production of bilirubin in spleen and peripheral tissues: Evidence for hemolysis was not apparent as the clinical markers, LDH, reticulocytes, and hemoglobin, were each stable. In a follow-up Gunn rat study conducted to further investigate any effect of ATV on hemolysis, rats administered up to 600 mg/kg of ATV by gavage had little increase in bilirubin.

Displacement of bilirubin from albumin during transport to the liver: Equilibrium dialysis determined that ATV did not affect the binding of bilirubin to albumin at physiological concentrations over the anticipated therapeutic concentration range.

Decreased uptake of bilirubin by liver cells from plasma: Rat hepatocyte studies showed that ATV has no effect on bilirubin uptake versus control at concentrations (30 - 100 μM) several-fold higher than the C_{max} (10 μM) in humans.

Displacement of bilirubin from the cytosolic binding protein (ligand) in liver cells: In circular dichroism studies evaluating the ability of ATV to displace bilirubin from any of several glutathione-S-transferase isoforms (GSTs), ATV had no effect on the binding of bilirubin to any of several GSTs at concentrations of 100 μM several-fold higher than the highest maximal concentrations (C_{max}) in humans (up to 10 μM).

Inhibition of Adenosine Triphosphate (ATP)-dependent conjugated bilirubin into bile canaliculi: The quantification of bilirubin fractions by HPLC definitively showed that there was no increase in direct bilirubin above the upper limit of normal and no consequent hepatotoxic process. The lack of acute direct hepatotoxicity, as reflected by no increases in direct bilirubin, was also supported by no detectable bilirubin in the urine of healthy subjects after multiple doses of ATV. These findings supported the hypothesis that no inhibition of bilirubin secretion was occurring at the level of canalicular transport.

Inhibition of bilirubin conjugation mediated by the UGT 1A1 isozyme: ATV, like IDV, inhibits the glucuronidation of bilirubin in a heterologously expressed human UGT 1A1 *in vitro* system, as well as in human liver microsomes. At clinically relevant concentrations, ATV, bound to purified UGT 1A1 isozymes, inhibited the conjugation of bilirubin.

In summary, ATV is associated with elevations in total bilirubin that are almost entirely due to increased unconjugated bilirubin levels. The mechanism, competitive inhibition of UGT 1A1 isoform, is one that has been observed with another drug in the PI class (IDV). The extensive clinical experience with IDV and with the inherited condition Gilbert's syndrome provide the important frame of reference by which to reasonably expect the ATV-associated bilirubin elevations to be benign. Furthermore, these elevations are not indicative of a hepatotoxic process.

8.5.1.2 Bilirubin Abnormalities in Clinical Trials of Atazanavir

Reviewers' Note: The following discussion of hyperbilirubinemia includes assessments of both safety and efficacy outcomes. Slight differences will be found in incidences of bilirubin, ALT, and AST from those found in Safety Tables 8.1.7.2, 8.2.7.2A, and 8.2.7.2B because the data used for this detailed review involve efficacy data which were not updated with the Updated Summary of Clinical Safety.

Among ARV treatment-naive subjects, Grade 1 - 4 total bilirubin elevations were observed in 86% and 91% of subjects in Study AI424034 and the Phase II studies, respectively; Grade 3 - 4 elevations were observed in 35% and 47%, respectively (Table 8.1.7.2). The incidence of elevated total bilirubin increased with higher ATV doses (Grade 1 - 4: 81% on ATV 200 mg increasing to 96% on ATV 600 mg; Grade 3 - 4: 31% on ATV 200 mg increasing to 66% on ATV 600 mg).

Among ARV treatment-experienced subjects in Study AI424043, the incidence of total bilirubin elevations was lower than that observed in the ARV treatment-naive population (Grade 1 - 4, 76%; Grade 3 - 4, 22%) (Table 8.2.7.2A).

In Study AI424045, the incidence of total bilirubin elevations among subjects receiving ATV 300/RTV (Grade 1 - 4, 88%; Grade 3 - 4, 45%) was consistent with those observed in ARV treatment-naive subjects treated with ATV 400 mg (Table 8.2.7.2B). The incidence of total bilirubin elevations among subjects receiving ATV 400/SQV was 68% and 17%, respectively.

8.5.1.3 Clinical Relevance

Elevation in unconjugated bilirubin is the most frequent ATV dose-related laboratory abnormality, and jaundice and/or scleral icterus are the most notable dose-related AEs attributable to ATV. Overall, 11% and 9% of subjects developed jaundice or scleral icterus, respectively. The clinical outcomes are considered cosmetic without safety-related consequences. Fewer than 2% of subjects discontinued for hyperbilirubinemia and/or jaundice and/or scleral icterus. This incidence is consistent with the observed 2% incidence of other AEs requiring treatment discontinuation for other HIV therapies, such as rash and CNS symptoms on EFV and diarrhea on NFV.

8.5.1.4 Dose Modifications and Treatment Discontinuation Due to Hyperbilirubinemia

The Phase III protocols outlined a dose reduction strategy, which included PK evaluation of plasma bilirubin and ATV levels for subjects with isolated hyperbilirubinemia (ie, elevated bilirubin without an increase in ALT/AST from baseline) or clinical jaundice. Subjects were monitored for the development of isolated hyperbilirubinemia or clinical jaundice. Criteria for dose reduction of ATV 400 mg were as follows:

- Subjects with confirmed elevations in total bilirubin > 5 x ULN were to be dose reduced as outlined in Table 8.5.1.4A.
- Subjects with clinical jaundice and a single elevated total bilirubin > 5 x ULN were to be managed in a similar fashion.

Dose modifications for the ATV 300/RTV regimen were similar to those for ATV 400 mg with the exception of the first four weeks of treatment when steady-state drug exposure and enzymatic activity for cytochrome P450 and UGT 1A1 were being reached and isolated hyperbilirubinemia and clinical jaundice did not automatically trigger ATV dose reduction.

Table 8.5.1.4A: ATV Dose Modifications for Hyperbilirubinemia and Clinical Jaundice

	ATV 400 mg	ATV 400 mg/SQV	ATV 300 mg/RTV
First requirement for dose reduction	ATV 200 mg	ATV 300 mg/SQV	ATV 200 mg/RTV
Subsequent requirement for dose reduction	Discontinuation from study	First occurrence: ATV 200 mg/SQV Second occurrence: Discontinuation from study	Discontinuation from study

Source: Protocols for Studies AI424034, AI424043, and AI424045

The proposed clinical use of ATV does not recommend dose modification for confirmed elevations in total bilirubin > 5 x ULN and clinical jaundice, because there are inadequate efficacy data among those subjects who reduce ATV dose and because few ATV dose reductions are expected to be required in the clinic. The infrequent need for discontinuation of ATV due to hyperbilirubinemia and/or its associated clinical signs, jaundice and/or scleral icterus, is depicted in Table 8.5.1.4B.

Table 8.5.1.4B: Discontinuation of Study Therapy Due to Hyperbilirubinemia, Jaundice and Scleral Icterus - Treated Subjects

	Number of Subjects (%)				
Event Leading to Discontinuation of Treatment[a]	**AI424034 ATV 400 mg n = 404**	**AI424007/41 AI424008/44 400 mg n = 279**	**AI424043 ATV 400 mg n = 144**	**AI424045 300 mg/RTV 100 mg n = 119**	**AI424045 400 mg/SQV 1200 mg n = 110**
Hyperbilirubinemia	1 (< 1)	0 (0)	1 (< 1)	0 (0)	0 (0)
Jaundice	1 (< 1)	1 (< 1)	1 (< 1)	0 (0)	0 (0)
Scleral icterus	2 (< 1)	0 (0)	1 (< 1)	0 (0)	0 (0)

Source: AI424034 (48 Week), AI424041 (ISR), AI424044 (ISR), AI424043 (24 Week ISR02) and AI424045 (16 Week ISR) Study Reports

[a] Subjects may have had more than one event; therefore, the overall number of subjects discontinuing due to these events is not necessarily cumulative.

Hyperbilirubinemia and/or its associated clinical signs, jaundice and/or scleral icterus, infrequently resulted in dose reductions of regimens containing ATV 400 mg or ATV 300/RTV (Table 8.5.1.4C).

Table 8.5.1.4C: Dose Reduction Due to Hyperbilirubinemia or Jaundice - Treated Subjects

Event Leading to Dose Reduction[a]	Number of Subjects (%)				
	AI424034 ATV 400 mg n = 404	AI424007/41 AI424008/44 400 mg n = 279	AI424043 ATV 400 mg n = 144	AI424045 300 mg/RTV 100 mg n = 119	AI424045 400 mg/SQV 1200 mg n = 110
Hyperbilirubinemia	20 (5)	15 (5)	2 (1)	3 (3)	0 (0)
Jaundice	1 (< 1)	0 (0)	3 (2)	0 (0)	0 (0)

Source: AI424034 (48 Week), AI424041 (ISR), AI424044 (ISR), AI424043 (24 Week ISR02), and AI424045 (16 Week ISR) Study Reports

[a] Subjects may have had more than one event; therefore, the overall number of subjects discontinuing due to these events is not necessarily cumulative.

The assessment of virologic response rates among ARV treatment-naive subjects showed that the TLOVR virologic response rates (LOQ = 400 c/mL) for subjects who dose reduced or interrupted their dose for > 3 days due to hyperbilirubinemia were slightly higher than the overall response (26/35, 74% and 23/31, 74%, respectively, vs 452/663, 68%) (Table 8.5.1.4D). The observed response rates (LOQ = 50 c/mL) for those with dose reductions were consistent with the overall rate (12/35, 34% vs 217/663, 33%) (Table 8.5.1.4E). Dose interruptions due to hyperbilirubinemia also resulted in a slightly reduced response rate (LOQ = 50 c/mL) compared with the overall rate (9/31, 29% vs 217/663, 33%).

These data suggest that infrequent dose interruptions or dose reductions do not impact the clinical efficacy of ATV. However, the limited number of subjects with dose reductions does not provide sufficient data to recommend dose reduction as a management approach; in clinical practice, patients who meet the dose reduction criteria should seek alternative therapy until additional data clarify clinical outcome after dose reduction.

Table 8.5.1.4D: TLOVR Response at Week 48 (LOQ Equals 400 c/mL) and Dose Modifications - ARV-Treatment Naive Treated Subjects

	Responder/Evaluable (%)		
	AI424034 Treatment Regimen: ZDV/3TC/(PI or NNRTI)	AI424008 Treatment Regimen: d4T/3TC/PI	AI424007 Stage II Treatment Regimen: ddI/d4T/PI
Analysis	ATV (QD) 400 mg N = 404	ATV (QD) 400 mg N = 181	ATV (QD) 400 mg N = 78
Overall	281/404 (70)	123/181 (68)	48/78 (62)
Dose reduction due to hyperbilirubinemia or jaundice	15/21 (71)	10/13 (77)	1/1 (100)
Interruptions due to hyperbilirubinemia (> 3 days)	12/17 (71)	9/11 (82)	2/3 (67)
Discontinuations due to hyperbilirubinemia[a]	0/1 (0)	--	--

TLOVR = Time to Loss of Virologic Response
Overall response rates for AI424007 and AI424008 are based on randomized subjects.
[a] Note: The TLOVR definition categorizes subjects who discontinue as 'treatment failures'.

Source: NDA Clinical Summary of Safety (Table 5.8.1.14C)

Table 8.5.1.4E: TLOVR Response at Week 48 (LOQ = 50 c/mL) and Dose Modifications - ARV Treatment-Naive Treated Subjects

	Responder/Evaluable (%)		
	AI424034 Treatment Regimen: ZDV/3TC/(PI or NNRTI)	AI424008 Treatment Regimen: d4T/3TC/PI	AI424007 Stage II Treatment Regimen: ddI/d4T/PI
Analysis	ATV (QD) 400 mg N = 404	ATV (QD) 400 mg N = 181	ATV (QD) 400 mg N = 78
Overall	131/404 (32)	60/181 (33)	26/78 (33)
Dose reduction due to hyperbilirubinemia or jaundice	6/21 (29)	5/13 (38)	1/1 (100)
Interruptions due to hyperbilirubinemia (> 3 days)	3/17 (18)	5/11 (45)	1/3 (33)
Discontinuations due to hyperbilirubinemia[a]	0/1 (0)	--	--

TLOVR = Time to Loss of Virologic Response
Overall response rates for AI424007 and AI424008 are based on randomized subjects.
[a] Note: The TLOVR definition categorizes subjects who discontinue as 'treatment failures'.

Source: NDA Clinical Summary of Safety (Table 5.8.1.14D)

8.5.1.5 Effect of Long-Term Treatment (Up to 108 Weeks) on Hyperbilirubinemia

Long-term treatment up to 108 weeks did not increase the incidence or the severity of hyperbilirubinemia among subjects continuing long-term therapy in the rollover studies, even at the higher dose of ATV 600 mg. No new clinical manifestations were observed.

8.5.1.6 Hyperbilirubinemia and Elevated ALT/AST

Elevations in direct bilirubin were observed infrequently in the clinical studies. Furthermore, the isolated direct bilirubin elevations (ie, no simultaneous hepatic transaminase elevations) observed in clinical trials are largely artifactual. A comparative study conducted by the Sponsor of the methodologies used to determine direct bilirubin identified that the techniques used by commercial labs overestimates direct bilirubin when total bilirubin is elevated. When more precise methodologies are used (HPLC) direct bilirubin was found to be normal. There was no evidence for a hemolytic process.

Grade 3 - 4 elevations in bilirubin were rarely associated with any Grade 3 - 4 elevations in ALT or AST on study; only ten subjects had both Grade 3 - 4 ALT or AST and Grade 3 - 4 total bilirubin elevations on-study (Table 8.5.1.6). Of these 10 subjects, five reported hepatitis B/C at baseline, and six subjects had concurrent Grade 3 - 4 transaminase and total bilirubin elevations. There was no evidence that these elevations in bilirubin were associated with a hepatotoxic process.

Table 8.5.1.6: Grade 3 - 4 ALT/AST and Total Bilirubin Elevations in Phase III Studies - Treated Subjects

	Observed/Evaluable (%)					
	No Grade 3 - 4 Total Bilirubin			Grade 3 - 4 Total Bilirubin		
	AI424034 ATV 400 mg N = 404	AI424043 ATV 400 mg N = 144	AI424045 ATV 300/RTV 100 mg N = 119	AI424034 ATV 400 mg N = 404	AI424043 ATV 400 mg N = 144	AI424045 ATV 300/RTV 100 mg N = 119
No Grade 3 - 4 ALT/AST	262/402 (65)	107/142 (75)	76/119 (64)	125/402 (31)	26/142 (18)	40/119 (34)
Grade 3 - 4 ALT/AST	9/402 (2)	7/142 (5)	1/119 (< 1)	6/402[a] (1)	2/142[b] (1)	2/119 (2)

Source: NDA Clinical Summary of Safety

[a] Grade 3 - 4 ALT/AST and Grade 3 - 4 total bilirubin measured > 50 days apart in three subjects.

[b] Grade 3 - 4 ALT/AST and Grade 3 - 4 total bilirubin measured 16 days apart in one subject.

8.5.1.7 Recommended Management of Hyperbilirubinemia

The mechanism, incidence, and clinical manifestations of hyperbilirubinemia due to ATV have been fully characterized. Importantly, elevations in indirect bilirubin have been disassociated from hepatocellular toxicity based on a understanding of the biologic mechanism (UGT) and based on a careful assessment of the hepatic transaminases from a large amount of data from Phase II and III clinical trials. In addition, no long-term sequelae of unconjugated hyperbilirubinemia (cholelithiasis, neurologic) were observed. Indeed, based upon the biology of unconjugated bilirubinemia, none are anticipated. Based upon this thorough assessment, clear recommendations for the management of hyperbilirubinemia are possible.

- Because there are limited data regarding the virologic outcome of subjects who have dose reduced, a reduction in dose is not recommended at this time. Therefore, in patients experiencing confirmed elevations in total bilirubin > 5 times the ULN, alternative antiretroviral therapy to ATV should be considered.
- Elevations in ALT or AST with concurrent elevations in total bilirubin should not be assumed to be due to ATV and therefore transaminase elevations warrant further clinical assessment and investigation.

8.5.1.8 Long-term Pharmacovigilance Assessment of Hyperbilirubinemia

The available data support the conclusion that hyperbilirubinemia associated with ATV is benign, not associated with hepatotoxicity, and readily manageable in individual patients. The Sponsor recognizes the importance and value of instituting a risk management plan by which to build on the safety experience obtained from clinical trials. The Sponsor anticipates instituting a risk management plan for hyperbilirubinemia that would include the following components:

- Post marketing surveillance of events that may be the consequence of long term (> 2 years) albeit small increases in unconjugated bilirubin;
- Physician and patient education programs including patient information leaflet;
- Appropriate labeling language for the prescribing physician.

8.5.2 Studies in Electrophysiology and Cardiac Conduction

Regulatory authorities have issued guidance regarding the evaluation of the cardiac effects of new drugs in both non-clinical and clinical settings. Following this guidance, the assessment of the ECG effects of ATV has included *in vitro* investigations, as well as investigations in healthy and HIV-infected subjects.

Non-Human Studies

Pharmacology safety evaluations were conducted to assess ATV's potential to prolong the QT interval. In rabbit Purkinje fibers, ATV minimally increased action potential duration (13% at 30 μM). This concentration is approximately four times the mean C_{max} and 17 times the mean Css in humans given ATV 400 mg/day. Possible effects on sodium and calcium currents were also evaluated *in vitro*, and weak inhibition of sodium currents (IC_{50} > 30 μM) and moderate inhibition of calcium currents (IC_{50} of 10.4 μM) were identified. In these *in vitro* studies, other PIs were also found to alter action potential duration and ion currents with potency equivalent to or greater than that of ATV.

Atazanavir was also evaluated in the *in vitro* I_{Kr} (HERG) and I_{Ks} potassium current assays along with several other PIs for comparison. Atazanavir produced weak inhibition of I_{Kr} current at concentrations up to 30 μM (15% at 30 μM); the IC_{50} was not established because only 15% inhibition was observed at the highest concentration (ie, IC_{50} exceeded 30 μM). NFV, SQV, and LPV inhibited I_{Kr} current amplitude with IC_{50}s of 7.9, 17.6, and 22.0 μM, respectively. IDV and RTV (IC_{50}s > 30 μM) inhibited I_{Kr} current at 30 μM by 23% and 46%, respectively. The rank order of potency for inhibition of I_{Kr} current was NFV > SQV > LPV > RTV > IDV~ATV. In the I_{Ks} assay, neither ATV, nor any of the PIs evaluated, produced significant inhibition of I_{Ks} current (IC_{50}s > 30 μM). For PIs as a class, the clinical significance of these weak inhibitory effects on several ion channels, including HERG, and modest prolongations of the action potential duration is not yet clear as prolongations of the QT_c interval by currently available PIs have been reported only for NFV and LPV/RTV.

In *in vivo* studies, no direct drug-related effects on cardiac function were noted in dogs treated with ATV for up to 9 months. Plasma concentrations of ATV at the high dose of 180 mg/kg/day in the 9-month toxicity study, which produced no ECG changes, were up to three times the C_{max} and seven times the AUC in humans given ATV 400 mg/day.

Human Studies

Investigations in humans, guided by a "Points to Consider" document issued in December 1997, have focused on the ECG parameter of greatest interest, the QT interval, and whether it is prolonged after study drug administration. That document suggests that QT intervals (msec) after Bazett's correction (QT_cB), should be assessed according to the following categories:

QT_cB (msec)	**Normal**	**Borderline**	**Prolonged**	**Significantly Prolonged**
Males	≤ 430	431 - 450	> 450	> 500
Females	≤ 450	451 - 470	> 470	> 500

This "Points to Consider" document further classifies the concern for the potential of a drug to induce arrhythmias including Torsades de Pointes (TdP) for different ranges of QT_cB changes from baseline (< 30 msec, 30 - 60 msec, > 60 msec) and in what follows ΔQT_cB < 30 msec is classified as normal, 30 - 60 msec is classified as borderline, and > 60 msec is classified as prolonged.

While common practice has been to utilize Bazett's correction for the QT interval, the optimal correction approach is a subject of controversy. Therefore QT_c data from the placebo controlled trial AI424076 and the Phase II/III trials have been corrected and analyses are presented using both Bazett's and Fridericia's corrections: hereafter represented as QT_cB and QT_cF respectively. It should be noted that Fridericia-based corrections were not submitted to FDA for review in the ATV NDA.

8.5.2.1 Studies Assessing Cardiac Conduction Effects of ATV in Healthy Subjects

Seven non-placebo-controlled clinical pharmacology studies to evaluate the effect of ATV exposure on ECG parameters were completed in healthy subjects. Doses of ATV at 200 mg through 800 mg once-daily were studied. ECG parameters were measured prior to and during study drug administration.

Equivocal effects of ATV on the QT_c interval were observed in these early non-placebo-controlled studies. In Study AI424039, the QT_c interval change from baseline decreased during dosing, while in Study AI424040, a weak signal for possible concentration-dependent increases in QT_c interval was observed. A dose- and concentration-dependent effect on PR interval was seen in these initial non-placebo-controlled studies. A PR interval > 200 msec is considered prolonged and is by definition first-degree atrio-ventricular block (1^{st} degree AV block). Further discussion of this effect will be presented in the context of Study AI424076 and the Phase II/III trials.

Definitive Placebo-Controlled Study AI424076

Study AI424076 was a definitive, placebo-controlled, double-blind, three-treatment, three-period, crossover study in 72 healthy subjects designed to determine the effect of

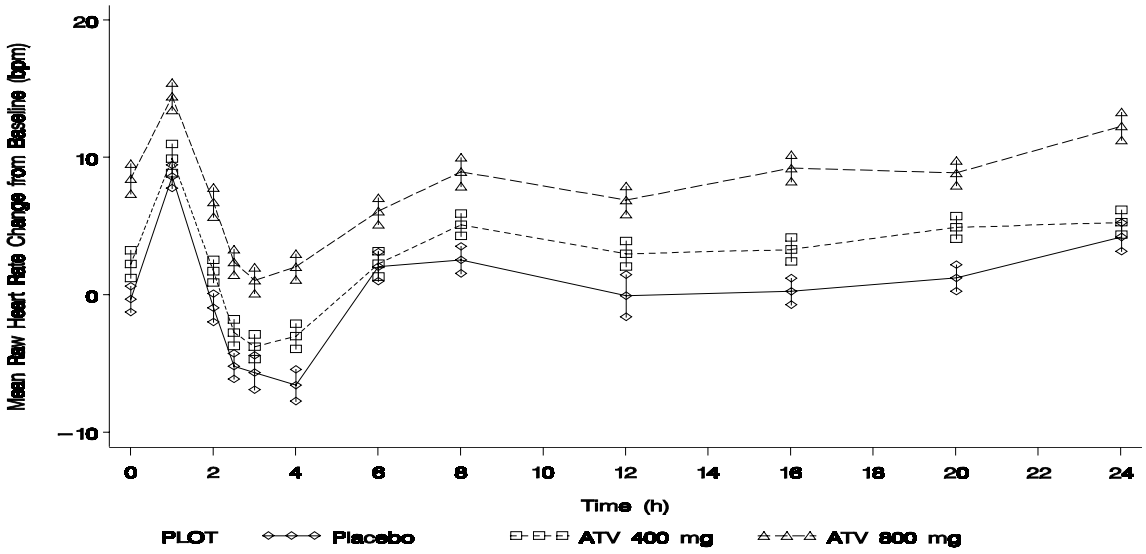
ATV (400 mg and 800 mg) on ECG parameters, specifically the QT_cB and PR intervals. While the proposed dose for ARV treatment-experienced patients (ATV 300/RTV) was not studied in AI424076, dosing with ATV 300/RTV results in concentrations intermediate between ATV 400 mg and ATV 800 mg.

Change from baseline maximum QT_cB to maximum QT_cB (Δ_1QT_cB Max) was selected for powering the study with respect to QT_cB since it relates to the longest QT_cB interval observed after study drug administration, and it compensates for intrinsic diurnal variability. Similarly, change from baseline maximum PR to maximum PR (Δ_1PR Max) was selected for powering the study with respect to PR. Additional analyses of QT_c using Fridericia's correction (QT_cF) are included below.

Heart Rate in Study AI424076

A plot of mean raw (time-matched) heart rate changes from baseline versus time since dosing on Day 6 is presented by treatment in Figure 8.5.2.1A. Atazanavir appears to be associated with a modest dose-dependent increase in heart rate compared to placebo. Since Bazett's formula tends to overcorrect the QT interval when heart rate increases, Fridericia's formula may be more appropriate than Bazett's for heart rate correction of QT for ATV. As stated in the February 6, 2003 FDA's Preliminary Concept Paper on 'The Clinical Evaluation of QT/QT_c Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs', "Bazett's formula is frequently used in clinical practice and in the medical literature. In general, however, Bazett's over-corrects at elevated heart rates and under-corrects at heart rates below 60 bpm and hence is not an ideal correction on which to base regulatory decisions. Fridericia's formula may be a more accurate correction formula than the Bazett's formula in subjects with altered heart rates."

Figure 8.5.2.1A: Plot of Mean Raw Heart Rate Changes from Baseline vs Time Since Dosing on Day 6



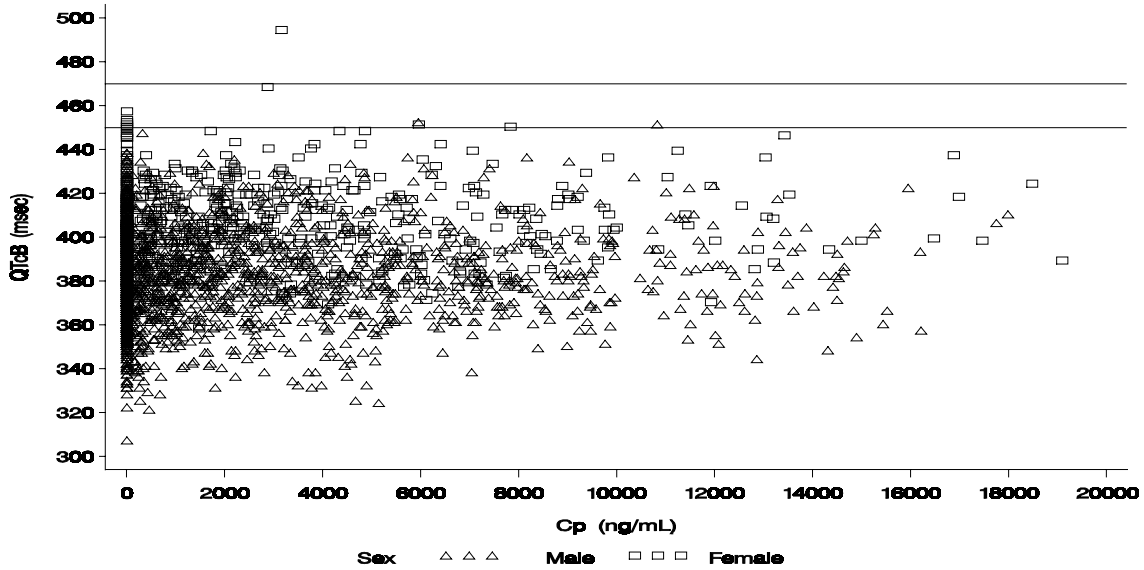
Source: Clinical Study Report for AI424076
Note: Vertical bars represent one SE of the mean.

QT_c Interval in Study AI424076

Results using Bazett's correction

A scatter plot of QT_cB intervals vs ATV plasma concentrations obtained at the same time as the ECG recordings is presented in Figure 8.5.2.1B.

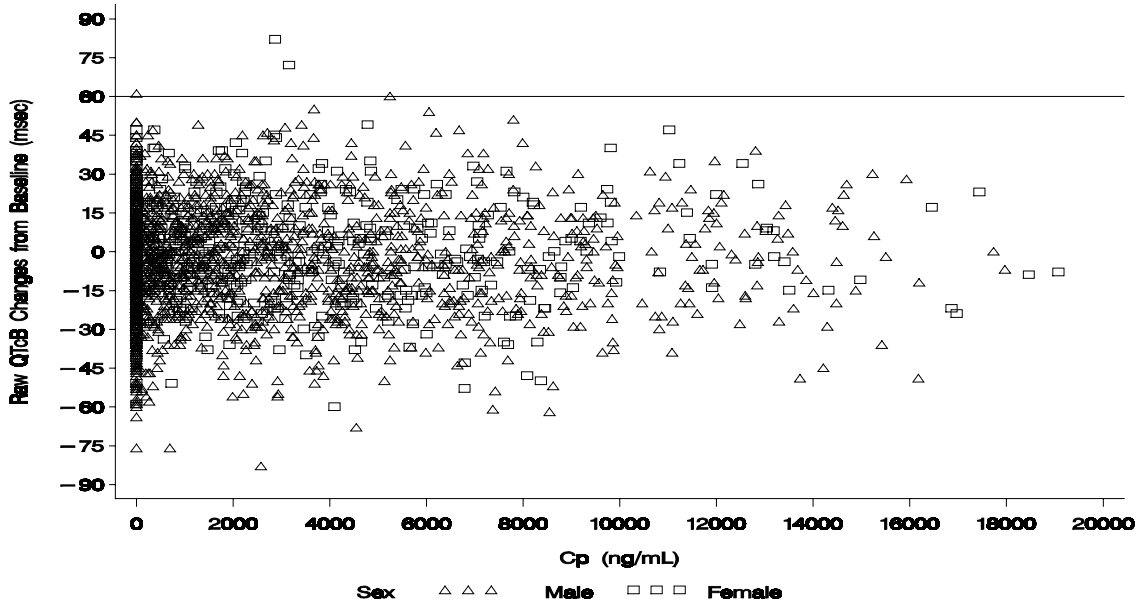
Figure 8.5.2.1B: Scatter Plot of QT_cB Intervals vs Atazanavir Plasma Concentrations



Source: Clinical Study Report for AI424076

A scatter plot of time-matched QT_cB changes from baseline vs ATV plasma concentrations obtained at the same time as the ECG recordings is presented in Figure 8.5.2.1C.

Figure 8.5.2.1C: Scatter Plot of Time-Matched QT_cB Changes from Baseline vs Atazanavir Plasma Concentrations



Source: Clinical Study Report for AI424076

Table 8.5.2.1A presents details of QT_cB intervals and heart rates associated with the ten highest ATV plasma concentrations. At these elevated concentrations (> 16000 ng/mL), there were no prolongations in QT_cB (QT_cB > 450 msec for males, QT_cB > 470 msec for females, ΔQT_cB > 60 msec).

In this table, QT_cB and heart rate values are those obtained on the same treatment and at the same clock time as the plasma concentrations. The ΔQT_cB and ΔHeart Rate are the time-matched changes from baseline. The QT_cB Max refers to the longest QT_cB observed in that subject on the study day corresponding to the plasma concentrations. The $\Delta_1 QT_cB$ Max is the time-matched change from baseline for QT_cB Max.

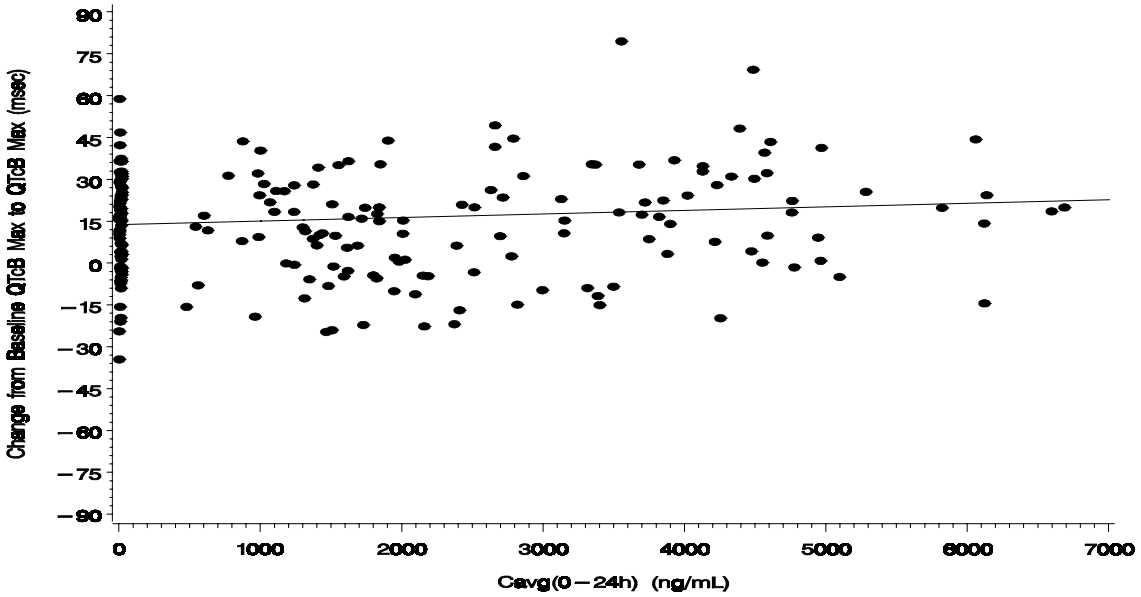
Table 8.5.2.1A: QT_cB Intervals at the Ten Highest Atazanavir Plasma Concentrations

Subject	Gender	ATV Cp (ng/mL)	Heart Rate (bpm)	Δ Heart Rate (bpm)	QT_cB (msec)	Δ QT_cB (msec)	QT_cB Max (msec)	Δ_1 QT_cB Max (msec)
AI424076-1-8	Male	16176	69	6	393	-49	413	2
AI424076-1-13	Female	16861	73	2	437	-22	451	22
		18460	68	7	424	-9		
AI424076-1-19	Female	17441	82	7	398	23	427	47
AI424076-1-24	Male	17964	79	8	410	-7	431	17
		17730	78	1	406	0		
AI424076-1-28	Female	16454	79	6	399	17	409	-12
		19071	74	8	389	-8		
AI424076-2-71	Female	16967	76	-3	418	-24	442	10
AI424076-2-72	Male	16191	65	8	357	-12	399	26

Source: Clinical Study Report for AI424076

A linear regression of $\Delta_1 QT_cB$ Max on the average plasma concentration from 0 to 24 hours after dosing (Cavg(0-24h)=AUC(0-24h)/24h) was performed on all available data from subjects who participated in Study AI424076, and a scatter plot and fitted regression line are presented in Figure 8.5.2.1D. The 95% CI for the population slope of the linear regression of $\Delta_1 QT_cB$ Max on ATV Cavg(0-24h) included zero, and the upper bound was 2.9 msec per 1000 ng/mL.

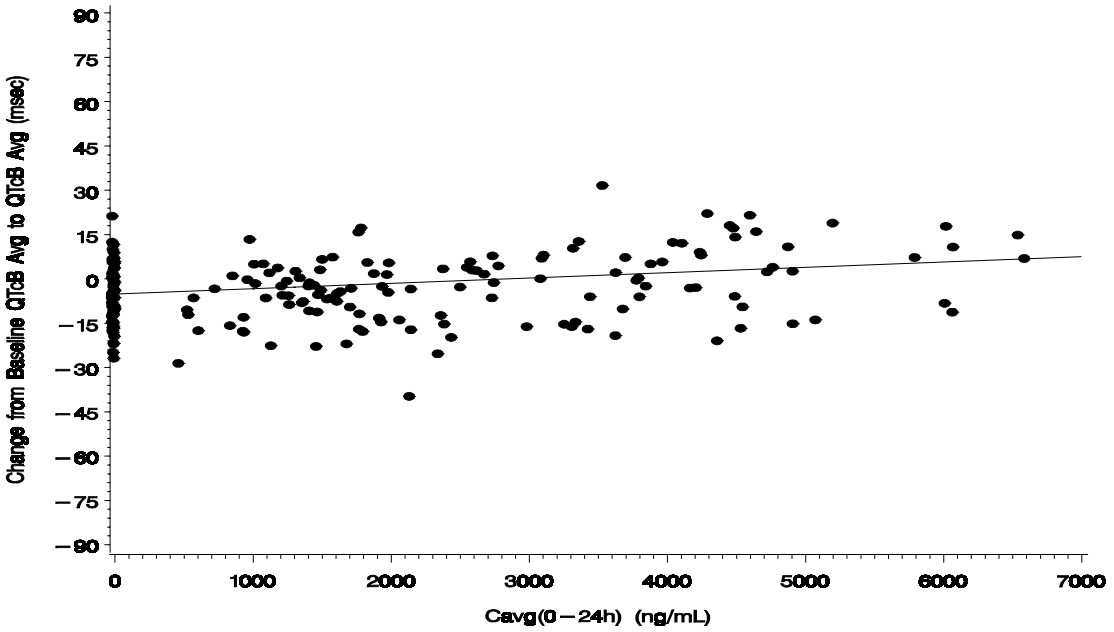
Figure 8.5.2.1D: Scatter Plot and Fitted Regression Line of Change from Baseline Maximum QT_cB to Maximum QT_cB on ATV Cavg (0-24h)



Source: Clinical Study Report for AI424076

A linear regression of Δ_1QT_cB Avg (difference between AUC(0-24h)/24h for QT_cB on Days 6 and -1, for each treatment period) on Cavg(0-24h) was also performed, and a scatter plot and fitted regression line are presented in Figure 8.5.2.1E. The 95% CI for the population slope of the linear regression of Δ_1QT_cB Avg on ATV Cavg(0-24h) was above zero [95% CI=(0.0009, 0.0028)], and the upper bound was 2.8 msec per 1000 ng/mL.

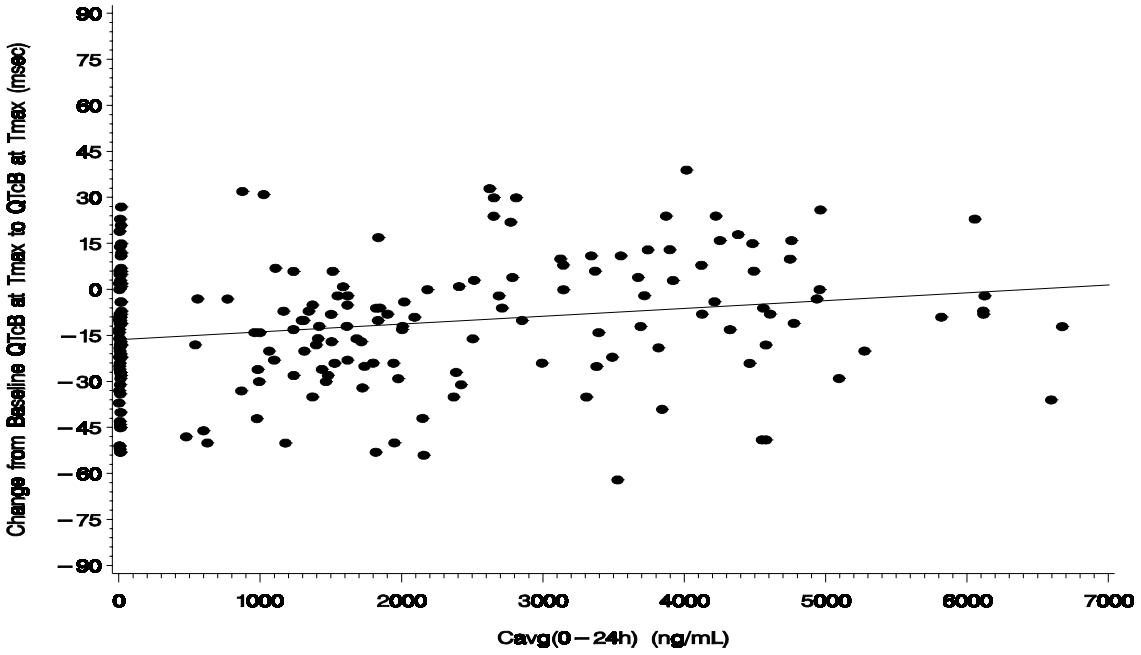
Figure 8.5.2.1E: Scatter Plot and Fitted Regression Line of Change from Baseline QT_cB Avg to QT_cB Avg on ATV Cavg (0-24h)



Source: Clinical Study Report for AI424076

A linear regression of Δ_1QT_cB at T_{max} (difference between QT_cB at T_{max} on Day 6 and the time-matched QT_cB on Day -1, for each treatment period) on Cavg(0-24h) was also performed, and a scatter plot and fitted regression line are presented in Figure 8.5.2.1F. The 95% CI for the population slope of the linear regression of Δ_1QT_cB at T_{max} on ATV Cavg(0-24h) was above zero [95% CI=(0.0009, 0.0042)], and the upper bound was 4.2 msec per 1000 ng/mL.

Figure 8.5.2.1F: Scatter Plot and Fitted Regression Line of Change from Baseline QT_cB at T_{max} to QT_cB at T_{max} on ATV Cavg (0-24h)



Source: Clinical Study Report for AI424076

Placebo-corrected, time-matched changes from baseline to maximum QT_cB were -5.1 msec for ATV 400 and +1.2 msec for ATV 800 mg. Placebo-corrected, time-matched changes from baseline to QT_cB Avg were -0.5 msec for ATV 400 and +5.4 msec for ATV 800 mg. Placebo-corrected, time-matched changes from baseline to QT_cB at T_{max} were -3.4 msec for ATV 400 and +7.9 msec for ATV 800 mg. Note that the mean Δ_1 QT_cB at T_{max} was negative for all treatments.

The frequency of subjects with a change in QT_cB interval > 60 msec was 0% for ATV 400, 1 (1%) for placebo, and 3 (5%) for ATV 800 (Table 8.5.2.1B), and the frequency of subjects with prolonged QT_cB interval (> 450 msec for males, > 470 msec for females) was 0% for placebo and ATV 400, and 2 (3%) for ATV 800. No subject had any ECG with QT_cB > 500 msec.

Table 8.5.2.1B: AI424076 QT_cB Electrocardiogram Data

ECG Parameter	Treatment: Placebo (n = 67)	Treatment: ATV 400 mg (n = 65)	Treatment: ATV 800 mg (n = 66)[a]
QT_cB > 500 msec, N (%)	0 (0%)	0 (0%)	0 (0%)
QT_cB > 450 msec (males)[b]	0 (0%)	0 (0%)	1 (2%)
QT_cB > 470 msec (females)[c]	0 (0%)	0 (0%)	1 (6%)
ΔQT_cB > 60 (msec), N(%)	1 (1%)	0 (0%)	3 (5%)
$\Delta_1 QT_cB$ Max (msec), Mean (SD)	17 (18)	14 (17)	21 (22)
Δ_1 QT_cB Avg (msec), Mean (SD)	-3 (10)	-3 (10)	3 (13)
Δ_1 QT_cB at T_{max} (msec), Mean (SD)	-15 (20)	-17 (18)	-4 (22)

Source: AI424076 Clinical Study Report

[a] Data from subject AI424076-1-29 on ATV 800 mg were excluded. This subject had no ECG with QT_cB > 450 msec or with ΔQT_cB > 60 msec at the 800 mg dose of ATV.

[b] Males: Placebo (N = 50), ATV 400 mg (N = 48), ATV 800 mg (N = 50)

[c] Females: Placebo (N = 17), ATV 400 mg (N = 17), ATV 800 mg (N = 16).

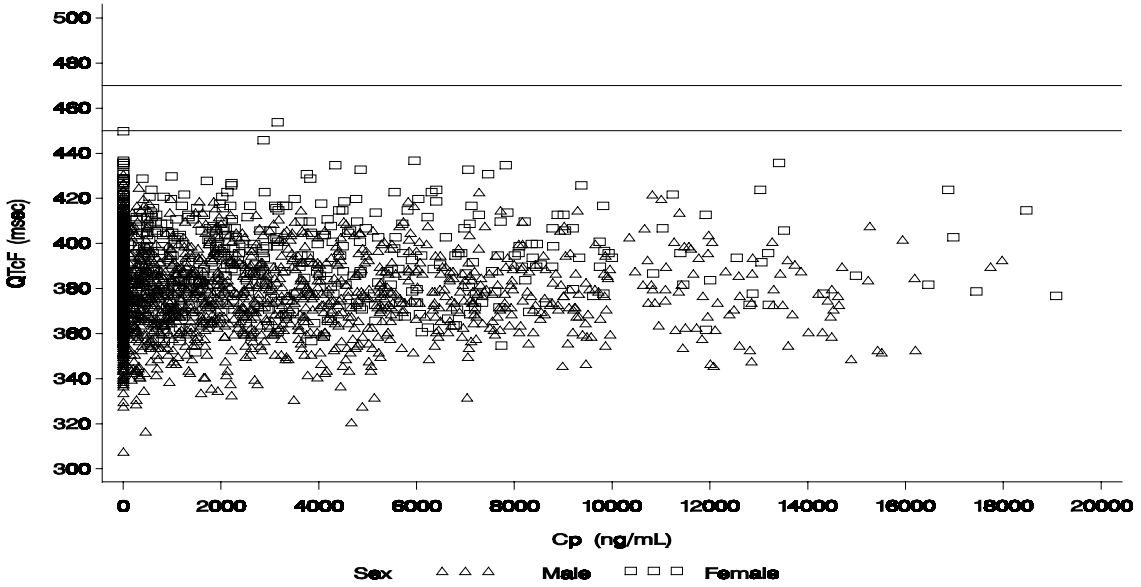
Utilizing the Bazett's correction and several measures of QT_cB change from baseline, for each additional 1000 ng/mL of Cavg(0-24h), the estimated QT_cB changes from baseline ranged between 0.7 and 2.5 msec. The largest of the upper bounds of the 95% confidence intervals for the slopes of the linear regressions on Cavg(0-24h) was 4.2 msec per 1000 ng/mL.

Results using the Fridericia correction

Similar analyses were performed for QT interval corrected for heart rate using Fridericia's formula.

A scatter plot of QT_cF intervals vs ATV plasma concentrations obtained at the same time as the ECG recordings is presented in Figure 8.5.2.1G.

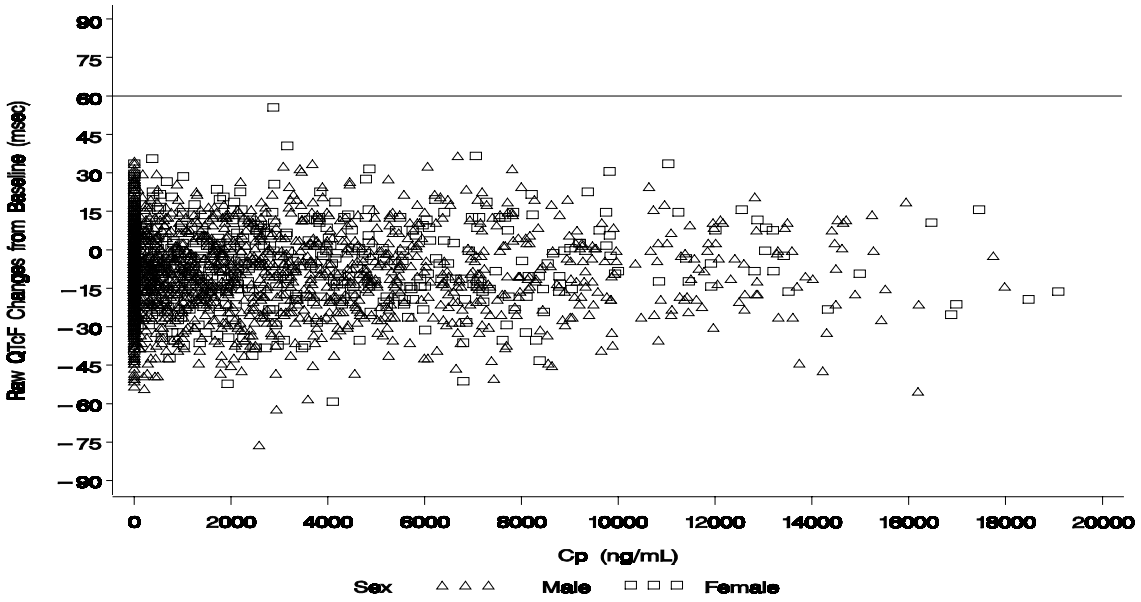
Figure 8.5.2.1G: Scatter Plot of QT_cF Interval vs Atazanavir Plasma Concentrations



Source: AI424076 Analysis for QT_cF

A scatter plot of time-matched QT_cF changes from baseline vs ATV plasma concentrations obtained at the same time as the ECG recordings is presented in Figure 8.5.2.1H.

Figure 8.5.2.1H: Scatter Plot of Time-Matched QT_cF Changes from Baseline vs Atazanavir Plasma Concentrations



Source: AI424076 Analysis for QT_cF

Table 8.5.2.1C presents details of QT_cF intervals and heart rates associated with the ten highest ATV plasma concentrations. As already noted for all the ECGs in this study, there were no prolongations in QT_cF (QT_cF > 450 msec for males, QT_cF > 470 msec for females, ΔQT_cF > 60 msec), at these elevated concentrations (> 16000 ng/mL).

In this table, QT_cF and heart rate values are those obtained on the same treatment and at the same clock time as the plasma concentrations. The ΔQT_cF and ΔHeart Rate are the time-matched changes from baseline. The QT_cF Max refers to the longest QT_cF observed on the study day corresponding to the plasma concentrations. The $\Delta_1 QT_cF$ Max is the time-matched change from baseline for QT_cF Max.

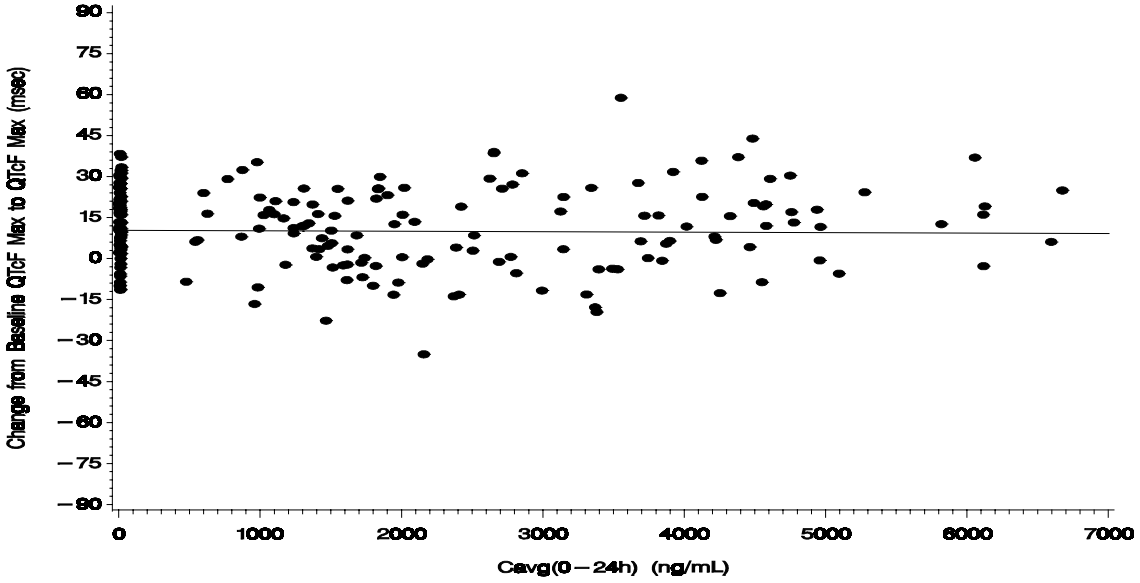
Table 8.5.2.1C: QT_cF Intervals at the Ten Highest Atazanavir Plasma Concentrations

Subject	Gender	ATV Cp (ng/mL)	Heart Rate (bpm)	Δ Heart Rate (bpm)	QT_cF (msec)	Δ QT_cF (msec)	QT_cF Max (msec)	Δ_1 QT_cF Max (msec)
AI424076-1-8	Male	16176	69	6	384	-54	399	-10
AI424076-1-13	Female	16861	73	2	423	-24	436	11
		18460	68	7	414	-18		
AI424076-1-19	Female	17441	82	7	378	17	406	35
AI424076-1-24	Male	17964	79	8	392	-13	407	14
		17730	78	1	389	-1		
AI424076-1-28	Female	16454	79	6	381	12	394	-5
		19071	74	8	376	-15		
AI424076-2-71	Female	16967	76	-3	402	-20	419	0
AI424076-2-72	Male	16191	65	8	352	-20	390	21

Source: AI424076 Analysis for QT_cF

A linear regression of Δ_1QT_cF Max on Cavg(0-24h) was performed and a scatter plot and fitted regression line are presented in Figure 8.5.2.1I. The 95% CI for the population slope of the linear regression of Δ_1QT_cF Max on ATV Cavg(0-24h) included zero, and the upper bound was 1.1 msec per 1000 ng/mL.

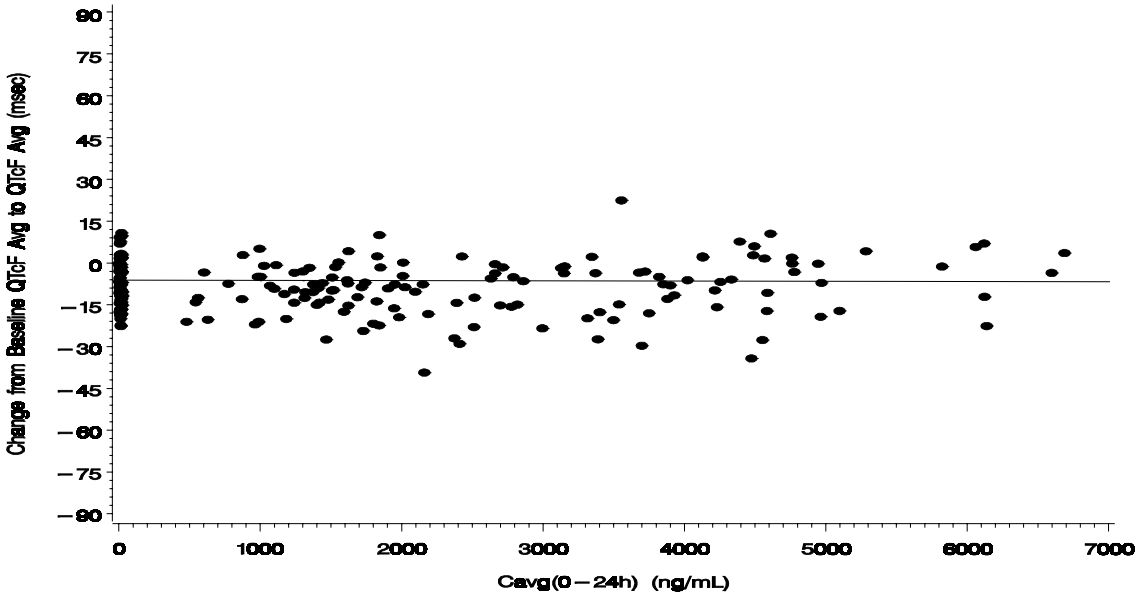
Figure 8.5.2.1I: Scatter Plot and Fitted Regression Line of Change from Baseline Maximum QT_cF to Maximum QT_cF on ATV Cavg (0-24h)



Source: AI424076 Analysis for QT_cF

A linear regression of Δ_1QT_cF Avg on Cavg(0-24h) was also performed, and a scatter plot and fitted regression line are presented in Figure 8.5.2.1J. The 95% CI for the population slope of the linear regression of Δ_1QT_cF Avg on ATV Cavg(0-24h) included zero, and the upper bound was 0.8 msec per 1000 ng/mL.

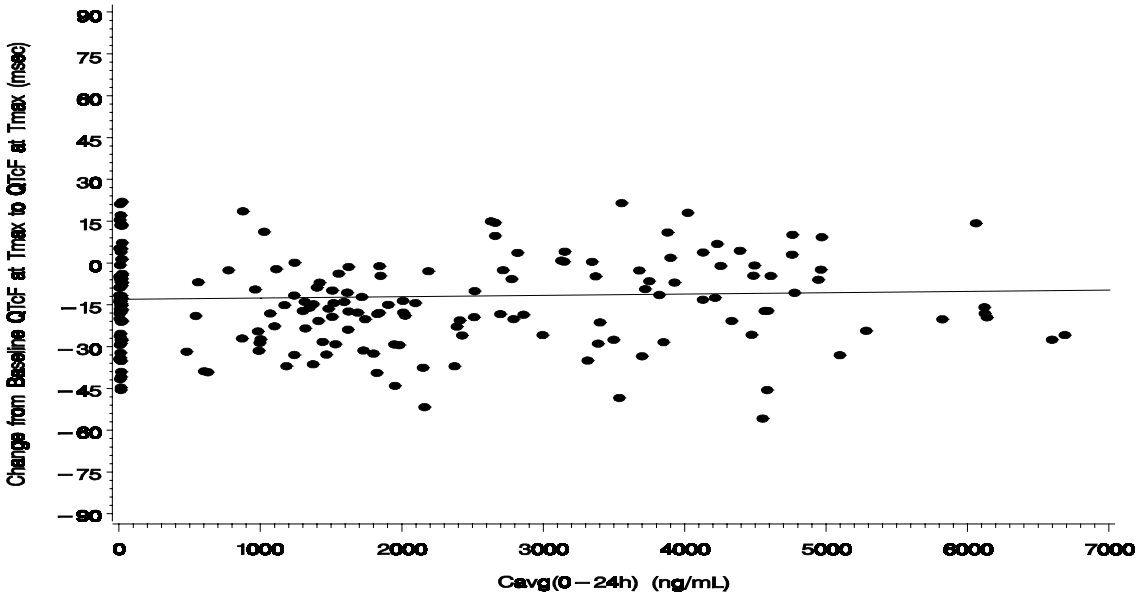
Figure 8.5.2.1J: Scatter Plot and Fitted Regression Line of Change from Baseline QT_cF Avg to QT_cF Avg on ATV Cavg (0-24h)



Source: AI424076 Analysis for QT_cF

A linear regression of Δ_1QT_cF at T_{max} on Cavg(0-24h) was also performed, and a scatter plot and fitted regression line are presented in Figure 8.5.2.1K. The 95% CI for the population slope of the linear regression of Δ_1QT_cF at T_{max} on ATV Cavg(0-24h) included zero and the upper bound was 1.8 msec per 1000 ng/mL.

Figure 8.5.2.1K: Scatter Plot and Fitted Regression Line of Change from Baseline QT_cF at T_{max} to QT_cF at T_{max} on ATV Cavg (0-24h)



Source: AI424076 Analysis for QT_cF

Placebo-corrected, time-matched changes from baseline to maximum QT_cF were -6.1 msec for ATV 400 and -3.4 msec for ATV 800 mg. Placebo-corrected, time-matched changes from baseline to QT_cF Avg were -3.0 msec for ATV 400 and -1.6 msec for ATV 800 mg. Placebo-corrected, time-matched changes from baseline to QT_cF at T_{max} were -6.3 msec for ATV 400 and 0.5 msec for ATV 800 mg. The mean Δ_1 QT_cF Avg and the mean Δ_1 QT_cF at T_{max} were negative for all treatments.

No subject had any ECG with a prolonged QT_cF interval (> 450 msec for males, > 470 msec for females) or with a change in QT_cF interval > 60 msec (Table 8.5.2.1D). No subject had any ECG with QT_cF > 500 msec.

Table 8.5.2.1D: AI424076 QT_cF Electrocardiogram Data

	Treatment		
ECG Parameter	**Placebo (n = 67)**	**ATV 400 mg (n = 65)**	**ATV 800 mg (n = 66)[a]**
QT_cF > 500 msec, N (%)	0 (0%)	0 (0%)	0 (0%)
QT_cF > 450 msec (males)[b]	0 (0%)	0 (0%)	0 (0%)
QT_c F> 470 msec (females)[c]	0 (0%)	0 (0%)	0 (0%)
ΔQT_cF > 60 msec, N(%)	0 (0%)	0 (0%)	0 (0%)
$\Delta_1 QT_cF$ Max (msec), Mean (SD)	11 (13)	6 (13)	9 (17)
$\Delta_1 QT_cF$ Avg (msec), Mean (SD)	-4 (8)	-6 (8)	-5 (11)
$\Delta_1 QT_cF$ at T_{max} (msec), Mean (SD)	-9 (17)	-15 (13)	-8 (17)

Source: AI424076 Analysis for QT_cF

[a] Data from Subject AI424076-1-29 on ATV 800 mg were excluded. This subject had no ECG with QT_cF > 450 msec or with ΔQT_cF > 60 msec at the 800 mg dose of ATV

[b] Male: Placebo (n = 50), ATV 400 mg (n = 48), ATV 800 mg (n = 50)

[c] Females: Placebo (n = 17), ATV 400 mg (n = 17), ATV 800 mg (n = 16)

Utilizing the Fridericia's correction and several measures of QT_cF change from baseline, for each additional 1000 ng/mL of Cavg(0-24h), the estimated QT_cF changes from baseline ranged between -0.8 and 0.5 msec. All 95% confidence intervals for the slopes for the linear regressions of QT_cF changes from baseline on Cavg(0-24h) included zero. The largest of the upper bounds of the 95% confidence intervals for the slopes of the linear regressions on Cavg(0-24h) was 1.8 msec per 1000 ng/mL.

Comparison of the results using QT_cB and QT_cF

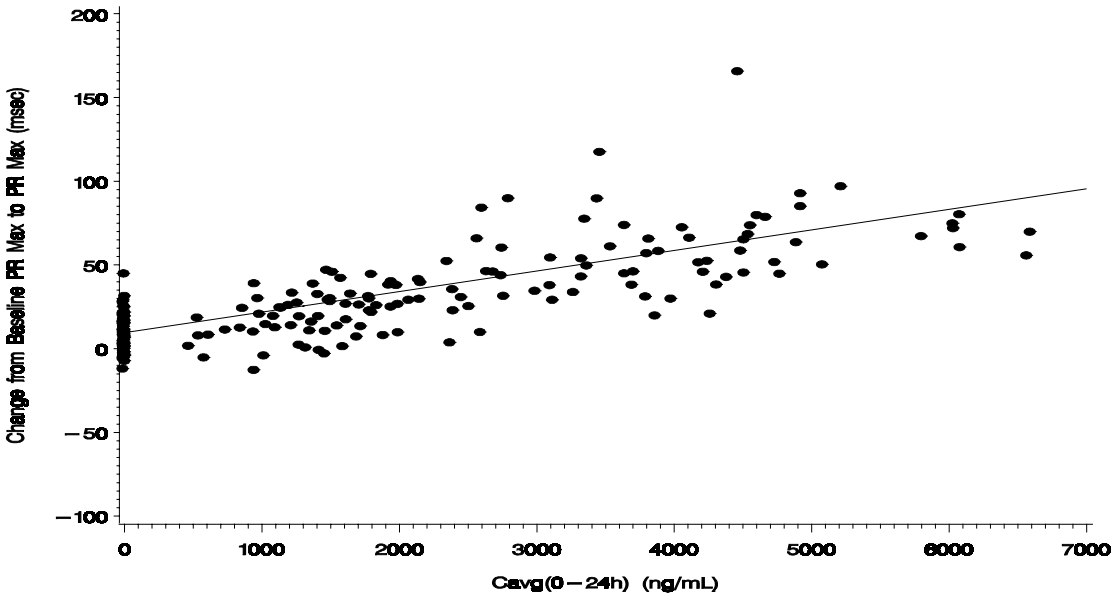
The results using Fridericia's correction demonstrate less ATV effect on QT_c in all analyses than when using Bazett's.

- Atazanavir is associated with a modest dose-dependent increase in heart rate, compared to placebo. In this setting, Fridericia's formula may be more appropriate than Bazett's formula for heart rate correction of QT;
- No outliers for QT_cF (>450 msec for males, > 470 msec for females) or for QT_cF changes from baseline (ΔQT_cF > 60 msec) were observed, regardless of which QT_cF change from baseline is evaluated;
- All 95% confidence intervals for the slopes for the linear regressions of QT_cF changes from baseline on C_{max} or Cavg(0-24h) included zero;
- The largest of the upper bounds of the 95% confidence intervals for the slopes was 1.8 msec per 1000 ng/mL;
- Placebo-corrected (difference between the adjusted means for ATV and for placebo) mean time-matched changes from baseline to QT_cF Max and to QT_cF Avg were negative for both the 400 mg and the 800 mg ATV doses. Placebo-corrected mean time-matched changes from baseline to QT_cF at T_{max} were negative for the 400 mg ATV dose and were +0.5 for the 800 mg ATV dose.

PR Interval in Study AI424076

A linear regression of Δ_1PR Max on Cavg(0-24h) was performed on all available data from subjects who participated in Study AI424076, and a scatter plot and fitted regression line are presented in Figure 8.5.2.1L. The 95% CI for the population slope of the linear regression of Δ_1PR Max on ATV Cavg(0-24h) was above zero, indicating that ATV has a statistically significant concentration-dependent effect on the PR interval. The upper bound of this CI was 13.9 msec per 1000 ng/mL.

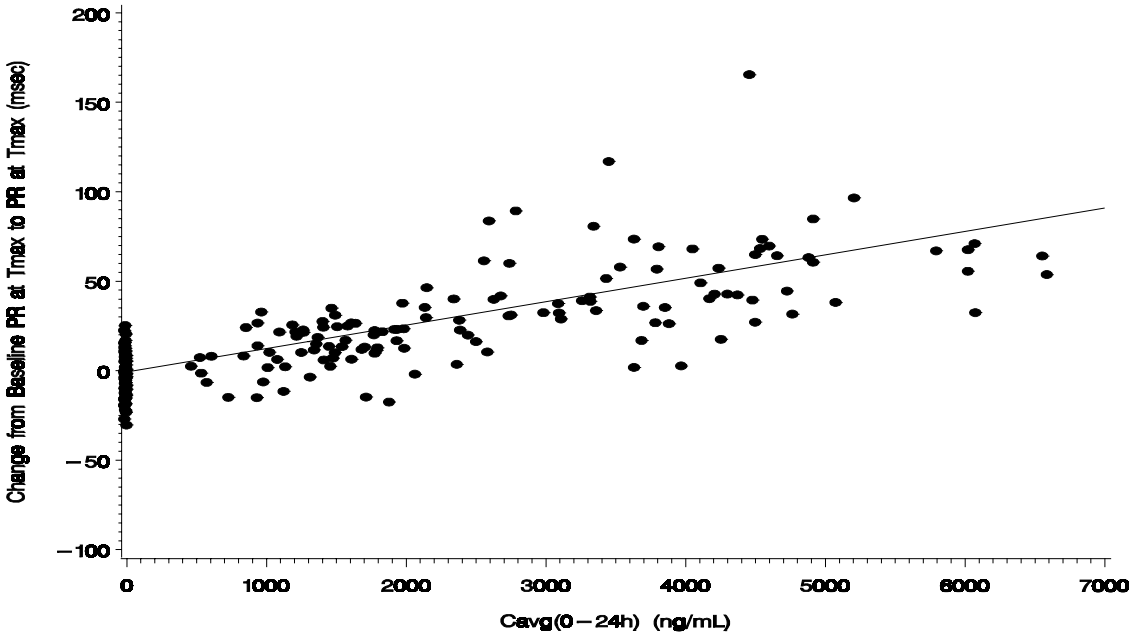
Figure 8.5.2.1L: Scatter Plot and Fitted Population Regression Line of Change from Baseline Maximum PR to Maximum PR on ATV Cavg (0-24h)



Source: AI424076 Clinical Study Report

A linear regression of Δ_1PR at T_{max} on Cavg(0-24h) was also performed, and a scatter plot and fitted regression line are presented in Figure 8.5.2.1M. The 95% CI for the population slope of the linear regression of Δ_1PR at T_{max} on ATV Cavg(0-24h) was above zero, indicating that ATV has a statistically significant concentration-dependent effect on the PR interval. The upper-bound of this CI was 14.9 msec per 1000 ng/mL.

Figure 8.5.2.1M: Scatter Plot and Fitted Regression Line of Change from Baseline PR at T_{max} to PR at T_{max} on ATV Cavg (0-24h)



Source: AI424076 Clinical Study Report

A PR interval > 200 msec is considered prolonged and is the definition of first degree atrioventricular block (1st degree AV block). PR intervals > 200 msec are often found in healthy young adults and a more stringent threshold of > 250 msec is also presented in what follows. In study AI424076, the frequency of subjects with PR interval between 200 and 250 msec was 1% for placebo, 14% for ATV 400, and 47% for ATV 800 (Table 8.5.2.1E). The frequency of subjects with PR interval > 250 msec was 0% for placebo and ATV 400, and 8 (12%) for ATV 800 (Table 8.5.2.1E). No episodes of second- or third-degree atrioventricular (AV) block were observed.

Table 8.5.2.1E: AI424076 PR Interval Electrocardiogram Data

ECG Parameter	Treatment		
	Placebo (n = 67)	ATV 400 mg (n = 65)	ATV 800 mg (n = 66)[a]
PR > 200 - 250 msec, N (%)	1 (1%)	9 (14%)	31 (47%)
PR > 250 msec, N (%)	0 (0%)	0 (0%)	8 (12%)
Δ_1 PR Max (msec) Mean (SD)	13 (11)	24 (15)	60 (25)
Δ_1 PR at T_{max} (msec) Mean (SD)	1 (13)	18 (13)	52 (28)

[a] Data from Subject AI424076-1-29 on ATV 800 mg were excluded.

8.5.2.2 Studies Assessing Cardiac Conduction Effects of ATV in HIV-Infected Subjects

In five clinical studies, a total of 1793 subjects (1253 males and 540 females) had at least one ECG tracing performed. Of these 1793 subjects, 920 (624 males and 296 females) were treated with ATV 400 mg and 117 (93 males and 24 females) were treated with ATV 300/RTV.

While the Phase II Studies AI424041, AI424044 and the Phase III study in naive subjects (AI424034) were ongoing, they were amended to include ECG measurements. Three serial ECGs (pre-dose [trough], 2 - 3 hours post-dose, and 6 - 12 hours post-dose) were performed. The interpretation of the ECG results was limited by several factors. First, no pre-study baseline measurement was available for comparison and in addition, many subjects had been receiving concomitant medications for various durations at the time of the ECG recordings. Secondly, the timing of the ECGs did not take into account diurnal variation. The design of the Phase III studies in antiretroviral experienced subjects, AI424043 and AI424045, attempted to limit these concerns by obtaining a baseline ECG measurement prior to study drug administration and by measuring serial ECG parameters (pre-dose [trough], 2 - 3 hours post-dose, and 6 - 12 hours post-dose) multiple times post dose. However, these studies did not include a washout period prior to enrollment, and therefore, prior drug(s) may have influenced the baseline measurement. Due to the limitations around baseline ECG data for the Phase II/III trials, only the incidence of on

study prolongations of QT_c and PR intervals are presented. Both QT_cB and QT_cF corrections are utilized in the presentations in Tables 8.5.2.2A and 8.5.2.2B. PR interval prolongations are presented in Table 8.5.2.2C.

Overall, the incidence of ATV-treated subjects experiencing an on-study QT_c interval prolongation (> 450 msec for males and > 470 msec for females) by either correction formula was low and comparable among treatment regimens. The majority of on-study QT_cB interval prolongations in ATV-treated subjects occurred in males (males: 20; females: 4), partially reflective of the greater number of males treated with ATV. Overall, no ATV-treated subjects and one EFV-treated subject reported a significantly prolonged QT_cB interval (> 500 msec). The incidence of on study prolongations with QT_cF was lower than with QT_cB.

Overall, across the five Phase II/III studies, as seen in Table 8.5.2.2C, the majority of ATV-treated subjects (86 - 96%) had post-dose maximum PR intervals ≤ 200 msec, regardless of treatment regimen. The incidence of subjects experiencing a post-dose PR interval prolongation (> 200 msec) was comparable among treatment regimens with most of the events occurring in Study AI424044. Four subjects treated with ATV had maximum PR intervals > 250 msec while one subject treated with EFV and one subject treated with LPV/RTV reported maximum PR intervals > 250 msec. No heart block greater than first degree was reported. Overall, across the five Phase II and III studies, PR interval prolongations > 200 msec were seen in 54 of 920 subjects (5.9%) receiving ATV 400 mg and in 5 of 117 subjects (4.3%) receiving ATV 300 mg/RTV 100 mg. This incidence was comparable to that seen for comparators: 5.2% for subjects receiving LPV/RTV and 8.5% for subjects receiving NFV.

Table 8.5.2.2A: On-Study QT_cB Interval Prolongation by Category and Gender - All Phase II/III Studies

	Number with QT_cB interval prolongation / Number Assessed (%)										
	AI424041[a]		AI424044		AI424034		AI424043	AI424045			
QT_{cB} Interval (msec)	ATV Combined N = 152	NFV N = 48	ATV 400 N = 173	ATV 600 N = 127	ATV 400 N = 353	EFV N = 329	ATV 400 N = 137	LPV/ RTV N = 141	ATV 300/ RTV N = 117	ATV 400/ SQV N = 105	LPV/ RTV N = 111
Males	**N = 103**	**N = 30**	**N = 108**	**N = 82**	**N = 226**	**N = 224**	**N = 107**	**N = 116**	**N = 93**	**N = 80**	**N = 84**
451 - 500	3/103 (3)	0/30 (0)	3/108 (3)	2/82 (2)	4/226 (2)	6/224 (3)	2/107 (2)	6/116 (5)	3/93 (3)	3/80 (4)	4/84 (5)
> 500	0/103 (0)	0/30 (0)	0/108 (0)	0/82 (0)	0/226 (0)	1/224 (< 1)	0/107 (0)	0/116 (0)	0/93 (0)	0/80 (0)	0/84 (0)
Females	**N = 49**	**N=18**	**N = 65**	**N = 45**	**N = 127**	**N = 105**	**N = 30**	**N = 25**	**N = 24**	**N = 25**	**N = 27**
471 - 500	2/49 (4)	0/18 (0)	0/65 (0)	0/45 (0)	0/127 (0)	1/105 (1)	1/30 (3)	1/25 (4)	0/24 (0)	1/25 (4)	1/27 (4)
> 500	0/49 (0)	0/18 (0)	0/65 (0)	0/45 (0)	0/127 (0)	0/105 (0)	0/30 (0)	0/25 (0)	0/24 (0)	0/25 (0)	0/27 (0)

Source: Updated Summary of Clinical Safety

[a] Two cohorts, one each from Studies AI424007 and AI424009, rolled onto Study AI424041. ECG analyses were performed on the AI424007 cohort only due to the very limited sample size of the AI424009 cohort.

Table 8.5.2.2B: On-Study QT_cF Interval Prolongation by Category and Gender - All Phase II/III Studies

	Number with QT_cF interval prolongation / Number Assessed (%)										
	AI424041[a]		AI424044		AI424034		AI424043	AI424045			
QT_cF Interval (msec)	ATV Combined N = 152	NFV N = 48	ATV 400 N = 173	ATV 600 N = 127	ATV 400 N = 353	EFV N = 329	ATV 400 N = 137	LPV/ RTV N = 141	ATV 300/ RTV N = 117	ATV 400/ SQV N = 105	LPV/ RTV N = 111
Males	**N = 103**	**N = 30**	**N = 108**	**N = 82**	**N = 226**	**N = 224**	**N = 107**	**N = 116**	**N = 93**	**N = 80**	**N = 84**
451 - 500	1/103 (<1)	0/30 (0)	1/108 (<1)	0/82 (0)	0/226 (0)	1/224 (<1)	0/107 (0)	1/116 (<1)	1/93 (1)	0/80 (0)	0/84 (0)
> 500	0/103 (0)	0/30 (0)	0/108 (0)	0/82 (0)	0/226 (0)	0/224 (0)	0/107 (0)	0/116 (0)	0/93 (0)	0/80 (0)	0/84 (0)
Females	**N = 49**	**N=18**	**N = 65**	**N = 45**	**N = 127**	**N = 105**	**N = 30**	**N = 25**	**N = 24**	**N = 25**	**N = 27**
471 - 500	0/49 (0)	0/18 (0)	0/65 (0)	0/45 (0)	0/127 (0)	0/105 (0)	0/30 (0)	0/25 (0)	0/24 (0)	0/25 (0)	0/27 (0)
> 500	0/49 (0)	0/18 (0)	0/65 (0)	0/45 (0)	0/127 (0)	0/105 (0)	0/30 (0)	0/25 (0)	0/24 (0)	0/25 (0)	0/27 (0)

Source: Updated Summary of Clinical Safety

[a] Two cohorts, one each from Studies AI424007 and AI424009, rolled onto Study AI424041. ECG analyses were performed on the AI424007 cohort only due to the very limited sample size of the AI424009 cohort.

Table 8.5.2.2C: On-Study PR Interval Prolongation by Category - All Phase II/III Studies

	Number with PR interval prolongation / Number Assessed (%)										
	AI424041[a]		AI424044		AI424034		AI424043		AI424045		
PR Interval (msec)	ATV Combined N = 152	NFV N = 48	ATV 400 N = 173	ATV 600 N = 127	ATV 400 N = 353	EFV N = 329	ATV 400 N = 137	LPV/ RTV N = 141	ATV 300/ RTV N = 117	ATV 400/ SQV N = 105	LPV/ RTV N = 111
≤ 200	144/152 (95)	43/48 (90)	158/173 (91)	109/127 (86)	336/353 (95)	319/329 (97)	129/137 (94)	133/141 (94)	112/117 (96)	99/105 (94)	106/111 (95)
201 - 250	8/152 (5)	5/48 (10)	13/173 (8)	18/127 (14)	16/353 (5)	9/329 (3)	8/137 (6)	8/141 (6)	5/117 (4)	5/105 (5)	4/111 (4)
> 250	0/152 (0)	0/48 (0)	2/173 (1)	0/127 (0)	1/353 (< 1)	1/329 (< 1)	0/137 (0)	0/141 (0)	0/117 (0)	1/105 (< 1)	1/111 (< 1)

Source: Updated Summary of Clinical Safety

[a] Two cohorts, one each from Studies AI424007 and AI424009, rolled onto Study AI424041. ECG analyses were performed on the AI424007 cohort only due to the very limited sample size of the AI424009 cohort.

8.5.2.3 Long-term Pharmacovigilance Assessment of Cardiac Conductivity

QT_c Interval Prolongation

The extensive evaluation of ATV for cardiac conduction effects identified a possible weak signal for effect on QT_cB. While reassuring that ATV has limited intrinsic effect on QT_c, data from AI424076 were developed in healthy volunteers, and it is unknown whether patients with serious pre-existing underlying heart disease (eg, HIV myocardiopathy) might have a different risk. Although Phase III data showed that on-study QT_c "outliers" appeared no more frequently in ATV subjects than in controls, these data have limitations, especially since the clinical trials excluded subjects with significant pre-existing structural or conduction-related heart disease, and no data set was large enough to have reliably detected very rare events thought to be associated with QT_c prolongation, namely "torsades de pointes".

Other than overdose, no foreseeable clinical situation would cause patients to be exposed to concentrations in excess of those associated with the maximum dose of 800 mg studied in Study AI424076. Nevertheless, it is anticipated that ATV could increase exposure of certain drugs (drug classes) that are associated with QT_c prolongation that might be co-administered. Representatives of these classes (eg, clarithromycin) were studied and appropriate recommendations developed to mitigate their risk.

Therefore, it is important to continue assessment of ATV for any possible rare QT_c effects in the context of post-approval studies, surveillance for very rare events, and development of appropriate labeling to guide clinicians and patients.

PR Interval Prolongation

Study AI424076 confirmed the already noted asymptomatic dose and concentration dependent prolongation of the PR interval by ATV. The Phase III data sets suggested this finding was not unique to ATV since it was seen in approximately the same incidence across ATV and the comparator regimens. As with previous Phase I and Phase II/III studies, no AV block greater than first-degree was noted.

In general, PR interval prolongation (PR > 200 msec) or first-degree AV block is usually a benign condition and has been seen in normal adults. Because it is frequent and appears to have limited prognostic significance, little is known of its risk in the non-HIV infected population and less in HIV-infected patients.

While PR prolongation with ATV was asymptomatic, it was nevertheless a clear finding with ATV (and the comparator agents). It is therefore important to both continue to assess this finding post-approval, by surveillance for rare events, as well as to provide appropriate cautionary labeling. The labeling will focus on avoiding interactions with drugs with additive effects on PR, such as calcium channel blockers (eg, diltiazem), as well as providing cautionary guidance for certain patients. Clinical trials excluded subjects with significant pre-existing structural or conduction-related heart disease so that the data showing the asymptomatic nature of the PR prolongation may not extend to patients with these conditions.

Conclusion

In conclusion, in the 1793 subjects receiving HAART regimens, the frequency of QT_c prolongation using either Bazett's or Fridericia's correction was comparable in the ATV, ATV 300/RTV, and comparator regimens. The numbers of subjects with on-study QT_c prolongation was lower when analyzed with QT_cF. No ATV-treated HIV-infected subject had a QT_c interval > 500 msec regardless of correction. All prolongations of the PR interval were asymptomatic and not associated with clinical findings. The frequency of first-degree AV block (PR > 200 msec) was low and comparable among subjects receiving ATV, ATV 300/RTV, and comparator regimens. No AV block greater than first-degree was observed in these subjects.

Based upon extensive evaluation *in vitro*, in animals, and in clinical trials, the risk for an untoward cardiac conduction event appears to be low. Nonetheless, appropriate patient/physician education, along with specific label precautions, particularly with respect to drug-drug interactions, is appropriate.

8.6 Overall Safety Conclusions

The safety profile of ATV has been assessed across a wide range of treatment experiences that represent the target treatment population. ATV-containing regimens were generally safe, well-tolerated, and comparable to several standard of care regimens, with an overall mean time on therapy of up to 87 weeks. Among all ATV-treated subjects, the most common Grade 1 - 4 AEs were infection and nausea and were comparable to comparator regimens. The most common Grade 2 - 4 (ie, moderate to very severe) treatment-related AEs reported in at least 2% of ATV-treated subjects were nausea, jaundice, lipodystrophy, rash, headache, vomiting, abdominal pain, and peripheral neurologic symptoms. Jaundice and scleral icterus were the only treatment-related AEs of moderate to very severe intensity that were reported at a higher incidence than on comparator regimens. Discontinuation of study therapy due to AEs was infrequent.

Deaths were reported infrequently and were mostly unrelated to study therapy for all studies. Other SAEs were generally evenly distributed among treatment regimens within each study; the cumulative incidence increased with increasing time on the study. The events were consistent with the known side-effect profile of the study drugs and almost all individual events were reported at a frequency ≤ 1%.

Other than elevations in indirect bilirubin, the laboratory abnormalities observed with ATV were unremarkable. The majority of hematologic abnormalities were mild to moderate and generally comparable among treatment regimens. Few serum chemistry abnormalities were reported on any treatment regimen. The majority of liver transaminase abnormalities were mild to moderate and were unrelated to UGT 1A1 inhibition-related hyperbilirubinemia.

Hyperbilirubinemia has been fully characterized with regard to its mechanism and the incidence with which it is observed. Hyperbilirubinemia associated with ATV is reversible with dosing interruptions or discontinuation and is clinically benign. Elevations in indirect bilirubin are adequately disassociated from hepatotoxicity.

The extensive ECG assessments of ATV have contributed to the overall understanding of the limited potential significance of *in vitro* assay results. ECG abnormalities were

observed with a low and comparable frequency for ATV and comparators, demonstrating that ATV has no greater liability than currently marketed ARV agents.

The safety of ATV has been adequately characterized to support its use for treatment of HIV infection as part of a HAART regimen at a dose of 400 mg QD in ARV treatment-naive subjects and at a dose of 400 mg QD or 300 mg "boosted" with RTV 100 mg QD in ARV treatment-experienced subjects.

9 OVERALL BENEFIT/RISK ASSESSMENT OF ATAZANAVIR

The overall benefit/risk assessment supports the use of ATV as a component of HAART regimens for the treatment of HIV-infected individuals. There is substantial experience highlighted in this briefing document assessing PK findings, clinical safety, efficacy and durability of effect that supports the use of ATV dosed at 400 mg once-daily in ARV treatment-naive patients. However, ATV 400 mg alone was not as efficacious as a RTV pharmacologically-enhanced PI regimen, specifically LPV/RTV, in ARV treatment-experienced patients. Preliminary data suggest ATV dosed QD as 300 mg "boosted" with RTV 100 mg has safety and efficacy comparable to LPV/RTV in the ARV treatment-experienced population. Atazanavir can be used safely with ARV agents of all classes, and with the expected array of concomitant medications used in HIV patients, with few contraindications.

ATV represents a significant therapeutic advance for HIV-infected patients. It provides added value on the basis of simplicity of administration, demonstrated efficacy in diverse HIV patient populations, a distinct viral resistance profile and a favorable safety and tolerability profile. ATV also has a unique and potentially important lack of effect on lipid parameters, including cholesterol and fasting triglycerides. The combination of the demonstrable long-term efficacy and the durable lipid benefit of ATV provide a very positive benefit whereby patients can achieve durable, long-term virologic control without the possible associated risk seen with other HAART therapies.

On the potential risk side are two clinical findings that appear to be quite manageable. First, prolongations of the PR and QT_cB intervals appear to be minimal and not unique to ATV. Overall, results of the placebo-controlled study AI424076 suggest minimal risk for clinically significant QT_c prolongation at ATV doses targeted for use in HIV-infected patients. Secondly, the hyperbilirubinemia noted during ATV treatment has been extensively characterized and found to largely represent a benign event similar in underlying mechanism to elevations that occur in individuals with Gilbert's syndrome. Jaundice or more subtle elevations in bilirubin concentrations that occur are readily reversible and manageable by patients and their health care team.

Overall, the balance of benefits and risks associated with ATV-containing HAART regimens is favorable for both ARV treatment-naive and treatment-experienced patient populations. For the ARV treatment-naive patient, the clinician and patient can expect to receive an efficacious, durable antiviral benefit that is similar to the current standard of care. Similarly, in ATV treatment-experienced patients, ATV provides effective antiviral activity when given as part of a HAART regimen. The simplicity of administration of ATV (two capsules once-daily with food) reduces the complexity of HAART regimens.

Another unique benefit of ATV for ARV treatment-naive patients who are early in their HIV disease course is the lack of elevations of lipid parameters, a benefit that is not associated with other PIs. It is anticipated that this superior lipid profile may translate into simplified regimens that avoid the need for co-administration of lipid lowering therapy.

A particularly important benefit of ATV for this patient population is the preservation of future treatment options because treatment emergent HIV resistance is slow to develop and because cross-resistance does not appear to evolve even with development of decreased susceptibility to ATV (which occurs very infrequently). Therefore, one would anticipate retained ability to use other members of the PI class following ATV failure.

The most notable untoward effect in patients receiving ATV is the development of hyperbilirubinemia. Some patients develop significant elevations (> 5 x the ULN) or clinical symptoms (ie, jaundice, scleral icterus) associated with these elevations. Since ATV-induced unconjugated hyperbilirubinemia is clinically benign and reversible, the only real consequence for patients with unacceptable elevations in bilirubin is that they may need to seek an alternative therapy.

Furthermore, dosing of patients with ATV for several years demonstrates no long-term sequelae. Finally, the incidence of clinically significant QT_c and PR interval prolongation occurring outside the normal threshold range for these ECG intervals in patients treated in ATV regimens is very low and comparable to comparator regimens.

In conclusion, ATV-containing regimens represent an important therapeutic option for both ARV treatment-naive and treatment-experienced patients.

10 CONCLUSIONS

Atazanavir has a unique profile that fulfills several medical needs that remain relevant for the treatment of HIV-infected patients: 1) a once-daily low pill burden (two capsules once per day) that simplifies regimens for both ARV treatment-naive and treatment-experienced patients; 2) a distinct HIV resistance profile; and 3) a favorable lipid and metabolic profile that has proven to be durable and may ultimately reduce cardiovascular risk in long-term HIV-infected survivors. Atazanavir is safe and well tolerated relative to comparator regimens across a broad spectrum of experience (ie, ARV treatment-naive to heavily treatment-experienced patients). The principal laboratory abnormality noted during the clinical development of ATV has been hyperbilirubinemia, and this finding is independent of hepatocellular toxicity, manageable, and reversible. The efficacy of ATV is similar to the standard of care in ARV treatment-naive patients when administered as 400 mg once daily, and preliminary data in ARV treatment-experienced patients suggest ATV may be effective when administered as 300 mg "boosted" with RTV 100 mg once daily.

Thus, ATV represents an important addition to enhancing and improving the management of HIV infection, and the balance of benefits and risks support the indication sought for its use in combination with other ARV agents for the treatment of HIV-1 infection in ARV treatment-naive and treatment-experienced patients.

11 PLANS FOR COMPLETING REQUIREMENTS FOR TRADITIONAL APPROVAL

Atazanavir is being reviewed under the rules for accelerated approval. The Sponsor will continue to follow all patients in Studies AI424043 and AI424045 with the intent to achieve a 48-week endpoint and complete the second pivotal trial required for traditional approval. The Sponsor will also conduct an additional adequate and well-controlled trial in ARV treatment-experienced patients to further substantiate the activity and safety of ATV combined with RTV relative to the standard of care. Final plans for this trial will be discussed with FDA.

LIST OF ABBREVIATIONS

Δ_1QTc Avg	difference between the QT_c areas under the curve over 24 hours divided by 24 hours, after study drug administration and prior to study drug administration
Δ_1QTc Max	difference between the maximum QT_c recorded after study drug administration and the QT_c recorded at the same clock time prior to study administration
Δ_1QTc T_{max}	difference between the first QT_c recorded at or after T_{max} and the QT_c recorded at the same clock time prior to study administration
3TC	lamivudine (Epivir®)
ABC	abacavir (Ziagen®)
ACTG	AIDS Clinical Trials Group
ADARC	Aaron Diamond AIDS Research Center
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALT or SGPT	alanine aminotransferase/serum glutamic-pyruvic transaminase
ANRS	Agence Nationale de Resherches surle SIDA
APV	amprenavir (Agenerase®)
ARDS	acute respiratory distress syndrome
ARV	antiretroviral
AST or SGOT	aspartate aminotransferase/serum glutamic-oxaloacetic transaminase
AT	as treated
ATP	adenosine triphosphate
ATU	Authorization for Temporary Utilization
ATV	atazanavir, BMS-232632
AUC	area under the curve
$AUC_{(0-24)}$	area under the curve from time zero to 24 hours later

AV	atrioventricular
Avg	average
BID	twice a day
B/L	baseline
BMS	Bristol-Myers Squibb
bpm	beats per minute
BUN	blood urea nitrogen
c/mL	copies (of RNA) per milliliter
CA	cancer
Cavg	average concentration
CD4	T cell type
CHF	congestive heart failure
CI	confidence interval
CK	creatinine kinase
C_{max}	maximum concentration
C_{min}	minimum concentration
CNS	central nervous system
COSTART	Coding Symbols for a Thesaurus of Adverse Reaction Terms
CSF	cerebrospinal fluid
Css	steady-state concentration
CT	computerized tomography
CV	cardiovascular
CYP	cytochrome P450
d4T	stavudine (Zerit®)
DCN	document control number
ddI	didanosine (Videx®)
DEXA	dual energy x-ray absorptiometry
dL	deciliter

EAP	Early Access Program
EC_{50}	dose of drug inhibiting virus replication by 50%
ECG	electrocardiogram
EFV	efavirenz (Sustiva®)
et al.	and others
FC	fold change
FDA	Food and Drug Administration
G-CSF	granulocyte colony-stimulating factor
GGT	gamma glutamyl transpeptidase
GLUT-1	glucose transporter
GLUT-4	insulin-sensitive glucose transporter
GST	glutathione-S-transferase isoform
h, hr	hour
HAART	highly active antiretroviral therapy
HDL	high density lipoprotein
HERG	human ether a-go-go related gene
HIV	human immunodeficiency virus
HL	asymptomatic hyperlactatemia
HPLC	high performance liquid chromatography
HTE	highly treatment-experienced
ICH	International Conference on Harmonization
IDV	indinavir (Crixivan®)
ISR	interim study report
ITT	intent to treat
IV	intravenous
Ki	inhibition rate constant
IC_{50}	dose of drug inhibiting virus replication by 50%
IV	intravenous

LAS	lactic acidosis syndrome
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LOCF	last observation carried forward
LOQ	limit of quantification
LPV	lopinavir
LPV/RTV	lopinavir/ritonavir (Kaletra®)
μg/mL	micrograms per milliliter
μM	micromolar
max or MAX	maximum
mg	milligram
mg/dL	milligrams per deciliter
mg/kg	milligrams per kilogram
mg/kg/day	milligrams per kilogram per day
min or MIN	minimum
mL	milliliter
mm^3	millimeters cubed
mmol/L	millimole per liter
msec	millisecond
n, N	number
NCEP	National Cholesterol Education Program
NFV	nelfinavir (Viracept®)
NFV⇒ATV	nelfinavir to atazanavir switch
ng	nanogram
ng·hr/mL	nanogram-hours per milliliter
ng/mL	nanograms per milliliter
nM	nanomolar
NIAID	National Institutes of Allergy and Infectious Diseases

NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NUC	nucleoside
NVP	nevirapine (Viramune®)
p	P-value
PACTG	Pediatric AIDS Clinical Trials Group
PD	pharmacodynamic
P-gp	P-glycoprotein
PI	protease inhibitor
PK	pharmacokinetic
PPT	plasma preparation tubes
PR	On an ECG tracing, the interval between the beginning of the P wave and beginning of the Q wave
QD	once a day
QRS	On an ECG tracing, the interval between the beginning of the Q wave and end of the S wave
QT	On an ECG tracing, the interval between the beginning of the Q wave and end of the T wave
QTc	On an ECG tracing, the interval between the beginning of the Q wave and end of the T wave, corrected for heart rate
QT_cB	On an ECG tracing, the interval between the beginning of the Q wave and end of the T wave, using Bazett's formula for heart rate correction
QT_cF	On an ECG tracing, the interval between the beginning of the Q wave and end of the T wave, using Fridericia's formula for heart rate correction
RBC	red blood cell
RNA	ribonucleic acid
RTV	ritonavir (Norvir®)
RT	reverse transcriptase
SAE	serious adverse event

SAT	subcutaneous adipose tissue
SE	standard error
SHL	symptomatic hyperlactatemia
SQV	saquinavir (Invirase®)
TAD	time-averaged difference
TAT	total adipose tissue
TdP	Torsades de Pointes
TFV	tenofovir (Viread®)
T-HALF	half-life
TID	three times a day
TLOVR	time to loss of virologic response
T_{max}	time to maximum concentration
UGT	uridine diphosphate glucuronosyl transferase
ULN	upper limit of normal
VAT	visceral adipose tissue
VR-C	virologic response - completers
VR-OC	virologic response - observed cases
VR-R	virologic response - randomized subjects
VR-T	virologic response - treated subjects
WBC	white blood cell
vs	versus
ZDV	zidovudine (Retrovir®)

Appendix 1: Atazanavir Clinical Development Program and Clinical Pharmacology Program

7 page(s) excluding cover page

Appendix 1: Atazanavir Clinical Development Program

Protocol Number	Population	Region	Treatment Regimens	Randomized/ Treated	Design
Phase III Studies					
AI424034	Naive	Africa, Asia, North and South America, Europe	ATV 400 mg QD or EFV 600 mg QD + ZDV/3TC	810/805	Double-blind, randomized, active controlled, 2-arms
AI424043	Experienced	Europe, North and South America	ATV 400 mg QD or LPV/RTV 400/100 mg BID + 2 NRTIs	300/290	Open-label, randomized, active controlled, 2-arms
AI424045	Highly Experienced "salvage"	Europe, North and South America	ATV/RTV 300/100 mg QD or ATV/SQV 400/1200 mg QD or LPV/RTV 400/100 mg BID + TFV/NRTI	358/347	Open-label, randomized, active controlled 3-arm study with a 2-week PI substitution lead-in phase
Phase II Studies					
AI424007	Naive	Europe, North and South America, Africa,	ATV (200, 400, or 500 mg) QD or NFV 750 mg TID + ddI/d4T	420/410	Open-label (blinded to ATV dose), randomized, active controlled, 4-arms
AI424008	Naive	Africa, Asia, Europe, North and South America	ATV (400 or 600 mg) QD or NFV 1250 mg BID + d4T/3TC	467/464	Open-label (blinded to ATV dose), randomized, active controlled, 3-arms
AI424009	Experienced	Europe, North and South America	ATV (400 or 600)/SQV 1200 mg QD or RTV 400 mg/SQV 400 mg BID + 2 NRTIs	85/82	Open-label (blinded to ATV dose), randomized, active controlled, 3-arms

Appendix 1: Atazanavir Clinical Development Program

Protocol Number	Population	Region	Treatment Regimens	Randomized/ Treated	Design
Rollover Studies					
AI424041	AI424007 or AI424009 completers	Africa, Europe, North and South America	Maintenance of therapy from prior study (ATV-treated subjects from AI424007 received ATV 400 mg QD)	NA/222	Non-randomized long-term maintenance study
AI424044	AI424008 completers	Africa, Asia, Europe, North and South America	Subjects on ATV in AI424008 remained on ATV; subjects on NFV switched to ATV 400 mg	NA/346	Non-randomized, long-term, comparator-switch study
Other Studies					
AI424020 (PACTG)	Pediatric Naive or Experienced	North America	ATV powder or capsule, dosage based on PK testing, as part of a standard-of-care HAART regimen	NA/48	Non-randomized, open-label study with dosing based on individual pharmacokinetic responses
AI424037 (Terminated)	Experienced (PI Naive)	Africa, North and South America	ATV 400 mg QD or NFV 1250 mg BID + 2 NRTIs	30/29	Double-blind, randomized, active controlled, 2-arms
AI424038 (NIAID)	Naive	North America	ATV 600 mg QD + ddI/d4T	NA/34	Non-randomized, open-label study in acute HIV or recent seroconversion
AI424049 (ADARC)	Experienced	North America	ATV 400 mg QD +ddI/d4T QD	23/23	Observational, randomized, open-label study to assess a once-a-day HAART
AI424069 (ACTG)	Experienced	North America	ATV 400 mg QD as part of a standard-of-care HAART regimen	NA/19	Open-label, 2-step study of PI-sparing regimens (Step 1) followed by ATV treatment after failure (Step 2)

Appendix 1: Atazanavir Clinical Development Program

Protocol Number	Population	Region	Treatment Regimens	Randomized/ Treated	Design
AI424074 (ANRS)	Experienced "salvage"	France	ATV/RTV 300/100 mg QD + TFV + 2 NRTIs	53/52	Open-label, randomized study with a 2-wk PI substitution lead-in phase
AI424900 (EAP/ATU)	Experienced "salvage"	Europe, North America	ATV 400 mg QD + standard-of-care HAART regimen	NA/389	Open-label, non-comparative, access program for high-need patients

Appendix 1 Clinical Pharmacology Program

Protocol (Country)	Study Design	Agent and Dose	Subjects (No. M/F) Age: Mean (range)	Endpoints
		SINGLE-DOSE STUDIES		
AI424001 (UK)	Randomized, double-blind placebo-controlled, cross-over, dose escalation, PK study.	ATV 100, 300, 600, 900, and 1200 mg QD	40 (40/0) 33 y (18 - 45)	Safety Tolerability PK, Bioavailability for capsule and prototype
AI424029 (USA)	Open-label, non-randomized study of PK, disposition of [^{14}C]-ATV.	^{14}C]-ATV 400 mg QD	12 (12/0) 33 y (20 - 50)	PK and elimination of ATV
		MULTIPLE-DOSE STUDIES		
AI424002 (UK)	Randomized, double-blind, placebo-controlled, ascending multiple dose study.	ATV 200, 400, 500, 600, 800 mg QD or 100, 200 mg BID	66 (66/0) 30 y (19 - 44)	Safety, Tolerability, and PK of ATV.
AI424040 (USA)	Open-label, randomized, 3-way crossover study.	ATV 200, 400, 800 mg QD	24 (22/2) 32 y (19 - 46)	Multiple-dose PK of ATV & effect on QTc interval.
AI424076 (USA)	Double-blind, randomized, placebo-controlled, multiple-dose, crossover study	ATV 400 or 800 mg QD	72 (54/18) 30 y (19 - 50)	To determine the effect of ATV on ECGs and QTc and PR intervals.

Appendix 1 Clinical Pharmacology Program

Protocol (Country)	Study Design	Agent and Dose	Subjects (No. M/F) Age: Mean (range)	Endpoints
		DRUG INTERACTION STUDIES		
AI424004 (USA)	Open-label, randomized, 4-way crossover PK study of ddI, d4T, ATV.	ATV 400 mg ddI 200 mg d4T 40 mg, All QD	32 (32/0) 32 y (19 - 49)	Effect of ATV on PK of ddI and d4T and vice-versa.
AI424012 (UK)	Open-label, randomized, dose-ranging PK study of ATV and SQV with a high fat meal.	ATV 400 mg SQV 800, 1200, 1600 mg All QD	24 (24/0) 31 y (20 - 45)	Effect of ATV on SQV PK.
AI424013 (USA)	Open-label, evaluation of ketoconazole on steady state PK of ATV.	ATV 400 mg Ketoconazole 200 mg All QD	16 (12/4) 28 y (19 - 47)	Effect of ketoconazole on ATV PK.
AI424016 (USA)	Open-label, non-randomized study between ATV and EFV.	ATV 400 mg EFV 600 mg All QD	31 (21/10) 32 y (18 - 56)	Effect of EFV on ATV PK.
AI424021 (USA)	Open-label, randomized, single sequence study of ATV and rifabutin with or without RTV.	ATV 400 or 600 mg Rifab.150 mg RTV 100 mg All QD	30 (24/6) 32 y (20 - 43)	Effect of rifabutin on ATV PK (with or without RTV).
AI424027 (USA)	Open-label, non-randomized, PK study of ATV and fixed dose 3TC/ZDV.	ATV 400 mg QD 3TC 150 mg + ZDV 300 mg BID	20 (19/1) 34 y (19 - 48)	Effect of ATV on ZDV or 3TC and effect of 3TC and ZDV on ATV PK.
AI424028 (USA)	Open-label, randomized study of ATV and RTV.	ATV 200 or 400 mg RTV 100 or 200 mg All QD	32 (32/0) 34 y (19 - 50)	Effect of RTV on ATV PK.
AI424030 (USA)	Open-label, non-randomized, multiple dose study.	ATV 400 mg OrthoNovum® 7/7/7 All QD	22 (0/22) 32 y (18 - 45)	Affect of ATV on PK of ethinyl estradiol or norethindrone.

Appendix 1 Clinical Pharmacology Program

Protocol (Country)	Study Design	Agent and Dose	Subjects (No. M/F) Age: Mean (range)	Endpoints
AI424033 (USA)	Open-label, randomized study of rifabutin and ATV with or without RTV.	ATV 400 or 600 mg Rifabutin 150 or 300 mg RTV 100 mg All QD	20 (16/4) 37 y (19 - 49)	Effect of ATV on rifabutin PK (with or without RTV).
AI424039 (USA)	Open-label, non-randomized, single-sequence study of ATV and EFV.	ATV 400 mg EFV600 mg RTV 200 mg All QD	20 (13/7) 37 y (23 - 49)	Effect of EFV and RTV on the steady-state PK of ATV.
AI424051 (USA)	Open-label, randomized, multiple dose study.	ATV 300, 400, 600 mg EFV 600 mg RTV 100 mg All QD	34 (32/2) 31 y (18 - 46)	Assess the effect of EFV with and without RTV on ATV PK.
AI424055 (USA)	Open-label, non-randomized, multiple dose study.	ATV 400 mg DLT 180 mg All QD	30 (19/11) 32 y (18 - 50)	Assess the effect of DLT and ATV on the PR interval.
AI424056 (USA)	Open-label, non-randomized, multiple dose study.	ATV 300 mg RTV 100 mg All QD	31 (23/8) 32 y (18 - 49)	Assess the effect of RTV and ATV on the QTc interval.
AI424057 (USA)	Open-label, non-randomized, multiple dose study.	ATV 400 mg Atenolol 50 mg All QD	20 (11/9) 36 y (21 - 50)	Assess the effect of Atenolol and ATV on the PR interval.
AI424058 (USA)	Open-label, non-randomized, multiple dose study.	ATV 400 mg QD clarithromycin 500 mg BID	30 (19/11) 31 y (18 - 47)	Assess the effect of clarithromycin and ATV on the QTc interval.

Appendix 1 Clinical Pharmacology Program

Protocol (Country)	Study Design	Agent and Dose	Subjects (No. M/F) Age: Mean (range)	Endpoints
		SPECIAL POPULATIONS		
AI424014 (USA)	Non-randomized, single-dose study on age and gender.	ATV 400 mg QD	60 (30/ 30) 15 Young females 28 y (19 - 39) 15 Elderly females 69 y (65 - 77) 15 Young males 25 y (19 - 39) 15 Elderly males 71 (65 - 81)	Effects of age & gender on ATV PK.
AI424015 (Germany)	Multiple center, open-label, non-randomized, single-dose study.	ATV 200 or 400 mg QD	32 (26/6) 54 y (40 - 68)	Effect of moderate to severe hepatic-impairment on ATV PK.
AI424011 (USA)	Open-label, non-randomized, deescalation study in subjects with previous hyperbilirubinemia.	ATV 600, 400, 200 mg QD	4 (4/0) 27 y (23 - 29)	Relationship of elevated total and unconjugated bilirubin and trough plasma concentrations (C_{min}).

Appendix 2: Nonclinical Pharmacology and Toxicology

9 page(s) excluding cover page

2 NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

2.1 Overview

The nonclinical safety profile of ATV has been extensively evaluated in safety pharmacology, pharmacokinetic/ADME, and toxicology studies using test systems and protocols accepted by ICH and international health authorities. ATV was well tolerated in rats, dogs, and mice with the liver identified as the principal target organ in all three species. In genotoxicity tests, ATV was positive in an *in vitro* cytogenetics assay (human peripheral blood lymphocytes) but was not mutagenic and did not cause DNA damage in three *in vivo* genotoxicity assays. Carcinogenicity studies are ongoing. ATV demonstrated no selective developmental toxicity and no effects on reproductive function or fertility in rats and/or rabbits. In the toxicology species, drug elimination was mainly by hepatic clearance, and biotransformation profiles were qualitatively similar across all species including humans.

Conclusions from the nonclinical evaluations are as follows:

- Safety pharmacology, pharmacokinetics, and toxicology studies were predictive of ATV's low potential for adverse effects in clinical trials.
- There were no nonclinical findings that preclude the marketing approval of ATV for the treatment of humans with HIV infection.

2.2 Safety Pharmacology Studies

ATV was evaluated in safety pharmacology studies to assess effects other than desired therapeutic activity. Effects on cardiovascular, CNS, and respiratory system functions were evaluated in a series of *in vitro* and *in vivo* studies.

In Vitro

Potential effects of ATV on cardiac action potential duration and cardiac ion channels (calcium, potassium, and sodium) were evaluated in a battery of *in vitro* studies at concentrations up to 30 μM. The results of these studies are as follows:

- ATV minimally increased action potential duration in the rabbit Purkinje fiber assay (APD_{90} increased 13% at 30 μM).
- ATV minimally inhibited cardiac sodium and potassium I_{Kr} (HERG-encoded) and I_{Ks} currents (IC_{50}s >30 μM).
- ATV moderately inhibited cardiac calcium current (IC_{50} = 10.4 μM).

Comparator HIV protease inhibitors (indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir were also evaluated in the rabbit Purkinje fiber and cardiac ion channel assays. These investigations showed that the other protease inhibitors also altered cardiac action potential duration and ion currents with equivalent or greater potency than ATV.

In Vivo

Potential effects of ATV on cardiovascular, CNS, and respiratory system functions were evaluated *in vivo* as components of the repeat-dose toxicity studies in rats and/or dogs:

- In dogs dosed orally with ATV for 2 weeks (90, 180, and 360 mg/kg/day), electrocardiographic changes (sinus bradycardia, prolongation of PR interval, prlongation of QT interval, and prolongation of QRS complex) were considered secondary to marked clinical toxicity (emesis and/or decreased food consumption leading to changes in serum electrolytes, body weight loss, and poor physical condition) and not to a direct effect of ATV.
- In dogs dosed orally with ATV for up to 9 months (90 mg/kg/day for 9 months; 180 mg/kg/day for 6 months), no signs of clinical toxicity occurred and no electrocardiographic changes were observed at plasma ATV concentrations comparable to those observed in the initial 2-week study. Plasma concentrations of ATV after 6 or 9 months of dosing rangedup to three times the Cmax and seven times the AUC in humans given 400 mg once daily.
- ATV had no effect on other cardiovascular parameters (ie, heart rate and heart sound) evaluated in dogs, and no effects on the function of the respiratory or central nervous system in rats (900 mg/kg/day for 6 months) and/or dogs.

The results from the *in vitro* cardiovascular assessments signaled the need for carefully designed clinical studies to assess potential cardiovascular risk.

2.3 Absorption, Distribution, Metabolism, and Excretion

The results of preclinical *in vitro* studies and *in vivo* pharmacokinetic/toxicokinetic studies in the mouse, rat, rabbit and dog with ATV are summarized below:

Absorption:

- Absolute oral bioavailability of ATV was 15.2% (PEG-400 suspension) in rats and 36.3% (capsules) in dogs, suggesting incomplete intestinal absorption and/or extensive first-pass metabolism of ATV.
- ATV may be a substrate for an apically located efflux pump (eg, P-glycoprotein, P-gp) and a weak inhibitor of P-gp with an IC_{50} value of ~29 μM based on *in vitro* Caco-2 cell model studies. P-gp inhibition by ATV may be of minimal clinical consequence as this effect has been noted at concentrations several-fold higher than the steady-state peak plasma concentrations in humans.

Distribution:

- The steady-state volume of distribution in rats (1.62 L/kg) and dogs (range 0.76 -2.45L/kg) was greater than the total body water indicating extravascular distribution and/or tissue protein binding.
- Drug-related radioactivity was extensively distributed. ATV-derived radioactivity was secreted in milk and also distributed to fetal tissues of the rat, suggesting placental transfer of the drug.
- The *in vitro* binding of ATV to mouse, rat, dog, and human serum proteins was comparable ranging from 86.5 - 92.8%. The human serum protein binding (86.5%) was not extensive and indicate that there is minimal potential for drug interactions in humans due to displacement of protein bound drugs, when co-administered with ATV.

Metabolism:

- The metabolic pathways of ATV in rats, dogs, and humans (see Clinical PK Section 4) are similar and involve monooxygenation, dioxygenation, glucuronidation, N-dealkylation, hydrolysis, and oxygenation with dehydrogenation.

- A major elimination pathway for ATV appears to be cytochrome P-450 (CYP)3A4-mediated conversion to oxygenated metabolites and excretion in the bile as either unchanged drug or metabolites.
- ATV is a moderate inhibitor of CYP3A4 (Ki = 2.35 μM) and uridine diphosphate-glucuronosyl transferase (UGT)1A1 (Ki = 1.9 μM) and may have the potential to alter the metabolic clearance of drugs that are metabolized by CYP3A4 and/or conjugated by UGT1A1.
- Three minor, circulating metabolites of ATV, BMS-421419, BMS-551160, and an unidentified keto metabolite [M41], have been detected in the rat and dog and also in humans.
- BMS-421419 and BMS-551160 are formed via N-dealkylation. Both metabolites are inactive against HIV and show no appreciable CYP inhibition considered to be of clinical concern. In addition, neither metabolite was more potent than ATV in inhibiting cardiac action potential or cardiac sodium, calcium, or potassium currents *in vitro*. Based on these findings, BMS-421419 and BMS-551160 are considered to be minor metabolites of ATV that are of no toxicological concern. The structure of the M41 metabolite is currently being confirmed via synthesis, therefore further characterization of this metabolite has not been conducted.
- Exposures to ATV metabolites BMS-421419 and BMS-551160 have been detected in most toxicology species, with systemic exposures to BMS-421419 being higher and exposures to BMS-551160 being lower in the animal species compared to relative exposures in humans.

Elimination:

- Minimal radioactivity (< 10%) was recovered in the urine and a substantial recovery (> 65%) was noted in the feces (following IV administration) suggesting that the major route of excretion of ATV and its metabolite(s) is via the bile.
- Terminal ATV elimination half-life (with intravenous administration), was 0.94 in the rat and 0.45 h in the dog.

2.4 Target Organ Toxicity

The nonclinical repeat-dose toxicity of ATV was evaluated in studies in rats, dogs, and mice of up to 9 months duration. ATV-related findings in all three species were generally confined to the liver and are described below:

2.4.1 Rat

- Minimal increases in serum total bilirubin (≥ 300 mg/kg/day)
- Minimal to moderate increases in liver weights and associated minimal to mild hepatocellular hypertrophy (≥ 100 mg/kg/day), which were considered an adaptive response consistent with hepatic enzyme induction
- Pale livers (900 mg/kg/day) and minimal to moderate hepatocellular cytoplasmic vacuolation (lipid) (≥ 100 mg/kg/day)
- No progression in hepatic alterations with longer (6 months) dosing; all effects were reversible after 2 months recovery except that liver weights in females at 900 mg/kg/day remained minimally increased.

In rats, none of the ATV-induced hepatic changes were accompanied by elevations in serum transaminases or microscopic evidence of cholestasis or degenerative liver changes. Female rats were more affected than males, which corresponded to higher systemic exposures to ATV. Systemic exposures (AUC) to ATV in male rats administered 900 mg/kg/day for 6 months, a well-tolerated dose producing no cytotoxic organ changes, are equivalent to exposure in humans given 400 mg once daily; those in female rats are four times the human exposure.

2.4.2 Dog

- Minimally increased serum total bilirubin (≥ 30 mg/kg/day)
- Minimally increased gamma glutamyltransferase (≥ 30 mg/kg/day) and minimally to moderately increased serum alkaline phosphatase (≥ 90 mg/kg/day) in individual animals
- Minimally increased liver weights (≥ 90 mg/kg/day)
- Minimal to moderate increases in alanine and aspartate aminotransferases were observed in dogs after 2 weeks of dosing (90, 180, and 360 mg/kg/day); similar changes not seen with longer treatment at comparable doses.

No drug-related gross or microscopic liver changes or microscopic evidence of cholestasis were observed in any of the studies in dogs. Systemic exposures (AUC) to ATV in dogs administered 180 mg/kg/day for 6 months, a well-tolerated dose producing

no cytotoxic tissue changes, are approximately two (males) and seven (females) times, respectively, exposure in humans given 400 mg once daily.

2.4.3 Mouse

- Mild increases in serum total bilirubin, minimal to marked increases in liver weights and hepatocellular hypertrophy, hepatocellular cytoplasmic vacuolation (lipid), and pale livers [40 (males) and 160 (females) mg/kg/day]
- Increased cellular glycogen [80 (males) and 640 (females) mg/kg/day]
- Hepatotoxicity [80 (males) and 640 (females) mg/kg/day], characterized by minimal to moderate elevations in serum transaminases and a low incidence of minimal hepatocellular single-cell necrosis in females

Systemic exposures (AUC) in male and female mice at the well-tolerated doses [40 (males) and 160 (females) mg/kg/day] are slightly below to four times, respectively, the exposure in humans given 400 mg once daily. The doses resulting in hepatotoxicity [80 (males) and 640 (females) mg/kg/day] produced exposures equivalent to those seen in humans (male mice) and 12 times those seen in humans (female mice), respectively. The high exposure to ATV in female mice may account in part for the increased hepatotoxicity.

In humans, elevations in total bilirubin (primarily indirect, unconjugated) was the most frequent laboratory abnormality observed on ATV-containing regimens and predicted in all toxicology animal species. ATV-induced hyperbilrubinemia is attributed to competitive inhibition of the UGT 1A1 enzyme, which is responsible for conjugation/glucoronidation of bilirubin.

Additional drug-related effects, which were not associated with target organ (liver) toxicity, were observed in female mice. These findings consisted of the following:

- Mild to moderate decreases in platelet counts (≥ 160 mg/kg/day)
- Minimal to mild increases in leukocytes, neutrophils, and lymphocyte counts (640 mg/kg/day) and morphologic changes in erythrocytes (640 mg/kg/day)
- Increased spleen weight and size and histologic evidence of increased splenic and hepatic extramedullary hematopoiesis in females (≥ 160 mg/kg/day), which were

interpreted as secondary effects related to the reduced platelet counts rather than direct drug effects.

A clinical or morphologic basis for the reduction in platelets was not determined. All of the ATV-induced hematological changes, which were limited to female mice, have no established clinical relevance as systemic exposures at doses producing these alterations were high (four to 12 times human exposure at the human dose of 400 mg per day), and similar consistent changes were not observed in rats and dogs treated chronically with ATV. Importantly, there have been no reports of thrombocytopenia in patients treated with ATV for over 1 year.

2.5 Genetic Toxicity

The genotoxic potential of ATV was evaluated in a battery of well established and validated *in vitro* and *in vivo* tests that fulfill registrational requirements. In the *in vivo* tests, ATV was administered up to the maximum dose (2000 mg/kg) recommended by international health authorities. The results of the *in vitro* and i*n vivo* genotoxicity studies are summarized below:

2.5.1 *In vitro* tests

- ATV was not mutagenic in an *in vitro* Ames assay at concentrations up to 2500 μg/plate.
- ATV was positive for clastogenicity in a peripheral human blood lymphocyte assay in both the absence (≥ 30 μg/ml) and presence (≥ 240 μg/ml) of metabolic activation. No increase in chromosomal aberrations was seen at a concentration (15 μg/ml) that, in the absence of metabolic activation, was approximately 3 times the maximum plasma concentration in humans given 400 mg once daily.

2.5.2 *In vivo* tests

- ATV did not induce DNA damage in an *in vivo* micronucleus study in rats at oral doses up to 2000 mg/kg. Plasma ATV exposures (Cmax and/or AUC) reached concentrations that were clastogenic *in vitro* (30 μg/ml) and were 1.5 (males) to 12 (females) times the exposure in humans given 400 mg once daily.
- ATV did not induce DNA damage in an *in vitro-in vivo* DNA repair study using hepatocytes from rats dosed orally up to 2000 mg/kg. The highest ATV liver

concentration was 6 times the lowest *in vitro* clastogenic concentration (30 µg/ml) and 33 times the peak plasma concentration in humans given 400 mg once daily.

- ATV did not induce DNA damage in duodenal cells from rats dosed orally up to 2000 mg/kg in an *in vivo* single-cell gel (comet) assay. The maximum concentration of ATV in the duodenum was 86 times the lowest *in vitro* clastogenic concentration (30 µg/ml) and 480 times the peak plasma concentration in humans given 400 mg once daily.

In summary, ATV was not mutagenic in the *in vitro* Ames assay but did induce chromosomal aberrations *in vitro* in both the presence and absence of metabolic activation. The mechanism for the *in vitro* clastogenicity is unknown. However, the fact that ATV did not produce DNA damage in a variety of rodent tissues *in vivo* (ie, bone marrow, liver, and duodenum) at plasma and tissue concentrations exceeding those that were clastogenic *in vitro* suggests the mechanism for the *in vitro* clastogenicity may not be biologically significant in animals and humans or has a threshold. Further, relevant tissue exposures in these *in vivo* studies significantly exceeded the plasma exposures in human patients under therapeutic conditions. Thus, based on the weight of evidence ATV does not pose a genotoxic risk to humans at therapeutic doses and exposures.

2.6 Reproductive and Development Toxicity

A complete battery of reproductive toxicity studies was conducted with ATV. The results from these studies are discussed below:

- In the fertility and early embryonic development study in rats, ATV altered estrous cycling at doses ≥ 100 mg/kg/day but had no effects on mating, fertility, or early embryonic development at doses up to and including 1400 mg/kg/day.
- In the embryo-fetal development studies in rats and rabbits, ATV produced no embryonic or fetal effects at maternally toxic doses (1920 mg/kg/day in rats and 60 mg/kg/day in rabbits).
- In the pre- and postnatal development assessment in rats, ATV-related findings were limited to mean body weight gain suppression in the F_1 generation from 4 days of age through the early postweaning growth period at the maternally toxic dose of 1000 mg/kg/day. This finding was considered likely to be secondary to the maternal body weight reduction rather than a direct effect of ATV. ATV had no effect on reproductive performance of the F_1 generation.

In conclusion, ATV demonstrated no selective developmental toxicity and no effects on reproductive function or fertility in rats and/or rabbits. Exposures were at least equal to or slightly greater than that observed in humans given 400 mg once daily.