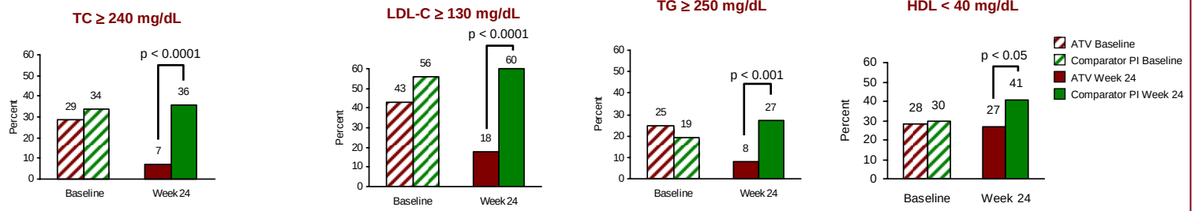
RESULTS (Cont'd)

Lipids

Figure 4. Lipid Levels Categorized by NCEP ATP III Guidelines



TC, Mean mg/dL	ATV	Comparator PI
Baseline	246	287
Week 24	209	281

Week 24 Mean % change from Baseline	ATV	Comparator	p Value
TC	-16%	+1%	p< 0.0001

LDL-C, Mean mg/dL	ATV	Comparator PI
Baseline	123	141
Week 24	103	135

Week 24 Mean % change from Baseline	ATV	Comparator	p Value
Fasting LDL-C	-16%	-5%	p < 0.01

TG, Mean mg/dL	ATV	Comparator PI
Baseline	204	201
Week 24	125	191

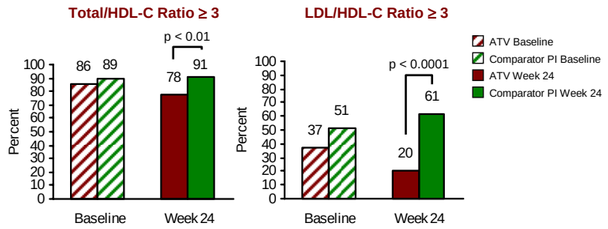
Week 24 Mean % change from Baseline	ATV	Comparator	p Value
TG	-38%	+1%	p< 0.0001

HDL-C, Mean mg/dL	ATV	Comparator PI
Baseline	50	50
Week 24	51	51

Week 24 Mean % change from Baseline	ATV	Comparator	p Value
HDL-C	+1%	-1%	p = NS

NS = Not Significant

Figure 5. Lipid Ratios Categorized by NCEP ATP III Guidelines



- For subjects initiating lipid-lowering therapy, subsequent lipid data were censored from the lipid analyses
- Subjects in the ATV arm experienced significant reduction of all measured atherogenic lipid fractions through week 24 (see Figure 4); the difference in mean percent change from baseline for non-HDL-C was -22% in the ATV arm vs 0% in the Comparator PI arm (p<0.0001)
- The percentage of subjects on lipid-lowering therapy prior to the study was comparable between the ATV and Comparator PI arms (8% vs 9%, respectively); however at week 24 the use of lipid-lowering agents was lower in subjects switching to ATV (8% vs 13%, p = NS)
- Median fasting glucose levels were comparable between the ATV and Comparator PI groups at baseline (89 mg/dL in the ATV group and 87 mg/dL in the Comparator PI group). No change in mean fasting glucose was observed for those who switched to ATV or remaining on unmodified therapy at week 24

Discussion

- In a study population with significant ARV experience, but no known previous PI virologic failures, a switch to ATV from a stable PI regimen demonstrated a statistically significant reduction in the risk of VReb at week 24
  - Differences in favor of the ATV arm were consistent throughout the multiple efficacy analyses conducted in this study
  - Fifty-five percent of subjects in the ATV arm switched from a RTV-boosted PI at study entry, with 36% of all subjects switching from LPV/RTV
- No relevant differences were observed for SAEs (other than deaths) or AEs leading to discontinuation
- Although hyperbilirubinemia was frequent in the ATV arm, only 1% of subjects discontinued due to ocular icterus or jaundice
- ALT and AST elevations were infrequent in those switching to ATV and were comparable to the control arm, also within those with HBV/HCV co-infection
- Atherogenic lipid parameters decreased significantly with lower use of lipid-lowering agents in the group switching to ATV as compared with those continuing other protease inhibitors (8% vs 13%, p = NS)

CONCLUSIONS

- The proportion of subjects with virological rebound at week 24 met the criteria for non-inferiority (ATV - Comparator PI) for subjects switching to an ATV-containing regimen
- The safety was comparable between arms, with less gastrointestinal events (and significantly less use of anti-diarrheal agents) in the ATV switch arm. Discontinuations due to ocular icterus/jaundice on ATV were infrequent
- Switching to an ATV-containing regimen resulted in a significant improvement in lipid parameters (and less use of lipid-lowering agents)
- Preliminary 24-week data from this 48-week study demonstrates that switching to ATV is a safe and efficacious option. Additional analyses through week 48 will be conducted to confirm these results

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Efficacy of Atazanavir (ATV) Based HAART in Patients Switched From a Stable PI or Boosted PI (PI/r) Treatment. Planned Week 24 Analysis of a Phase IIIb 48-Week Multicenter, Open-label, Randomized, Prospective Study: The SWAN Study

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Poster # WePe6.3C15

BACKGROUND

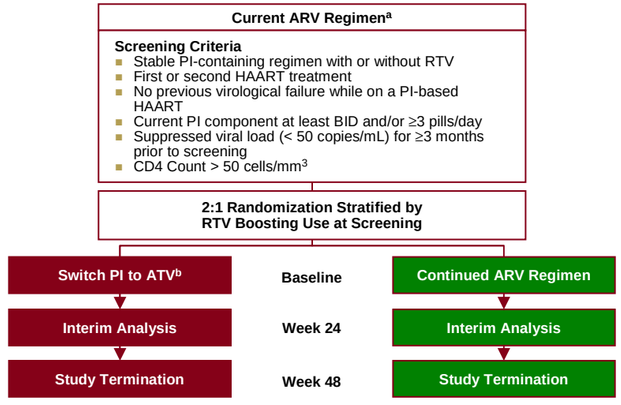
- Atazanavir (ATV) is a potent, well-tolerated, once-daily (QD) HIV protease inhibitor (PI) extensively studied in naive and experienced patients
- In a Phase IIIB trial (AI424-044), virologic suppression was maintained or improved after switching patients with low viral load from the PI nelfinavir to QD ATV. In addition, improvement in lipid parameters (total cholesterol [TC], fasting low-density lipoprotein cholesterol [LDL-C], fasting triglycerides [TG]) was demonstrated in clinical trials and cohort studies for the patients switched to ATV-containing HAART. Similar findings were observed in trial AI424-067, where patients with hyperlipidemia but virologically controlled had the PI component in a variety of non-ATV containing PI-based regimens switched to ATV
- Limitations of other PI-based regimens include a higher frequency of gastrointestinal side effects, dyslipidemia, greater pill burden and the potential for increased polypharmacy due to the frequent necessity of concomitant anti-diarrheal or lipid-lowering medications
- Regimen simplification may lead to improved adherence, a reduced risk of antiretroviral-resistance, and less potential for drug interactions
- The current trial (AI424-097) was designed to evaluate the efficacy and safety of a switch to ATV (or ATV/ritonavir [RTV] if in association with tenofovir disoproxil fumarate [TDF]) in HIV-infected patients experiencing virologic suppression but seeking regimen simplification

OBJECTIVES

- Primary
  - Compare the proportion of subjects with virologic rebound (VReb) ≥ 50 copies/mL through 48 weeks between subjects who switch to an ATV-containing HAART regimen and those who remain on an unmodified PI-containing HAART regimen
- Secondary
  - Time to VReb for subjects with HIV RNA < 50 copies/mL at baseline
  - Magnitude of change from baseline in CD4 count
  - Frequency and severity of all clinical and laboratory adverse events (AEs), and discontinuations for AEs
  - Percentage of subjects with viral load > 1,000 copies/mL
  - Changes from baseline in fasting lipids
    - TC
    - LDL-C
    - HDL Cholesterol (HDL-C)
    - Non-HDL Cholesterol (non-HDL-C)
    - TG
  - Changes in fasting glucose

METHODS

Figure 1: Study Design



[a] Comparator PI(s) (with or without RTV at a dose of 200 mg or less) + backbone
[b] ATV 400 mg QD + unchanged backbone. Only when TDF was part of the backbone, ATV/RTV 300/100 mg QD was used

Statistical Analyses

- The study was designed with 90% power to demonstrate non-inferior rates of VReb between the two regimens for the primary analysis, comparing the proportions of subjects with VReb at week 48. The ATV regimen was declared to be non-inferior to the Comparator PI regimen if the upper limit of the 95% CI for the difference in proportions was < 12%. A minimum of 372 subjects randomized in a 2:1 ratio provided at least 90% power to demonstrate non-inferiority for the primary analysis. The present report includes results of the planned week 24 interim analysis
- Study population was stratified by use of boosted vs unboosted PI at randomization
- Efficacy and lipid analyses included data through 24 weeks for all randomized subjects. Mean percent changes from baseline and standard errors for lipid parameters were computed on the log scale and back transformed
- Safety analyses included all data available through time of analysis for all treated subjects until last patient reached 24 weeks. Serious AEs (SAEs) and deaths were included without regard to treatment status at time of onset for enrolled subjects

RESULTS

Demographics, Prior Antiretroviral History and Disposition

Table 1: Subject Demographics

	Treatment Regimen		
	ATV N = 278	Comparator PI N = 141	Total N = 419
Age			
Median (Min, Max)	40 (18, 68)	41 (23, 74)	40 (18, 74)
Gender			
Male, % (n)	84 (234)	79 (111)	82 (345)
Female, % (n)	16 (44)	21 (30)	18 (74)
Race			
White, %	88	88	88
Black/Mixed, %	9	11	9
Other, %	3	1	2
AIDS, %	27	30	28
Baseline HIV RNA: Median (log_{10} c/mL) (Min, Max)	1.69 (1.69, 3.64)	1.69 (1.69, 4.80)	1.69 (1.69, 4.80)
Baseline HIV RNA <50 copies/mL, % (n)	93 (259)	94 (133)	94 (392)
Baseline CD4: Median (cells/mm^3) (Min, Max)	492 (83, 1645)	489 (115, 1388)	491 (83, 1645)
Co-infection HCV and/or HBV, % (n)	32 (80)	31 (38)	31 (118)
Baseline Cardiovascular Risk Factors ≥ 1, %	68	72	69

Table 2: Prior Antiretroviral History

	Treatment Regimen		
	ATV	Comparator PI	Total
Years on Prior PI Therapy (mean (SE))	3.4 (0.13)	3.3 (0.18)	3.4 (0.10)
- Subjects on PI with RTV at baseline (%)	55	54	54
- Subjects on lopinavir(LPV)/RTV at baseline (%)	36	38	37
- Subjects on PI without RTV at baseline (%)	45	46	46
Years on Prior NRTI Therapy (mean (SE))	4.0 (0.16)	3.7 (0.22)	3.9 (0.13)
- Subjects on TDF at baseline (%)	9	8	9
Years on Prior NNRTI Therapy (mean (SE))	1.4 (0.16)	1.1 (0.25)	1.3 (0.14)
- Subjects on NNRTI at baseline (%)	0	0	0

Note: Baseline data includes subjects having prior ARV experience up to 90 days from the dose start date

Table 3: Subject Disposition*

	Treatment Regimen		
	ATV	Comparator PI	Total
Randomized Subjects	278	141	419
Treated – n (%)	274 (99)	133 (94)	407 (97)
Discontinued[a] Prior to Week 24 – n (%)	22 (8)	9 (6)	31 (7)
Adverse Event	11(4)	1 (<1)	12 (3)
Lack of Efficacy	1 (<1)	0	1 (<1)
Death	0	1 (<1)	1 (<1)
Subject Withdrew Consent	2 (<1)	4 (3)	6 (1)
Other[b]	8 (3)	3 (2)	11 (3)
Discontinued[a] on or after Week 24 – n (%)	13 (5)	13 (9)	26 (6)
Adverse Event	5 (2)	5 (4)	10 (2)
Lack of Efficacy	0	1 (<1)	1 (<1)
Death	0	3 (2)	3 (<1)
Subject Withdrew Consent	1 (<1)	1 (<1)	2 (<1)
Other[b]	7 (3)	3 (2)	10 (2)
Completed Study through Week 48	25 (9)	8 (6)	33 (8)
Continuing on Treatment – n (%)	214 (77)	103 (73)	317 (76)

* At time of interim analysis
[a] Reason for discontinuation per investigator assessment
[b] Includes: lost to follow-up, poor/non-compliance, pregnancy, subject no longer meets study criteria and other

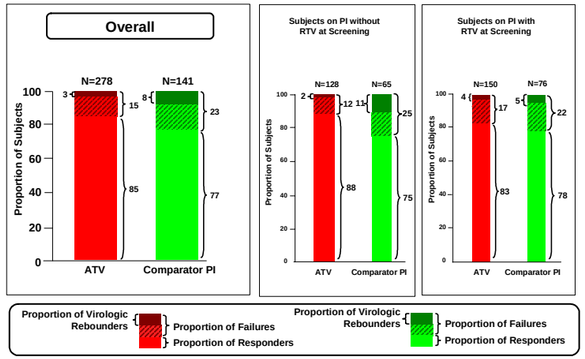
- Mean time on study therapy was 29 weeks for both regimens at the time of this interim analysis
- More subjects in the Comparator PI arm discontinued before starting treatment after learning their random assignment to continue unmodified therapy

Efficacy

- The efficacy analysis at week 24 demonstrated that the proportion of subjects with VReb at week 24 was significantly lower in the ATV group (3%; 8/278) than in the Comparator PI group (8%; 11/141) (pairwise difference ATV- Comparator PI, -4.9; 95% CI: -9.1, -0.7; p < 0.05)
  - To account for the higher post-randomization pre-treatment dropout rate for those subjects assigned to continue on unmodified therapy, two sensitivity analyses were performed for the primary endpoint. The first analysis assumed no VReb for subjects leaving the Comparator PI arm but not for subjects in the ATV arm. The second analysis was conducted on the treated (as opposed to randomized) population. Both analyses confirmed the efficacy of the switch to ATV

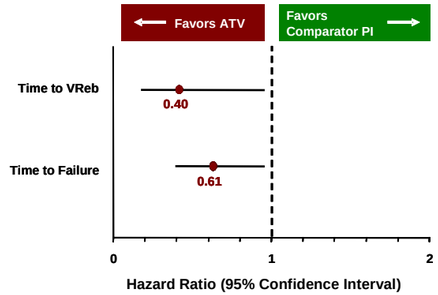
RESULTS (Cont'd)

Figure 2. Proportion of Virologic Rebounders† and Failures‡



† VReb = 2 consecutive HIV RNA levels (or last one only before discontinuation) ≥ 50 copies/mL
‡ Failure = VReb, never initiating study therapy, or discontinuation of study therapy

Figure 3. Overall Hazard Ratio Estimates* for Time to Virologic Rebound and Time to Failure



*Overall hazard ratio is stratified by screening PI:
Time to VReb = 0.40 (0.17, 0.97); Time to Failure = 0.61 (0.39, 0.95)

- Hazard ratios (95% CI) for VReb [ATV:Comparator PI] in the unboosted PI and boosted PI strata were 0.21 (0.05, 0.81) and 0.73 (0.21, 2.59), respectively
- Changes in CD4 counts were similar across treatment groups with a mean change of +12 cells/mm^3 in the ATV arm and +15 cells/mm^3 in the Comparator PI arm

Safety

Table 4. Key Safety Results

	ATV N = 274	Comparator PI N = 133
Deaths – n (%)	0	5 (4)[a]
Other SAEs – n (%)	22 (8)	9 (6)
AEs leading to discontinuation – n (%)	16 (6)	6 (5)
Grade 2-4, Treatment-related AEs ≥ 2%		
Ocular icterus	8 (3)	0
Jaundice	6 (2)	0
Abdominal pain	2 (< 1)	2 (2)
Diarrhea	0	2 (2)
Grade 3-4 Lab Abnormalities – n/evaluable (%)		
Neutrophil reduction	5/262 (2)	2/127 (2)
ALT elevation	11/272 (4)	6/130 (5)
AST elevation	5/272 (2)	3/130 (2)
Total bilirubin elevation	103/272 (38)	3/130 (2)
Hepatitis Co-infected		
– ALT elevation	11/79 (14)	4/38 (11)
– AST elevation	5/79 (6)	3/38 (8)
– Total bilirubin elevation	36/79 (46)	2/38 (5)

[a] Deaths (n) in the Comparator PI related to septic shock (1), malignancy (1), depression (1), and overdose of a narcotic drug (1). No information on causality could be obtained for the fifth death

- The switch to ATV (vs Comparator PI) did not lead to an increase in the discontinuation rates due to AEs (6% vs 5%), or the incidence of SAEs (8% vs 6%) or deaths (0% vs 4%)
- On-treatment emergent AEs of any grade related to gastrointestinal toxicity (diarrhea, nausea, vomiting or abdominal pain) were higher on the Comparator PI arm than in subjects switching to ATV: 15/133 (11%) in the Comparator PI arm vs 17/274 (6%) in the ATV arm (p = NS). The use of anti-diarrheal agents for subjects who switched to ATV was significantly lower than for the Comparator PI arm (2% vs 7%, p < 0.05)
- Grade 3-4 ALT or AST elevations occurred with similar frequency in both arms. A higher incidence of ALT and AST elevations occurred in co-infected subjects, with similar frequency across treatment groups
- Grade 3-4 elevations in total bilirubin were reported in 38% of the subjects on ATV and in 2% of the subjects on the Comparator PI. Elevations in total bilirubin for subjects with ALT or AST elevations were experienced by 3% of subjects in the ATV arm and no subjects in the Comparator PI arm
- Jaundice or ocular icterus of any grade (27/274 [10%]) was reported for subjects on ATV, with only 3 cases (1%) of grade 3-4 jaundice or ocular icterus. One percent of subjects in the ATV arm discontinued due to ocular icterus or jaundice