Atazanavir/Ritonavir (ATV/r) + Abacavir/Lamivudine (ABC/3TC) in Antiretroviral (ART)-Naïve, HIV-1 Infected, *HLA-B*5701* Negative Subjects Demonstrates Efficacy and Safety: the ARIES Trial

H-1250a

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Abstract

Background: Results from ACTG A5202 have raised questions of a higher rate of virologic failure (VF) in subjects on ABC/3TC with a baseline (BL) HIV-1 RNA (vRNA) ≥100,000 c/mL. ARIES was enrolled concurrently with and utilizes the same regimen as one arm of A5202.

Methods: Subjects with screening vRNA ≥1000 c/mL and any CD4+ enrolled in this open-label study of ATV/r + ABC/3TC followed by randomization (1:1) at Week (Wk) 36 to maintain or drop RTV. Study-defined VF was failure to achieve vRNA <400 c/mL by Wk 30 or confirmed rebound ≥400 c/mL. Additional analysis of A5202 primary efficacy endpoint (vRNA ≥1000 c/mL at/after Wk 16 and before Wk 24 or confirmed rebound ≥200 c/mL at/after Wk 24) was conducted.

Results: 515 subjects (ITT-E) included in this non-comparative pre-planned analysis: median age 38; 83% male; 62% white; 13% CDC Class C; vRNA 5.08 $\log_{10}$ c/mL; CD4+ 199 cells/mm^3. Drug-related Grade 2-4 clinical AEs were reported in 142 (28%), most commonly hyperbilirubinemia (13%) and diarrhea (4%).

Week 36 Results, n/N (%)	ABC/3TC + ATV/r N=515
vRNA<50/200 c/mL, TLOVR	410/515 (80%)/422/515 (82%)
BL vRNA <100,000 c/mL	190/227 (84%)/193/227 (85%)
BL vRNA≥100,000 c/mL	220/288 (76%)/229/288 (80%)
Utilizing A5202 primary efficacy endpoint	96.5%
BL vRNA <100,000 c/mL	98.1%
BL vRNA≥100,000 c/mL	95.1%
VF	15/515 (3%)
CD4+ cell count (Δ BL)	+171 cells/mm^3

Of 15 cases of VF, 5 and 10 occurred in the <100,000 c/mL and ≥100,000 c/mL strata, respectively.

Conclusions: The combination of ABC/3TC + ATV/r demonstrated potent antiviral activity through 36 weeks of follow-up in this population of ART-naïve subjects. Based on the ACTG A5202 endpoint, similar virologic success rates were achieved irrespective of VL strata.

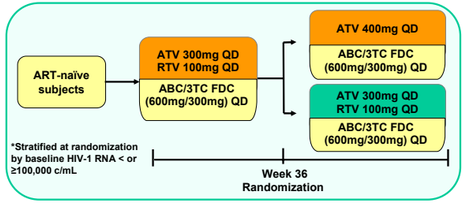
Introduction

- ARIES is designed as a treatment strategy study to assess the efficacy and safety of a simplification regimen of abacavir (ABC)/lamivudine (3TC) + atazanavir (ATV) after an induction regimen of ABC/3TC + ATV/ritonavir (RTV, r) in antiretroviral (ART)-naïve patients.
- Interim results from the AIDS Clinical Trials Group (ACTG) A5202 have raised questions of an elevated rate of virologic failure (VF) in subjects on ABC/3TC with a baseline (BL) HIV-1 RNA (vRNA) ≥100,000 copies/mL (c/mL).[1]
- ARIES was enrolled concurrently with A5202 and evaluates one of the same regimens (ATV/r + ABC/3TC) used in A5202.
- A planned 36 Week interim analysis was performed to assess the efficacy and safety of ATV/r in combination with ABC/3TC in ART-naïve subjects.

Methods

- ARIES subjects were ART-naïve, HIV-1 infected, *HLA-B*5701* negative, with plasma vRNA ≥1000 c/mL at the time of screening and no CD4+ cell count restrictions.
- The primary endpoint is the proportion of subjects achieving vRNA <50 c/mL at Week 84 by time to loss of virologic response (TLOVR) analysis.
- Protocol-specified VF was defined as failure to achieve vRNA <400 c/mL by Week 30 or confirmed rebound ≥400 c/mL after achieving <400 c/mL.
- A pre-planned Week 36 non-comparative interim analysis was performed to evaluate efficacy and safety.
- An additional analysis utilizing the A5202 VF definition (vRNA ≥1000 c/mL at or after Week 16 and before Week 24 or confirmed rebound ≥200 c/mL at Week 24) was performed to determine the proportion of responders through Week 36 by baseline VL stratification (<100,000 c/mL and ≥100,000 c/mL) .

Figure 1. Study Design



Results

Table 1. Baseline Characteristics, ITT-E Population

	ABC/3TC + ATV/r N=515 n (%)
Mean age, years	38
Male	429 (83%)
Race and Ethnicity	
White/Caucasian	321 (63%)
African American	167 (32%)
Other	27 (5%)
Hispanic or Latino	95 (18%)
Hepatitis Status	
Hepatitis B	1 (<1%)
Hepatitis C	33 (6%)
Median baseline plasma HIV-1 RNA ($\log_{10}$ c/mL)	5.08
vRNA <100,000 c/mL	227 (44%)
vRNA ≥100,000 c/mL	288 (56%)
Median baseline CD4+ cell count (cells/mm^3)	199
<50 cells/mm^3	69 (13%)
50 to ≥200 cells/mm^3	190 (37%)
>200 cells/mm^3	256 (50%)

Table 2. Subject Disposition, ITT-E Population

	ABC/3TC + ATV/r N=515 n (%)
Completed	442 (86%)
*Entered into Randomization Phase	419 (81%)
Subject Withdrawals by Week 36	73 (14%)
Adverse event	16 (3%)
Lost to follow-up	16 (3%)
Insufficient viral load response	11 (2%)
Noncompliance	9 (2%)
Other	9 (2%)
Subject decision	7 (1%)
Protocol defined virologic failure[1]	5 (<1%)

*Not all subjects who completed 36 weeks met criteria for randomization.
1. As per investigator reason noted on the Case Report Form (CRF).

Figure 2. Proportion of Subjects with vRNA <50 c/mL and <400 c/mL through Week 36, ITT-E Population

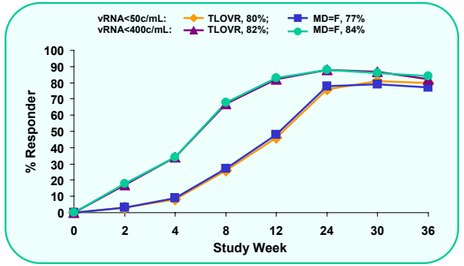
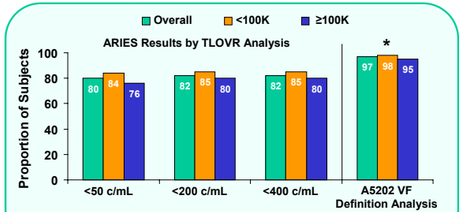


Figure 3. Overall and Stratified Results for ARIES by Baseline Viral Load through Week 36, ITT-E Population



*The data depicted here are for the ARIES results, using the A5202 VF definition (vRNA ≥1000 c/mL at or after Week 16 and before Week 24 or confirmed rebound ≥200 c/mL at Week 24)

- Median CD4+ cell counts at Week 36 were 372 cells/mm^3.

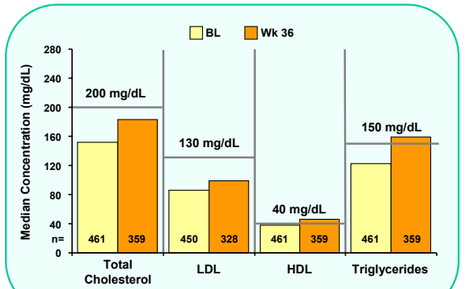
Protocol-Defined Virologic Failure

Table 3. Proportion of Subjects with Protocol-Defined Virologic Failure

	ABC/3TC + ATV/r N=515 n/N (%)
Protocol Defined Virologic Failure	15 (3%)
Failure to achieve <400 c/mL by Week 30	5 (<1%)
Confirmed rebound after achieving <400 c/mL	10 (2%)

- Treatment interruption or non-compliance was reported for 11/15 of the subjects with VF.
- No major PI mutations emerged on treatment for subjects meeting VF criteria.
- Treatment emergent NRTI mutations (4/15, 27%) were primarily M184I/V or mixes.
- 14/15 (93%) subjects with VF had viral isolates phenotypically susceptible to all study drugs; isolate in 1 subject exhibited reduced susceptibility to 3TC at time of VF.

Figure 4. Summary of Median Fasting Lipid Changes, Safety Population



Acknowledgements

The authors would like to extend their thanks to the subjects who participated in this trial and to the study investigators, study coordinators, and the GSK study team for their invaluable contributions.

References

1. ACTG 5202. *XVII International AIDS Conference* 2008. Mexico City, Mexico. Abstract THAB0303.
2. Young, B. et al. *AIDS* 2008;22:1673.

Table 4. Safety Population

	ABC/3TC + ATV/r N=515 n (%)
Any Grade 2-4 Adverse Event (AE)	339 (66%)
Treatment-Related Grade 2-4 AE, ≥3%	142 (28%)
Hyperbilirubinemia[1]	68 (13%)
Diarrhea	19 (4%)
Any Serious AE	39 (8%)
All Treatment-Related SAEs[2]	6 (1%)
Hypersensitivity[3]	4 (<1%)
Hepatobiliary disorders	2 (<1%)
Gastrointestinal disorders	1 (<1%)
Headache	1 (<1%)

1. Reported as an AE by the investigator. Grade 3-4 hyperbilirubinemia occurring as a lab toxicity, regardless of whether or not it was reported as an AE occurred in 209/511 (41%) of subjects.
2. Subjects could have experienced more than one SAE.
3. The four cases of hypersensitivity were suspected ABC hypersensitivity events.[2]
*One death (Castleman's disease/hepatic/renal failure) occurred during the study period which was not considered treatment-related by the investigator.

Discussion

- Stratified response rates by baseline vRNA (<100,000 and ≥100,000 c/mL) showed apparent differences for the <50 c/mL endpoint. However this difference was not noted for the <200 c/mL or for the <400 c/mL endpoint suggesting that differences in virologic response between strata may have been driven by the inability of some subjects to reach undetectable (<50 c/mL) viral loads by Week 36. As noted previously, approximately 56% of the population enrolled in this study had a baseline vRNA ≥100,000 copies/mL
- Utilizing the A5202 VF definition, consistent results, both overall and stratified by baseline viral load (<100,000 and ≥100,000 copies/mL) were noted.
- Few treatment-related Grade 2-4 AEs (28%) were observed over 36 weeks with clinical hyperbilirubinemia being the most common (13%) as would be expected with this regimen. Additionally, few subjects discontinued study due to AEs (3%).

Conclusions

- The combination of ATV/r + ABC/3TC demonstrated potent virologic efficacy through 36 weeks of study.
- Consistent results were obtained using the A5202 endpoint, regardless of viral load strata.
- The rate of protocol-defined virologic failure was low (3%).
- Overall, few treatment-related Grade 2-4 AEs (28%) were observed over 36 weeks.