Six Abacavir/Lamivudine (ABC/3TC) Clinical Trials Show Robust Virologic Responses in ART-Naive Patients for Baseline (BL) Viral Loads (VL) of ≥100,000 c/mL and <100,000 c/mL

H-1251

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Background

A. A5202 Study[1]

- This was a Phase IIIB, randomized, partially blinded, four-arm equivalence study to compare efficacy, safety, and tolerability of 4 initial therapies for HIV-1 infection using an NRTI backbone of ABC/3TC versus TDF/FTC.
- The primary efficacy endpoint was time to virologic failure (VF) defined as:
  - Early failure (wks 16-24): confirmed HIV RNA ≥1000 c/mL
  - Later failure (wks 24 on): confirmed HIV RNA ≥200 c/mL
- The primary safety endpoint was time to first Grade 3 or 4 sign, symptom or lab abnormality at least one grade higher than baseline.
- Primary results
  - Time to VF was significantly shorter in the ABC/3TC than TDF/FTC arm (HR=2.33, 95% CI 1.46-3.72, p=0.0003), occurring in 57 and 26 subjects respectively.
  - In a secondary cross-sectional analysis (prior VF and regimen changes included), the proportion (95% CI) with HIV RNA <50 c/mL at week 48 was 75% (69%-80%) for ABC/3TC and 80% (74%- 85%) for TDF/FTC (p=0.20).
  - Subjects receiving ABC/3TC had shorter time to grade 3/4 AEs (HR=1.87, 95% CI 1.43-2.43, p<0.0001), predominantly general body aches and lipid increases. Suspected drug hypersensitivity was reported in 7% of each NRTI group.

B. GSK analyses[2] of 6 recent clinical trials (including recent HEAT study) using A5202 endpoints:

- Virologic response was consistent between low and high VL strata (by 48 weeks, 87% to 95% of subjects did not experience virologic failure).
- HEAT data showed non-inferiority of ABC/3TC with TDF/FTC at 96 weeks.
- The safety endpoint outcome was similar regardless of VL strata.
- HEAT data indicated that both ABC/3TC & TDF/FTC regimens were well-tolerated, have comparable safety, and few study discontinuations due to AEs.

Methods

- We present the results from 6 clinical trials using ABC/3TC-containing regimens using different endpoints to assess the impact of baseline viral load on virologic response
- The proportion of patients with HIV-1 RNA <50 copies/mL and HIV-1 RNA <400 copies/mL by time to loss of virologic response (TLOVR) at 48 weeks are presented by baseline viral load strata (<100,000 and ≥100,000c/mL)
- The safety endpoint analyzed was used in A5202 (as defined in Background)
- Analyses using the primary efficacy endpoint defined in A5202 have been presented previously[2]
- Studies included in the analysis are summarized in Table 1:

Table 1. Summary of Key Details of Clinical Studies Included in Analysis

Study identifier	Study design	Drug regimen	Number of patients enrolled in each arm
CNA30024	Randomized, double-blind, non-inferiority	ABC 300 mg bid 3TC 150 mg bid EFV 600 mg QD	324
CNA30021	Randomized, double-blind	ABC 600 mg QD 3TC 300 mg QD EFV 600 mg QD	384
		ABC 300 mg bid 3TC 300 mg QD EFV 600 mg QD	386
ESS30009	Randomized, open-label	ABC/3TC 600/300 mg QD EFV 600 mg QD	169
COL102060 (SHARE)	Open-label	ABC/3TC 600/300 mg QD ATV/RTV 300/100 mg QD	111
KLEAN	Open-label, non-inferiority	ABC/3TC 600/300 mg QD LPV/RTV 400/100 mg bid	444
		ABC/3TC 600/300 mg QD FPV/RTV 700/100 mg bid	434
HEAT	Randomized, double-blind, placebo-matched	ABC/3TC 600/300 mg QD LPV/RTV 400/100 mg QD	343
		ABC/3TC 600/300 mg QD TDF/FTC 200/300 mg QD	345

Note: ABC = abacavir; bid = twice daily; 3TC = lamivudine; EFV = efavirenz; QD = once daily; ATV = atazanavir; RTV = ritonavir; LPV = lopinavir; FPV = fosamprenavir; FTC = emtricitabine;TDF = tenofovir.

Results

Table 2. Baseline and demographic characteristics of subjects from studies included in analysis

Characteristics	Subjects with baseline HIV-1 RNA <100,000 copies/mL	Subjects with baseline HIV-1 RNA ≥100,000 copies/mL	All subjects
	N=1599	N=1341	N=2940
Sex, n (%)			
Male	1261 (79)	1127 (84)	2388 (81)
Age, years			
Mean (sd)	36.6 (9.67)	38.8 (10.06)	37.6 (9.91)
Min-max	18.0-74.0	17.0-78.0	17.0-78.0
Race, n (%)			
White	827 (52)	762 (57)	1589 (54)
Black	514 (32)	366 (27)	880 (30)
Asian	29 (2)	19 (1)	48 (2)
Other	62 (4)	54 (4)	116 (4)
Ethnicity			
Hispanic	167 (10)	140 (10)	307 (10)
Non-Hispanic	1432 (90)	1201 (90)	2633 (90)
HIV-1 RNA $\log_{10}$ copies/ml			
Mean (sd)	4.41 (0.473)	5.48 (0.356)	4.89 (0.681)
Min-max	1.69-5.0	5.0-7.13	1.69-7.13
HIV-1 RNA (copies/ml), n (%)			
<1,000	15 (<1)	-	15 (<1)
1,000-9,999	273 (17)	-	273 (9)
10,000-49,999	762 (48)	-	762 (26)
50,000-99,999	549 (34)		549 (19)
≥100,000	-	1341 (100)	1341 (46)
CD4+ (cells/mm³)			
Mean (sd)	285.4 (168.82)	191.2 (148.24)	242.4 (166.48)
Min-max	19.0-1883.0	19.0-903.0	19.0-1883.0
CD4+ category (cells/mm³), n (%)			
0-49	82 (5)	255 (19)	337 (11)
50-99	86 (5)	200 (15)	286 (10)
100-199	318 (20)	317 (24)	635 (22)
200-349	677 (42)	374 (28)	1051 (36)
350-499	276 (17)	145 (11)	421 (14)
≥500	158 (10)	50 (4)	208 (7)
Missing	2 (<1)	0	2 (<1)

Note: ABC = abacavir; 3TC = lamivudine; EFV = efavirenz; ATV = atazanavir; RTV = ritonavir; sd = standard deviation

Figure 1. Proportion of Patients with HIV-1 RNA <50 c/mL

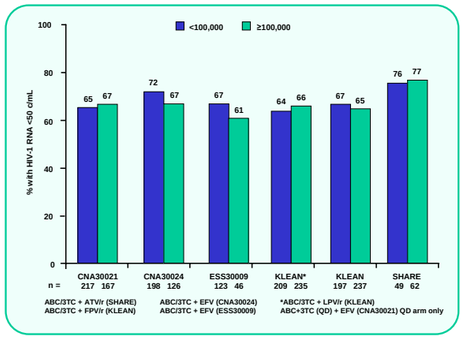


Figure 2. Proportion of Patients with HIV-1 RNA <400 c/mL

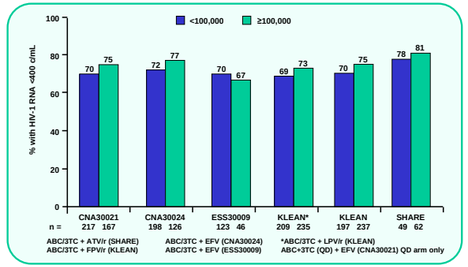
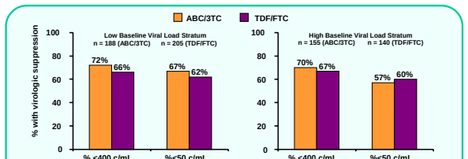


Fig 3. HEAT: Virologic Response at 48 Weeks (TLOVR)



Baseline HIV-1 RNA	ABC/3TC (n=343)	TDF/FTC (n=345)
100,000 c/mL	188 (55%)	205 (59%)
100,000 - <250,000 c/mL	68 (20%)	75 (22%)
250,000 - <500,000 c/mL	37 (11%)	33 (10%)
≥500,000 c/mL	50 (15%)	32 (9%)

Efficacy Summary

- Analysis of 5 clinical trials demonstrate robust results regardless of baseline viral loads (Figures 1 and 2).
- In the HEAT study, ABC/3TC performed similarly to TDF/FTC in both viral load strata (Figure 3).
- Kaplan-Meier analyses and 95% confidence intervals were calculated for the high viral load stratum of each study in the analysis and for the all studies combined (Figure 4):
  - Of the 7 confidence intervals, 5 exclude 84%, the A5202 estimate for ABC/3TC, suggesting that the majority of studies have different results from the A5202 result.
  - Based on the weighted mean of these 6 studies (weight=inverse variance), the confidence interval from the 1027 subjects excludes the 84% estimate from A5202.
- Thus, results from GSK studies are consistently different from the A5202 result.

Figure 4. Week 48 Kaplan-Meier estimates and 95% confidence interval on the probability of not meeting the virology failure criteria as defined in A5202

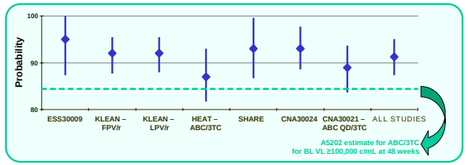


Table 3. Number (%) of subjects meeting primary safety endpoint defined in A5202 for the high baseline VL stratum at 48 weeks. Incidences ≥2% shown

Adverse event/ laboratory toxicity	CNA30024 ABC+3TC+EFV (N=126) Gr 3	CNA30024 ABC+3TC+EFV (N=126) Gr 4	CNA30021 ABC+3TC+EFV (N=166) Gr 3	CNA30021 ABC+3TC+EFV (N=166) Gr 4	ESS30009 ABC/3TC+EFV (N=46) Gr 3	ESS30009 ABC/3TC+EFV (N=46) Gr 4	COL102060 (SHARE) ABC/3TC+ ATV/RTV (N=62) Gr 3	COL102060 (SHARE) ABC/3TC+ ATV/RTV (N=62) Gr 4	KLEAN ABC/3TC+ LPV/RTV (N=237) Gr 3	KLEAN ABC/3TC+ LPV/RTV (N=237) Gr 4	KLEAN ABC/3TC+ FPV/RTV (N=235) Gr 3	KLEAN ABC/3TC+ FPV/RTV (N=235) Gr 4
Dreams	2 (2)	0	-	-	-	-	-	-	-	-	-	-
Headaches	2 (2)	0	-	-	-	-	-	-	-	-	-	-
ALT	7 (6)	4 (3)	5 (3)	1 (<1)	1 (2)	0	1 (2)	0	-	-	-	-
AST	4 (3)	4 (3)	6 (4)	1 (<1)	1 (2)	0	1 (2)	0	-	-	-	-
Cholesterol	-	-	-	-	-	-	-	-	14 (6)	0	14 (6)	0
Triglycerides	8 (6)	0	5 (3)	3 (2)	-	-	2 (3)	0	12 (5)	0	11 (5)	4 (2)
Amylase	2 (2)	0	-	-	-	-	-	-	-	-	-	-
Glucose	2 (2)	0	-	-	-	-	1 (2)	0	-	-	-	-
Allergic reaction	-	-	5 (3)	1 (<1)	-	-	-	-	-	-	-	-
Neutrophils	-	-	5 (3)	0	-	-	-	-	6 (3)	1 (<1)	10 (4)	3 (1)
Conjunctivitis	-	-	-	-	1 (2)	0	-	-	-	-	-	-
Diarrhea	-	-	-	-	1 (2)	0	-	-	-	-	-	-
Drug hypersensitivity	-	-	-	-	1 (2)	0	2 (3)	1 (2)	7 (3)	0	5 (2)	1 (<1)
Gastroenteritis	-	-	-	-	1 (2)	0	-	-	-	-	-	-
Major depression	-	-	-	-	-	-	-	-	-	-	-	-
White blood count	-	-	-	-	2 (4)	0	-	-	-	-	-	-
Abdominal pain	-	-	-	-	-	-	1 (2)	0	-	-	-	-
Deep vein thrombosis	-	-	-	-	-	-	1 (2)	0	-	-	-	-
Dyspepsia	-	-	-	-	-	-	0	1 (2)	-	-	-	-
Dyspnea	-	-	-	-	-	-	1 (2)	0	-	-	-	-
Hematuria	-	-	-	-	-	-	1 (2)	0	-	-	-	-
Hemoptysis	-	-	-	-	-	-	1 (2)	0	-	-	-	-
Acute renal failure	-	-	-	-	-	-	1 (2)	0	-	-	-	-
Lipase	-	-	-	-	-	-	2 (3)	0	-	-	-	-

Note: ABC = abacavir; bid = twice daily; 3TC = lamivudine; EFV = efavirenz; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ATV = atazanavir; RTV = ritonavir; FPV = fosamprenavir; LPV = lopinavir.

Table 4. HEAT Study: Number (%) of subjects meeting primary safety endpoint defined in A5202 for the high baseline viral load stratum at 48 weeks. Incidences ≥2% shown.

	ABC/3TC (N=155)	TDF/FTC (N=140)
GFR decreased	3(2%)	3(2%)
Diarrhea	2(1%)	3(2%)
Drug hypersensitivity	3(2%)	1(<1%)
Pneumonia	3(2%)	1(<1%)
Phosphorus	5(3%)	3(2%)
Neutrophils	3(2%)	4(3%)
Triglycerides	5(3%)	1(<1%)
Cholesterol	5(3%)	0(0%)
Glucose	1(1%)	3(2%)
ALT	4(3%)	1(<1%)
AST	1(<1%)	3(2%)

Safety Summary

- Grade 3-4 adverse events and laboratory toxicities were infrequent in high viral load stratum (0-1% for grade 3, 0-<1% for grade 4), although higher lipid and liver function toxicities were observed in 2 studies (CNA30024: 6% for grade 3 triglycerides, 3% for grade 4 ALT and AST; KLEAN: 6% for grade 3 cholesterol, 5% for grade 3 triglycerides) for the high viral load stratum.
- In the HEAT study, Grade 3-4 adverse events and laboratory toxicities were comparable between both groups for the high viral load stratum.

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Discussion

The differences in results in the high viral load strata between A5202 and our analyses of 6 GlaxoSmithKline studies may be attributed to a number of factors, some of which are discussed below:

1. Does demographics explain the difference in results between A5202 and GSK studies?

- A5202 enrolled 1,858 eligible subjects
  - 43% had screening RNA ≥100,000 copies/mL
  - 85% were men, 26% Black, 25% Hispanic
  - Mean baseline HIV-1 RNA was 5.1 log copies/mL, CD4 cell count was 181 cells/mm³
- HEAT alone enrolled 688 eligible subjects
  - 45% had baseline RNA ≥100,000 copies/mL
  - 82% were men, 36% Black, 20% Hispanic
  - Mean baseline HIV-1 RNA was 4.87 log copies/mL, CD4 cell count was 215 cells/mm³
- Combined GSK studies in analysis enrolled 2,940 eligible subjects
  - 46% had baseline RNA ≥100,000 copies/mL
  - 81% were men, 30% Black, 10% Hispanic*
  - Mean baseline HIV-1 RNA was 4.89 log copies/mL, CD4 cell count was 242 cells/mm³
- In general, study populations are quite similar in demographics, and it is unlikely that demographics can explain the difference in results between A5202 and GSK studies

*Hispanic patient representation in older GSK studies may be under-represented since ethnicity data was not collected separately in these studies.

2. Does sample size explain the difference in results between A5202 and HEAT?

- A larger sample size has more power to declare a small difference to be statistically significant than a smaller trial for the same endpoint
  - Example
    - Study A: N=1000 per arm; treatment difference 4.5%
    - Study B: N=500 per arm; treatment difference 4.5%
- A study with a larger sample size could have treatment differences that are larger, similar to, OR smaller than that seen in a study with a smaller sample size
  - Study A: N=1000 per arm; treatment difference 8%, 4.5%, or 2%
  - Study B: N=500 per arm; treatment difference 4.5%
  - A larger study does NOT mean that a larger difference will be observed.
- The larger sample size of A5202 does not explain why the treatment difference seen in A5202 is larger than in the HEAT study.

3. So, why are the A5202 and GSK results different?

- Different 3rd drugs used
- Different study conduct and follow-up
- A5202 endpoints are different from HEAT (and most other HIV studies) although when these endpoints were evaluated in HEAT, the same magnitude of difference was not observed.
- Potential treatment interruptions
- Potential differences in adherence
- Resistance testing not performed in all patients at entry in A5202
- Baseline imbalance is an important but unknown factor. Although randomization will prevent this, the potential for imbalance exists.

Conclusions

- Analysis of 6 clinical trials with commonly used efficacy endpoints demonstrate robust results irrespective of baseline viral loads.
- Ongoing analysis by the ACTG may provide insight into why differences were seen in the A5202 data presented to date.
- Neither ABC/3TC nor TDF/FTC may be optimal for all patients; the risk/benefits of each drug should be assessed for the individual patient.

References

1. Sax P, Tierney C, Collier A, et al. ACTG 5202: Shorter time to virologic failure (VF) with abacavir/lamivudine (ABC/3TC) than tenofovir/emtricitabine (TDF/FTC) as part of combination therapy in treatment-naive subjects with screening HIV RNA ≥100,000 c/mL. Presented at the XVII International AIDS Conference, 3-8 August 2008, Mexico City. Latebreaker abstract THAB0303.
2. Pappa K, Hernandez J, Ha B, et al. Abacavir/lamivudine (ABC/3TC) shows robust virologic responses in ART-naive patients for baseline (BL) viral loads (VL) of ≥100,000c/mL and <100,000c/mL by endpoint used in ACTG5202.Presented at the XVII International AIDS Conference, 3-8 August 2008, Mexico City. Latebreaker abstract THAB0304.