

# Abacavir + Lamivudine (ABC/3TC) Fixed Dose Combination Tablet Once Daily Compared with Abacavir and Lamivudine Twice Daily in HIV-1 Infected Subjects Over 48 Weeks (ESS30008, SEAL)

## Introduction

A fixed dose combination (FDC) product of two marketed antiretrovirals, abacavir (Ziagen<sup>®</sup>, ABC) and lamivudine (EpiVir<sup>®</sup>, 3TC) was developed to reduce pill burden and dosing frequency. One goal of the FDC tablet was to improve dosing convenience which may lead to improved adherence and potentially better clinical outcomes. The ABC/3TC FDC tablet (as a component of combination therapy) simplifies a regimen already utilized in clinical practice by allowing one tablet to be administered once daily.

The FDC of ABC and 3TC was approved by the US Food and Drug Administration in August 2004 as Epzicom<sup>™</sup>. In December 2004 the European Commission approved the same FDC under the trade name Kivexa<sup>™</sup>.

## Methods

ESS30008 was a 48-week, Phase III, randomized, open-label, multicenter study. The study population was composed of HIV-1 infected subjects who initiated antiretroviral therapy (ART) with ABC BID + 3TC BID in combination with a protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI). Subjects were required to have been controlled (HIV-1 RNA <400 copies/mL) on the initial regimen for at least 3 months and have CD4+ cell counts ≥50 cells/mm<sup>3</sup> at screening to be eligible for enrollment.

Subjects were randomized (1:1) to continue ABC + 3TC BID or switch to the ABC/3TC FDC tablet QD. Randomization was stratified by the 3<sup>rd</sup> agent (PI or NNRTI) and all subjects continued the initial PI or NNRTI.

In cases of intolerance to the PI or NNRTI, subjects could substitute another licensed antiretroviral within the same class for the 3<sup>rd</sup> agent and continue on study. However, no substitutions for or changes to randomized treatment were allowed.

**Virologic Failure Definition:** Virologic failure was defined in the protocol as confirmed plasma HIV-1 RNA ≥1265 copies/mL (0.5 log<sub>10</sub> copies/mL increase over 400 copies/mL).

All subjects who met the definition of virologic failure were withdrawn from the study.

**Statistical Methods:** The primary efficacy endpoint was the proportion of non virologic failures (responders). Non-inferiority analysis was based on a 2-sided 90% Confidence Interval (equivalent to a 1-sided 95% CI) with a delta of -0.12.

The primary analysis population was Intent-to-Treat (ITT), which included all randomized subjects.

For virologic endpoints, the Missing=Failure (M=F) dataset was used for analysis and included all subjects in the ITT population. Subjects who discontinued randomized treatment for any reason and/or who had missing values at a given time point were considered failures.

**Viral Resistance Methods:** The ViroSeq<sup>™</sup> HIV-1 Genotyping System from Applied Biosystems was used for generating viral genotypes. A modification to this test was used for samples with plasma HIV-1 RNA <1000 copies/mL. Reverse transcriptase (RT) and protease (PRO) mutations associated with the development of resistance to antiretroviral therapy and included in these analyses were from the International AIDS Society (IAS) Drug Resistance Mutation Group updated in October 2003.

## Results

**Study Population:** 260 subjects were enrolled from sites in the United States, Costa Rica, Panama, and Puerto Rico.

Table 1: Demographics and Baseline Characteristics

	ABC/3TC FDC QD N=130	ABC+3TC BID N=130
<b>Median age (range), years</b>	38(23-64)	38 (21-65)
<b>Male gender, n (%)</b>	104 (80%)	109 (84%)
<b>Race, n (%)</b>		
White	50 (38%)	48 (37%)
Black	38 (29%)	32 (25%)
Hispanic	41 (32%)	48 (37%)
<b>Median baseline HIV-1 RNA (range), copies/mL</b>	<50 (49-12640)*	<50 (49-210)*
<b>Median baseline CD4+ cell count (range), cells/mm<sup>3</sup></b>	565 (104-1638)	549 (89-1352)
<b>Randomization strata, n (%)</b>		
PI	46 (35%)	44 (34%)
NNRTI	84 (65%)	86 (66%)
<b>Median duration (range) of prior ABC+3TC therapy, months</b>	23 (3-47)	22 (6-48)

\*All values reported as <50 copies/mL were assigned a value of 49 for statistical purposes. Note: Although all subjects had HIV-1 RNA <400 copies/mL at screen, 2 subjects had levels >400 copies/mL at baseline.

Table 2: Subject Accountability Through Week 48

	ABC/3TC FDC QD N=130	ABC+3TC BID N=130
<b>Number (%) subjects completed through Week 48</b>	119 (92%)	117 (90%)
<b>Primary reason for premature discontinuation, n</b>		
Adverse event*	0	2
Consent withdrawn	2	2
Lost to follow up	3	2
Protocol violation	0	1
Protocol-defined virologic failure	2	4
Other†	4	2

\*AEs leading to study discontinuation were not treatment-related and included: weight gain and lymphoma. †Other reasons for study discontinuation were noncompliance (1), relocation (3), pregnancy (1), and site closure (1).

Table 3: Background ART

	ABC/3TC FDC QD N=130	ABC+3TC BID N=130
<b>Background NNRTI</b>	<b>84 (65%)</b>	<b>88 (68%)</b>
Efavirenz (EFV)	79 (61%)	82 (63%)
Nevirapine (NVP)	6 (5%)	6 (5%)
<b>Background PI</b>	<b>46 (35%)</b>	<b>44 (34%)</b>
Fosamprenavir + ritonavir	23 (18%)	21 (16%)
Nelfinavir	20 (15%)	16 (12%)
Amprenavir ± ritonavir	1 (<1%)	3 (2%)
Saquinavir ± ritonavir	0	3 (2%)
Other PI*	2 (<1%)	2 (<1%)

\*Other PI included Indinavir, ritonavir, lopinavir, and atazanavir. Note: Within class substitutions for background ART were permitted and thus subjects may be counted more than once.

## Efficacy:

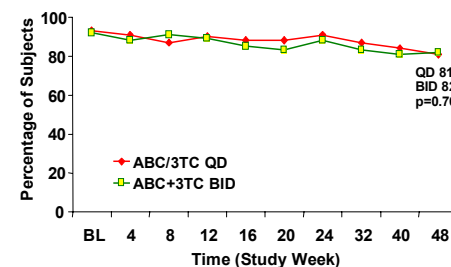
Table 4: Proportion of Responders (Non-Virologic Failures) Through Week 48 (ITT M=F)

	ABC/3TC FDC QD N=130	ABC+3TC BID N=130	Point Estimate	90% CI
<b>Stratified CI</b>				
PI	91%	93%	1.6	-3.3, 6.5
NNRTI	96%	93%		
<b>Unstratified CI</b>	95%	93%	1.5	-3.4, 6.4

A high proportion of subjects in both treatment groups were responders (non virologic failures) (ABC/3TC QD, 95%; ABC+3TC BID, 93%). Noninferiority of ABC/3TC FDC administered QD compared to ABC+3TC administered as separate components BID was established (90% CI: -3.4, 6.4). Response rates were comparable between subjects taking NNRTI and PI background ART.

An exploratory analysis using a stricter definition of virologic failure (confirmed HIV RNA ≥50 copies/mL) also demonstrated non-inferiority of ABC/3TC FDC QD [ABC/3TC QD, 90%; ABC+3TC BID, 85% (90% CI: -1.4, 12.2)].

Figure 1: HIV-1 RNA <50 copies/mL Through Week 48 (ITT M=F)



CD4+ cell counts were high at baseline (median 554 cells/mm<sup>3</sup>) and relatively stable in both treatment groups. Median CD4+ cell counts at Week 48 were 524 cells/mm<sup>3</sup> and 574 cells/mm<sup>3</sup> for the ABC/3TC QD and ABC+3TC BID treatment groups, respectively.

## Safety/Tolerability:

Table 5: Most Common (≥3%) Grade 2-4 Adverse Events through Week 48

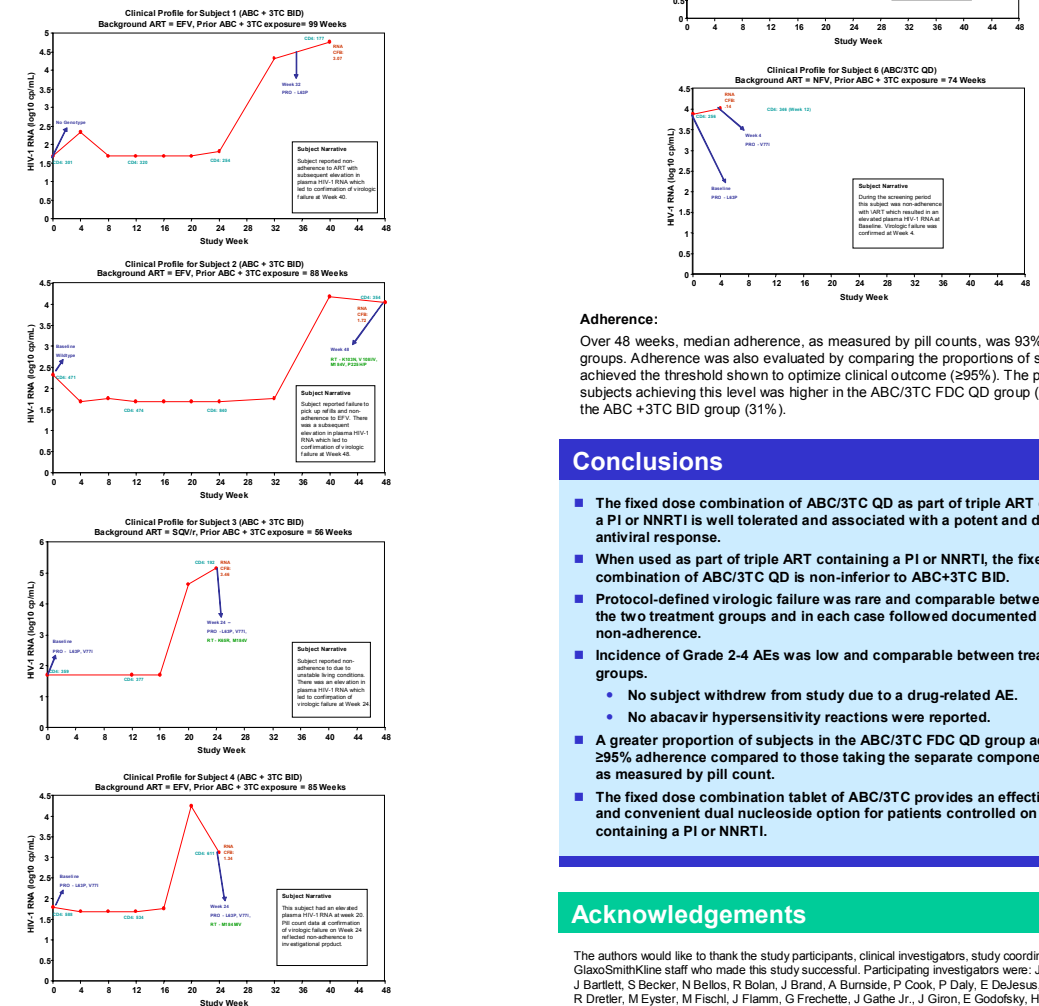
	ABC/3TC FDC QD N=130	ABC+3TC BID N=130
<b>Subjects with ANY Grade 2-4 AE</b>	<b>68 (52%)</b>	<b>72 (55%)</b>
Upper respiratory infection	5 (4%)	4 (3%)
Nasopharyngitis	5 (4%)	6 (5%)
Nausea	5 (4%)	1 (<1%)
Headache	6 (5%)	5 (4%)
Hypercholesterolemia	0	4 (3%)

ABC and 3TC (both as individual components administered BID or as a FDC QD) were well tolerated in this population with a median of 22 months experience on this dual nucleoside backbone. Two subjects withdrew due to an AE however these events (weight gain and lymphoma) were not treatment-related. Seven subjects (5 in ABC/3TC QD and 2 in ABC+3TC BID) reported Serious Adverse Events through Week 48; none were related to study drug. Additionally, as expected in this abacavir-experienced population, no hypersensitivity reactions were reported.

## Virologic Failure and Viral Resistance:

The rate of virologic failure was low in both treatment groups (ABC/3TC FDC QD: 2 subjects; ABC+3TC BID: 4 subjects) and in each case followed documented ART non-adherence. Of the six subjects meeting virologic failure criteria, 4 were in the NNRTI strata and 2 were in the PI strata.

Figure 2: Clinical Profiles for Subjects Meeting Virologic Failure Criteria



## Adherence:

Over 48 weeks, median adherence, as measured by pill counts, was 93% in both groups. Adherence was also evaluated by comparing the proportions of subjects who achieved the threshold shown to optimize clinical outcome (≥95%). The proportion of subjects achieving this level was higher in the ABC/3TC FDC QD group (39%) than in the ABC + 3TC BID group (31%).

## Conclusions

- The fixed dose combination of ABC/3TC QD as part of triple ART containing a PI or NNRTI is well tolerated and associated with a potent and durable antiviral response.
- When used as part of triple ART containing a PI or NNRTI, the fixed dose combination of ABC/3TC QD is non-inferior to ABC+3TC BID.
- Protocol-defined virologic failure was rare and comparable between the two treatment groups and in each case followed documented ART non-adherence.
- Incidence of Grade 2-4 AEs was low and comparable between treatment groups.
  - No subject withdrew from study due to a drug-related AE.
  - No abacavir hypersensitivity reactions were reported.
- A greater proportion of subjects in the ABC/3TC FDC QD group achieved ≥95% adherence compared to those taking the separate components BID as measured by pill count.
- The fixed dose combination tablet of ABC/3TC provides an effective, tolerable, and convenient dual nucleoside option for patients controlled on triple ART containing a PI or NNRTI.

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