U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	022-577 / S-0000	
Drug Name:	VIREAD® (tenofovir disoproxil fumarate (DF)) oral powder	
Indication(s):	The treatment of HIV-1 infection in pediatric subjects from 2 to <12 years of age.	
Applicant:	Gilead	
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Keywords: Viread oral power, GS-US-104-0352, Pediatric Study, Non-inferiority.

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1. EXECUTIVE SUMMARY

Executive Summary (bottom-line)

The purpose of this NDA is to get the indication of using Viread (Tenofovir disoproxil fumarate (DF)) in the treatment of HIV-1 infected **pediatric subjects from 2 to <12 years of age**. The formation of Viread depends on the subject's weight, 300 mg tablets for subject's weight >37 kg and oral powders 8 mg/kg (up to 300 mg) for subject's weight ≤37 kg. Oral powder also could be given for subjects who were unable to swallow the tablet.

The applicant submitted one randomized, open-label, parallel-group, multicenter, phase 3 clinical trial to evaluate the efficacy, pharmacokinetics, and safety of tenofovir DF (**TDF**, 300-mg tablets or oral powder 8 mg/kg) in HIV-1 infected children with 2 to < 12 years of age, naive to tenofovir DF, on a stable highly active antiretroviral therapy (HAART) regimen including either stavudine (**d4T**) or zidovudine (**ZDV**), and had plasma HIV-1 RNA levels <400 copies/mL at baseline (GS-US-104-0352).

The primary objective of the study is to assess the efficacy of switching to tenofovir DF (**TDF**) compared to continuing stavudine or zidovudine (the control arm, **D4T_ZDV**) in maintaining virologic suppression (plasma HIV-1 RNA < 400 copies/mL) in HIV-1 infected children at Week 48.

This is a non-inferiority (NI) trial with the NI margin of -15%, which is a clinical margin since there is no appropriate way to establish statistical NI margin here.

The pre-defined primary efficacy analysis did not meet the pre-specified NI margin. The difference of the proportions of subjects with plasma HIV-1 RNA<400 copies/mL at Week 48 between the TDF arm and the control arms is -8.5% with 95% confidence interval (CI) of [-21.5%, 4.5%].

The post-hoc snapshot analysis of the primary efficacy endpoint is -0.3% with 95% CI of [-13.4%, 12.9%]. The snapshot analysis algorithm is the currently recommended approach for the primary efficacy analysis for the HIV trials.

Out of 97 randomized subjects, 5 of them had age ≥12 and <16. If excluding these 5 subjects from the snapshot analysis, the suppression rate of the TDF arm was 88.6% (39/44), and 89.6% (43/48) for the control arm. The rate difference is -0.9% with 95% CI of [-13.7%, 11.8%].

Overall, the lower bound of 95% CI of the suppression rate difference at Week 48 is just bouncing around NI margin -15% depending on the method used as well as the age restriction. There is no multiplicity test adjustment due the pediatric trial.

Because of the efficacy results at Week 48, the Agency recommended the sponsor to extend the study to 96 weeks before this NDA submission with all subjects in the control arm switched to the TDF treatment. Ie, all subjects received TDF treatment after Week 48. The suppression rate

at Week 96 for all subjects who received at least one dose of TDF was 86.4% (57/66) with the 95% CI of [75.7%, 93.6%].

Key statistical issues:

1. Snapshot analysis vs. pre-specified primary efficacy analysis.

The pre-specified primary efficacy analysis only checks the HIV-1 RNA viral load with the Week 48 visit window, study day 295 to minimum of study day 378 and the first dose date of extension phase TDF. After the trial finished, the Agency recommended that the snapshot algorithm will be the preferred method for the primary efficacy analysis of all HIV trials. Even though the snapshot analysis was the post-hoc analysis for this trial, there is no multiplicity adjustment for this analysis during the review process.

2. Out of 97 randomized subjects, 5 subjects had age ≥12 and <16 years.

Even though one of inclusion criteria is that the subject must be 2 to <12 years of age, there were 5 subjects enrolled into the study with age ≥12. The age and the status of HIV-1 RNA viral load at Week 48 were summarized in Table 1 below.

Table 1: The Status of HIV-1 RNA at Week 48 for 5 Subjects with Age ≥12 Years

Treatment Arm[1]	Age at Day 1, Subjid (Status of <400 Copies/mL at Week 48[2])			
	12	13	14	15
TDF	9039 (Yes), 9079 (No)	9018 (Yes)		9045 (Yes)
D4T_ZDV			9014 (Yes)	

[1]: In the review, TDF stands for switching to tenofovir DF treatment arm, and D4T_ZDV stands of continuing stavudine or zidovudine treatment arm.

[2]: Status of <400 copies/mL at Week 48: "**Yes"** means the subject maintain the HIV-1 RNA suppression at Week 48, and "**No"** means the subject did not maintain its HIV-1 RNA suppression at Week 48, which is the failure.

If these 5 subjects were excluded from the final analyses, the primary efficacy analyses results from both original approach and snapshot approach are listed in Table 2 below. **The snapshot results will be used in the label.**

Table 2: The Virologic Outcome at Week 48 (HIV-1 RNA <400 Copies/mL) of 92 subjects (age ≥2 and <12 years)

TDF	D4T_ZDV	Rate Diff	95% CI
Original Approach			
Normal approximation of Rate Difference (TDF - D4T_ZDV)*			
37/ 44 (84.1%)	44/ 48 (91.7%)	-7.6%	[-22.8%; 6.7%]
CMH Weighted of Rate Difference (TDF - D4T_ZDV)			
37/ 44(84.1%)	44/ 48(91.7%)	-7.6%	[-21.6%; 6.4%]

Snapshot Approach

Normal approximation of Rate Difference (TDF - D4T_ZDV)*			
39/ 44 (88.6%)	43/ 48 (89.6%)	-0.9%	[-13.7%; 11.8%]

*: These two results are copied from the sponsor's tables submitted in S0015 and the counts have been verified by the stat reviewer. All others are generated by the FDA statistical reviewer.

Be note that these analyses did include two subjects (9044 and 9054) as success. Please see the next section for detailed discussion regarding these two subjects.

The disposition of these 92 subjects is listed in Table 3 below. The two subjects who discontinued due to safety, tolerability, or efficacy reasons are subjid=9092 and 9093 in TDF arm. There are only two subjects (9075 in TDF arm, and 9068 in control arm) discontinued before Week 48 due to withdrew consent.

In the label, only one subject who discontinued before Week 48 in TDF arm and had increased HIV-1 RNA viral load was counted as discontinued due to virological failure. Another subject who discontinued before Week 48 in TDF arm due to the safety, tolerability (parent stopping dosing child) was counted as discontinued due to other. As a result, there are 2 subjects in TDF arm discontinued before Week 48 due to other instead of one.

Table 3: Subject Disposition for Subjects with Age <12 Years at Week 48 for Study GS-US-104-0352 (ITT)

Status	TDF	d4t_ZDV	Total
Status at Week 48 (Completed or Not)			
Total	44	48	92
YES	41(93.2%)	47(97.9%)	88(95.7%)
NO	3(6.8%)	1(2.1%)	4(4.3%)
Reasons of Incompletion at Week 48			
Safety, Tolerability, or Efficacy reasons	2(4.5%)	.(. %)	2(2.2%)
Withdrew Consent	1(2.3%)	1(2.1%)	2(2.2%)

The only subject who had ≥12 years and discontinued before Week 48 is subjid=9079 and the reason is withdrew consent.

3. In the snapshot analysis, two subjects (9044 and 9054) had new drug (LPV/r) added during the randomization phase and should be counted as failure according to the snapshot rules instead of success as the sponsor analysis suggested.

According to the snapshot algorithm, if there is a switch drug or adding new drug during the course of the trial after the first visit, the subject will be counted as a failure regardless the HIV-1 RNA viral load within the analysis window.

Two subjects (9044 and 9054) had new drug (LPV/r) added during the randomization phase and were counted as success because the HIV-1 RNA viral loads were <400 copies/mL within Week 48 window. The explanation the sponsor provided was that both patients discontinued nelfinavir according to instructions from the manufacturer, and there was no evidence of virologic failure prior to the switch to LPV/r, and because the change in background regimen was a within-class protease inhibitor switch which occurred in the context of viral suppression, Gilead considers that both subjects maintained virologic suppression in the Week 48 snapshot analysis.

The detailed response is the following:

"Gilead confirms that Subject 9044 and Subject 9054 initiated LPV/r therapy during the randomized phase of the Study GS-US-104-0352. However, in neither case was LPV/r added to an existing regimen as treatment intensification; rather, both subjects were switched from nelfinavir therapy to LPV/r. Subject 9044, who was randomized to the TDF treatment group and took concurrent FTC throughout the randomized phase, discontinued nelfinavir on 08 June 2007 (Study Day 122) and initiated LPV/r on the same day. Subject 9054, who was randomized to the d4T or AZT treatment group and took Combivir (AZT and 3TC) throughout the randomized phase, discontinued nelfinavir on 12 June 2007 (Study Day 119) and initiated LPV/r on the same day. Viral RNA for both subjects was suppressed at <50 copies/mL at all study visits proceeding the change in protease inhibitor therapy.

Per the investigator, the change in protease inhibitor therapy in both cases was due to a communication from the manufacturer on 08 June 2007 containing a notification that a specified lot of nelfinavir was being recalled and advising providers to suspend dosing with nelfinavir due to the "risk of mutations."

Because both patients discontinued nelfinavir according to instructions from the manufacturer, and there was no evidence of virologic failure prior to the switch to LPV/r, and because the change in background regimen was a within-class protease inhibitor switch which occurred in the context of viral suppression, Gilead considers that both subjects maintained virologic suppression in the Week 48 snapshot analysis."

Even though we did not agree with the sponsor in terms of the interpretation of snapshot algorithm, subject 9044 was randomized to TDF arm and subject 9054 was randomized to D4T_ZDV arm and the impact on the final results is minor. As you can see in Table 4, the results either by the sponsor or by FDA's reviewer are almost the same.

Table 4: The Virologic Outcome at Week 48 (HIV-1 RNA <400 Copies/mL) Snapshot

Sponsor's results by counting 9044 and 9054 as success

TDF	D4T_ZDV	Rate Diff	95% CI
Exact Method of Rate Difference (TDF - D4T_ZDV)			
42/ 48 (87.5%)	43/ 49 (87.8%)	-0.3%	[-14.6%; 14.0%]
CMH Weighted of Rate Difference (TDF - D4T_ZDV)			
42/ 48(87.5%)	43/ 49(87.8%)	-0.2%	[-14.0%; 13.6%]

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-------------------------------------------------------------------------
FDA's results by counting 9044 and 9054 as failure
-------------------------------------------------------------------------
  Exact Method of Rate Difference (TDF - D4T_ZDV)
    41/ 48 (85.4%)     42/ 49 (85.7%)      -0.3%       [-15.7%;   14.7%]

  CMH Weighted of Rate Difference (TDF - D4T_ZDV)
    41/ 48( 85.4%)     42/ 49( 85.7%)      -0.1%       [-14.7%;   14.4%]
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2. INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Viread to include treatment of HIV-1 infection in pediatric patients 2 to <12 years of age.

2.1.2 History of Drug Development

Tenofovir disoproxil fumarate (tenofovir DF, TDF, Viread®) is a nucleotide reverse transcriptase inhibitor (NtRTI). Viread tablets (containing 245 mg of tenofovir disoproxil as fumarate, equivalent to 300 mg tenofovir DF or 136 mg of tenofovir) are approved in the United States (US), the European Union (EU), and other countries worldwide in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus type 1 (HIV-1) infection and chronic hepatitis B virus (HBV) infection in adults (≥18 years of age). Viread tablets are also approved in the US and Canada for use in HIV-1 infected adolescents (≥12 years of age and weighing ≥35 kg). In Europe, the Committee for Medicinal Products for Human Use concluded that available clinical data in HIV-1 infected, antiretroviral treatment-experienced adolescents were inadequate to support the use of tenofovir DF in this population. This section presents a summary of the efficacy data for tenofovir DF that are pertinent to the assessment of efficacy in HIV-1 infected subjects 2 to < 12 years of age.

2.1.3 Study Reviewed

The detailed design characteristics of the phase 3 study were described below. The principal clinical efficacy data for tenofovir DF in pediatric subjects 2 to < 12 years of age are from an ongoing, long-term, Phase 3 clinical study sponsored by Gilead Sciences, GS-US-104-0352. Both the commercially available 300-mg tenofovir DF tablet and a tenofovir DF oral powder formulation suitable for use in younger children are being investigated in the study. Based on results from earlier pharmacokinetic studies conducted in pediatric subjects, the dose of tenofovir DF used in this pivotal study was 8 mg/kg (actual body weight) to a maximum of 300 mg/day. This submission presents interim data through at least 96 weeks for all subjects in the study, based on clinical study reports (CSRs) for GS-US-104-0352 (m5.3.5.1, GS-US-104-0352 Week

48 CSR and Week 96 CSR). **Only Week 48 data will be reviewed in detail because all subjects were treated with TDF after Week 48 and there is no comparison.**

Study GS-US-104-0352 is a randomized, open-label, parallel-group, multicenter, Phase 3 study evaluating the efficacy, pharmacokinetics, and safety of tenofovir DF (300-mg tablets or oral powder 8 mg/kg) in HIV-1 infected children. Eligible subjects were 2 to < 12 years of age (children up to 16 years old could be enrolled if they were previously enrolled in emtricitabine Study GS-US-162-0111 in Panama), naive to tenofovir DF, on a stable highly active antiretroviral therapy (HAART) regimen including either stavudine or zidovudine, and had plasma HIV-1 ribonucleic acid (RNA) levels < 400 copies/mL.

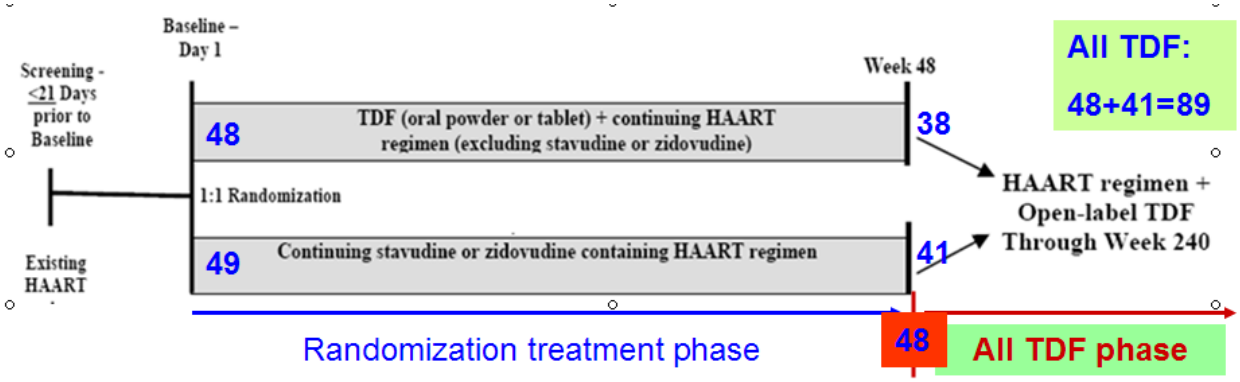

Figure 1: Study Design Diagram of GS-US-104-0352

The first 48 weeks of this study consisted of a randomized, open-label, parallel-group treatment period (the randomized phase). Eligible subjects were randomized in a 1:1 ratio to either replace stavudine or zidovudine with tenofovir DF (TDF) or continue stavudine or zidovudine (D4T_ZDV) in their current HAART regimen. Randomization was stratified by whether a subject was currently receiving stavudine or zidovudine. In the tenofovir DF group, tenofovir DF 300-mg tablets were given for subjects weighing > 37 kg, and tenofovir DF oral powder 8 mg/kg (up to 300 mg) was given for subjects weighing ≤ 37 kg or for those unable to swallow the tablet. No substitution of stavudine, zidovudine, or tenofovir DF was allowed during the initial 48 weeks of the study. Changes in the other components of the HAART regimen were permitted only for toxicity management.

Following completion of the randomized phase, eligible subjects were given the option to roll over into 2 consecutive 96-week study extensions (collectively referred to as the extension phase) to receive open-label tenofovir DF for a total duration of up to 240 weeks. The extension phase will provide long-term efficacy assessment.

The study enrolled HIV-1 infected male and female subjects, 2 to < 12 years of age, with plasma HIV-1 RNA < 400 copies/mL. Subjects were naive to tenofovir DF, and were on a stable stavudine- or zidovudine-containing HAART regimen for at least 12 weeks prior to study entry.

Baseline and post baseline efficacy assessments included plasma HIV-1 RNA levels (analyzed using the Roche COBAS® Amplicor HIV-1 Monitor Test, Version 1.5 [range: 50 to 100,000 copies/mL]; cluster determinant 4 (CD4) cell counts and CD4% (assessed using a dual-platform method, in which lymphocyte counts were assessed by an automated hematology analyzer, and CD4% was obtained by flow cytometry), and plasma banking. In addition, HIV-1 genotyping was performed in a virology sub-study of subjects who met the criteria for virologic failure (defined as 2 consecutive measurements of plasma HIV-1 RNA >1000 copies/mL that could not be attributed to non-adherence); those who were maintained on study drug and had HIV-1 RNA ≥ 400 copies/mL (assessed at 48-week intervals during the study); or those who discontinued study drug and had HIV-1 RNA ≥400 copies/mL on their last study visit prior to discontinuing study drug.

Primary Efficacy Endpoint: the percentage of subjects with HIV-1 RNA <400 copies/mL at Week 48.

Key Secondary Endpoints: The secondary efficacy endpoints in this study are:

- The percentage of subjects with HIV-1 RNA<50 copies/mL at Week 48;
- Change from baseline in CD4%;

Analysis populations

- **The ITT analysis set** includes subjects who were randomized, received at least 1 dose of study medication, and did not violate any major entry criteria. Efficacy analyses were performed using ITT analysis set.

- **The per protocol (PP) analysis set** includes subjects who met the above ITT criteria and had no major protocol deviations (defined as baseline HIV-1 RNA ≥ 400 copies/mL). It was used only to confirm the primary ITT analyses of the number and percentage of subjects with HIV-1 RNA < 400 copies/mL. Results for the PP analysis set were similar to those for the ITT analysis set and are not described further in this summary.

- **The randomized and treated (RAT) analysis set** includes subjects who were randomized into the study and received at least 1 dose of study medication. It was the primary analysis set for demographics, baseline characteristics, and safety.

In addition, the following three treatment groups were defined:

Randomized Tenofovir DF (TDF): This group included all subjects who replaced stavudine or zidovudine with tenofovir DF while continuing on their other antiretroviral agents during the randomized phase of the study (Weeks 0–48). Data collected after subjects received their first extension phase dose of tenofovir DF were excluded from the summaries for this treatment group, with the exception of dual energy x-ray absorptiometry (DEXA) data.

Randomized Stavudine or Zidovudine (d4T_ZDV): This group included all subjects who continued on the same stavudine- or zidovudine-containing ARV regimen during the randomized phase of the study (Weeks 0–48). Data collected after subjects received their first extension phase dose of tenofovir DF were excluded from the summaries for this treatment group, with the exception of DEXA data.

Treatment comparisons were only made between the two randomized treatment groups (i.e., tenofovir DF versus stavudine or zidovudine).

All Tenofovir DF group (All TDF): This group included all subjects who were initially randomized to tenofovir DF (including randomized data and available extension phase data) and subjects initially randomized to stavudine or zidovudine who switched to tenofovir DF in the extension phase. The latter subjects had their baseline reset and data from the date of the subject's first dose of tenofovir DF were included. This was used for the Week 96 analysis in CSR.

Sample size calculation:

The primary efficacy endpoint was the number and percentage of subjects with HIV-1 RNA <400 copies/mL at Week 48. With the planned sample size of 100 subjects (50 per group), the study had at least 80% power to establish noninferiority with respect to the difference in the percentages of subjects maintaining HIV-1 RNA <400 copies/mL at Week 48 between subjects who switched from stavudine or zidovudine to tenofovir DF and those who continued on stavudine or zidovudine. In the above power calculation, it was assumed that the respective percentages of subjects maintaining HIV-1 RNA <400 copies/mL is 92% for subjects switching to tenofovir DF and 90% for subjects continuing stavudine or zidovudine, as estimated from previous Gilead Sciences studies. An equivalence limit of –15% was set for the lower boundary of a 2-sided 95% confidence interval (CI) of the difference in percentages of subjects maintaining HIV-1 RNA < 400 copies/mL. This is just a clinical non-inferiority margin.

All CIs, statistical tests, and resulting p-values for the randomized phase of the study were reported as 2 sided. Significance tests were assessed with $\alpha = 0.05$.

Approved. Viread 40mg powder

2.2 Data Sources

The submission under NDA 22,577/S-0000 contains the efficacy, safety, and some genotyping results for subjects from the Phase III Study GS-US-104-0352. This reviewer conducted efficacy analyses to verify sponsor's results, included the following two parts:

1. Reviewing the protocol, statistical analysis plan, efficacy results and conclusions in the following submitted documents entitled "Statistics Section":
    - Module 1- labeling materials
    - Module 2- 2.5 Clinical Overview and 2.7.3 Summary of Clinical Efficacy
    - Module 5- Clinical Study Reports (CSRs) of its Phase III Study GS-US-104-0352.

2. Converting SAS transportable files '*.xpt' in \analysis\datasets\48wk subfolder as analysis datasets, some of the raw datasets in \tabulations\legacy\48wk subfolder into SAS data files for verification based on the definitions in 'define.pdf', 'blankcrf.pdf', and Statistical Analysis Plan (SAP) in the CSR. These files are under CDER Electronic Document Room (EDR) directory of

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3. STATISTICAL EVALUATION

One phase 3 study, GS-US-104-0352, will be reviewed under following section. All Tables and Figures are generated by the stat reviewer, otherwise the citation will be provided.

3.1 Data and Analysis Quality

Overall, the reviewer can reproduce the primary analysis dataset (ADEFFI and ADEFFRT), and ADSL under the 48wk subfolder for study GS-US-104-0352, and ADEFFI under integrated summary of efficacy (ISE) for the snapshot results. There are some minor difference (two subjects 9044 and 9054) and please see the section of Key statistical issues for details.

The documents the sponsor provided are sufficient enough for the reviewer to conduct his review.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study GS-US-104-0352 is a randomized, open-label study evaluating safety and efficacy of switching stavudine or zidovudine to tenofovir DF versus remaining on stavudine or zidovudine in virologically suppressed HIV-1 infected children, aged 2 to 12 years (inclusion criteria allowed for enrollment of 5 subjects from another Gilead sponsored-study, GS-US-162-0111, who were up to 16 years of age).

The first 48 weeks of this study consisted of a randomized, open-label, active-controlled treatment period. Eligible subjects were randomized in a 1:1 ratio to either replace stavudine or zidovudine with tenofovir DF (TDF) or continue stavudine or zidovudine (D4T_ZDV) in their current HAART regimen for 48 weeks. Randomization was stratified by whether a subject was currently on stavudine or zidovudine. Changes to the subject's pre-study HAART regimen were only permitted for toxicity management, following discussion with the medical monitor. Otherwise, each HAART regimen was to remain as prescribed prior to study entry.

After completing 48 weeks of treatment in their assigned treatment groups, eligible subjects from both treatment groups were given the option to roll over into 2 consecutive 96-week study extensions (collectively referred to as the extension phase) to receive open-label tenofovir DF for a total duration of up to 240 weeks. Subjects initially randomized to stavudine or zidovudine could switch treatment to tenofovir DF in the study extension if the investigator determined that tenofovir DF would be safe and beneficial for the subject.

The **primary objective** is to assess the efficacy of switching to tenofovir DF compared to continuing stavudine or zidovudine in maintaining virologic suppression (plasma HIV-1 RNA <400 copies/mL) in HIV-1 infected children at Week 48.

The **primary efficacy endpoint** is the proportion of subjects with HIV-1 RNA concentrations <400 copies/mL at Week 48.

The statistical hypotheses for the primary endpoint are:

- Null Hypothesis: tenofovir DF group is more than 15% worse than the stavudine or zidovudine group with respect to the proportion of subjects maintaining HIV-1 RNA concentrations <400 copies/mL at Week 48.

- Alternate Hypothesis: tenofovir DF group is no more than 15% worse than the stavudine or zidovudine group with respect to the proportion of subjects maintaining HIV RNA <400 copies/mL at Week 48.

The **key secondary objectives** of this study (Weeks 0–48) were as follows:

- To evaluate the safety and tolerability of tenofovir DF in HIV-1 infected children
- To evaluate the effects of switching from stavudine or zidovudine to tenofovir DF versus continuing stavudine or zidovudine on bone mineral density (BMD), fasting lipid parameters, and fat distribution
- To evaluate the pharmacokinetics of tenofovir in a subset of HIV-1 infected children receiving tenofovir DF oral powder formulation

The **secondary efficacy endpoints** include:

- The proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48;
- CD4+ cell count and CD4% change from baseline;

The primary efficacy analysis will be conducted on the ITT subjects analysis set. Missing values caused by discontinuation from study before Week 48 or any other reason will be treated as failure (Missing = Failure). A two-sided 95% confidence interval for the difference (tenofovir DF group – stavudine or zidovudine group) in the primary endpoint will be constructed. The tenofovir DF group will be declared noninferior to the stavudine or zidovudine group if the lower confidence bound of the difference is greater than −0.15.

The difference in two proportions ($P_1 – P_2$) and its confidence interval will be calculated using the normal approximation.

The primary efficacy endpoint was also summarized using a US Food and Drug Administration (FDA)-requested snapshot analysis that was not defined in the study protocol.

Analysis Windows

Missing Data and Outliers

A missing datum for a given study visit window may be due to any of the following:

- A visit occurred in the window but data were not collected or were unusable

- A visit did not occur in the window
- A subject permanently discontinued from study before reaching the window.

In the analysis of percentage of subjects with HIV-1 RNA concentrations < 400 copies/mL or < 50 copies/mL by visit, subjects with missing data will be included in the analysis for that visit as a failure (excluded from the number of subjects with viral load below the specified limit but included in the denominator for the percentage [Missing = Failure]).

The **analysis visit windows** are listed in Table 5 below. The reviewer only validated Week 48 data (randomization phase) using the visit windows for first part of the table from baseline visit to Week 48 visit.

Table 5: The Visit Windows for HIV-1 RNA, CD4, Hematology, Chemistry, and Vital Signs Used in the Study for First 48 Weeks and All TDF Group*

Visit ID	Visit Windows for the Randomized Groups	Visit Windows for the All TDF Group
Baseline	Study Day ≤ 1	Study Day ≤ 1 [a]
Week 2	2 ≤ Study Day ≤ 21	NA
Week 4	22 ≤ Study Day ≤ 42	2 ≤ Study Day ≤ 56
Week 8	43 ≤ Study Day ≤ 84	NA
Week 12	NA	57 ≤ Study Day ≤ 126
Week 16	85 ≤ Study Day ≤ 140	NA
Week 24	141 ≤ Study Day ≤ 210	127 ≤ Study Day ≤ 210
Week 36	211 ≤ Study Day ≤ 294	211 ≤ Study Day ≤ 294.
Week 48	295 ≤ Study Day ≤ min (378, first dose date of extension phase TDF)[b]	295 ≤ Study Day ≤ 378
Week 60	NA	379 ≤ Study Day ≤ 462
Week 72	NA	463 ≤ Study Day ≤ 546
Week 84	NA	547 ≤ Study Day ≤ 630
Week 96	NA	631 ≤ Study Day ≤ 714
Week 108	NA	715 ≤ Study Day ≤ 798
Week 120	NA	799 ≤ Study Day ≤ 882
Week 132	NA	883 ≤ Study Day ≤ 966
Week 144	NA	967 ≤ Study Day ≤ 1050

a Subjects assigned to stavudine or zidovudine in the randomized phase will have their last value prior to the first dose of OL TDF included as "Baseline" in subject listings. Prior data will have derived visit = 'N/A'.

b For HIV RNA data, the upper bound of the Week 48 visit window for the two randomized groups is as follows:

Min (378, last randomized dose date + 2 days) for subjects not enrolling into extension phase;

Min (378, first dose date of extension phase tenofovir DF), for subjects enrolling to extension phase

NOTE: If HIV-1 RNA values are collected more than 2 days after the subject discontinues study drug, these values will be excluded from analysis. All CD4 counts and percentages collected will be included in analysis (i.e., no data is cut).

*: this table was copied from Week 48 SAP.

When a single value is needed and there are multiple non-missing observations exist in a window, then records will be chosen based on the following:

- Select the record closest to the nominal day for that visit, except for DEXA data where the latest value in the time window will be selected.
- If there are two visits equidistant from the nominal day, take the latest.
- If there is more than one record on the selected day, take the average (arithmetic or geometric mean as appropriate). If there are two values on the same day, the second may be a retest because there was a problem with the first test (for example, specimen hemolyzed.) In these cases, the retest value should be used.

Definitions for randomization phase of first 48 weeks:

- **Study Day 1** (Randomized Groups) is defined as the day of first dose of study medication. For subjects never dosed with study drug, age will be calculated from the date of screening.
- **Baseline values** are defined as the last non-missing value collected on or prior to Study Day 1,
- **Last dose date** in Randomized Phase is the maximum non-missing end date of study drug, as recorded in the study drug administration case report form (CRF) page (SAS dataset EX where variable EXTRT is not equal to "TDF EXTENSION") for subjects who discontinue study drug in the first 48 weeks (SAS dataset STUDCOMP, variable COMPYN = ('Y','N') and variable phase='WEEK 48').

Definitions for extension phase of all TDF group:

- **Study Day 1** (All TDF Group) is the day of first dose of study medication for subjects randomized and treated with tenofovir DF in the randomized phase. For subjects who switch from stavudine or zidovudine in the randomized phase to tenofovir DF in the extension phase, study day 1 for the All TDF group will be the date of first tenofovir DF dose in the extension phase of the study.
- **Baseline values:** For subjects who were on stavudine or zidovudine during the randomized phase of the study, and switched to tenofovir DF in the extension phase, their baseline will be reset when summarizing extension phase data in the All Tenofovir DF group. **Extension phase baseline values for switching subjects** are defined as the last non-missing value collected on or prior to the first dose date of extension phase tenofovir DF, except DEXA data. The baseline values and extension phase Study Day 1 will not be reset for the subjects who continue tenofovir DF in the extension phase.
- **Last dose date** in Randomized Phase is the maximum non-missing end date of study drug, as recorded in the study drug administration case report form (CRF) page (at least one record in SAS dataset EX with EXTRT="TDF EXTENSION" and a non-missing start date) for those who received TDF in the extension phase.

- For interim analyses such as the Week 24 IDMCs, the last available CRF or laboratory date on or prior to the cut-off date will be assumed to be the last randomized dose date for subjects who do not meet the above criteria.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

3.2.2.1 Randomization

The randomization in the study was stratified by the original regimen either d4T or ZDV. As you can see in Table 6, the numbers of subjects for both arms within each stratum are balanced. The randomization seems OK. Also, the randomized treatment (TrtP) is the same as the actual treatment (TrtA) for all randomized subjects, ie, there was no mis-dosed subject in the study.

Table 6: The Numbers of Subjects by Stratification Factor for both Arms

Actual Treated \ **prior ARV**	ZDV	d4T	Sub-total
Group A (switched to: TDF)	31	17	48
Group B (original: D4T_ZDV)	30	19	49
Sub-total	61	36	97

3.2.2.2 Disposition

There were 127 subjects screened and a total of 97 subjects were randomized and received at least 1 dose of medication (48 tenofovir DF, 49 stavudine or zidovudine) at 9 study sites (6 in the US [randomized 22], 1 in Panama [randomized 72], and 2 in the UK [randomized 3]). Of the 97 randomized and treated subjects, 92 completed the 48-week randomized phase (44 tenofovir DF, 48 stavudine or zidovudine). The subject disposition table listed in Table 7.

Table 7: Subject Disposition at Week 48 for Study GS-US-104-0352 (ITT)

Status	TDF	d4t_ZDV	Total
Status at Week 48 (Completed or Not)			
Total	48	49	97
YES	44(91.7%)	48(98.0%)	92(94.8%)
NO	4(8.3%)	1(2.0%)	5(5.2%)
Reasons of Incompletion at Week 48			
Safety, Tolerability, or Efficacy reasons	2(4.2%)	.(. %)	2(2.1%)
Withdrew Consent	2(4.2%)	1(2.0%)	3(3.1%)
Entered the Extended Phase (Yes/No)			
YES	38(79.2%)	41(83.7%)	79(81.4%)
NO	6(12.5%)	7(14.3%)	13(13.4%)
Continued Dosing in the Extended Phase (Yes/No)			
Y	35(72.9%)	41(83.7%)	76(78.4%)
N	3(6.3%)	.(. %)	3(3.1%)
Reasons of Dropping out of Extended Phase			
Investigator's Discretion	2(4.2%)	.(. %)	2(2.1%)
Safety, Tolerability, or Efficacy reasons	1(2.1%)	.(. %)	1(1.0%)

In the tenofovir DF group (**TDF arm**), 2 subjects discontinued tenofovir DF due to safety, tolerability, or efficacy reasons (parent stopped trying to dose 1 subject and 1 subject had an increase in viral load), and 2 subjects withdrew consent (1 subject was unable to comply with protocol visits, and the other subject did not like the powder and therefore did not take study drug regularly). One subject in the stavudine or zidovudine group (**D4t_ZDV arm**) withdrew consent (subject did not want to undergo dual-energy x-ray absorptiometry [DEXA] evaluations).

In the tenofovir DF group, 38 of the 44 subjects who completed the randomized phase continued on to the extension phase of the study. Six subjects did not consent to continue into the extension phase. In the stavudine or zidovudine group, 41 of the 48 subjects who completed the randomized phase continued on to the extension phase of the study. Six subjects did not consent to continue into the extension phase. Consent was obtained for the other subject, but the subject did not continue in the extension phase due to investigator discretion.

Seventy-nine subjects received tenofovir DF in the extension phase (38 who were initially randomized to tenofovir DF and 41 who were initially randomized to stavudine or zidovudine [the (d4T or ZDV)/TDF group]). At the time of the data cutoff for the Week 96 analysis, 71 subjects were ongoing in the study.

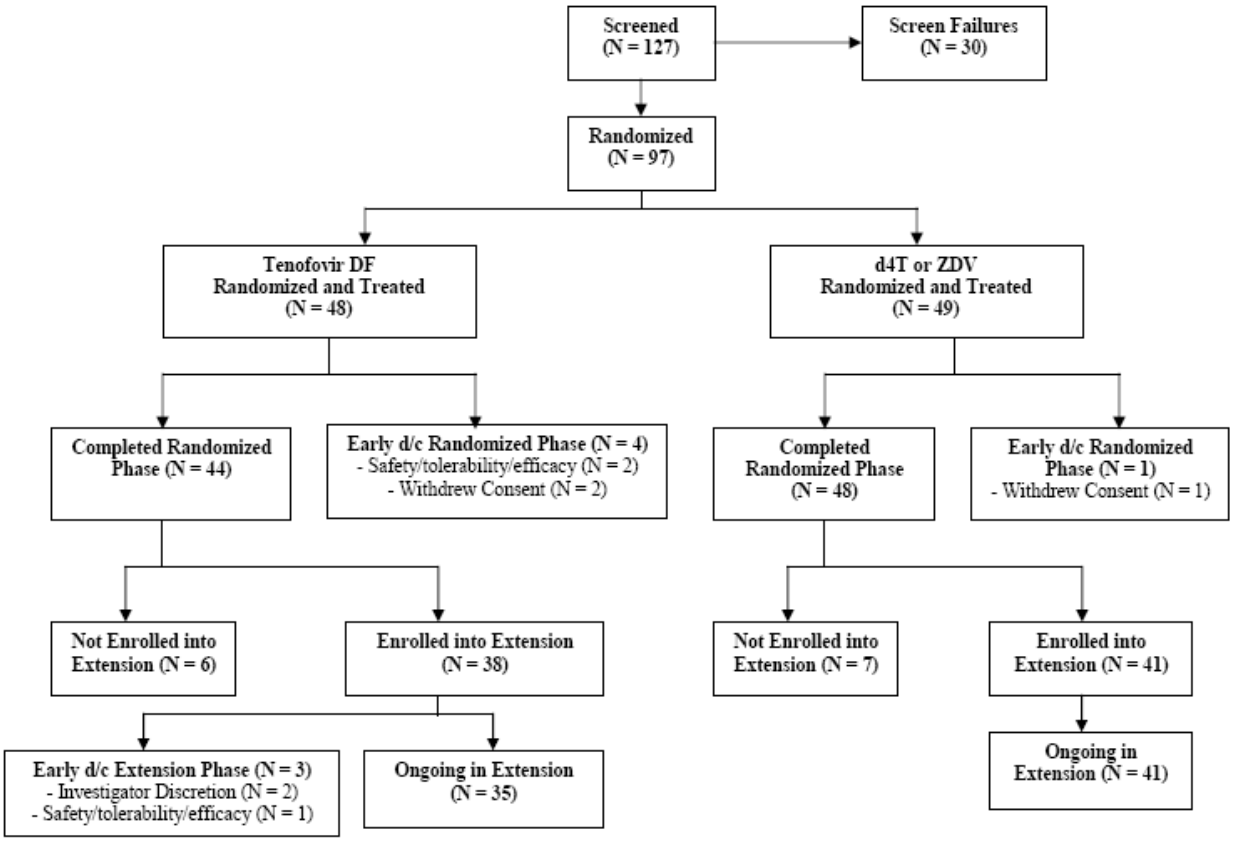

Figure 2: Patient Disposition through Week 96 for the Study (Copied from Week 48 CSR).

One note is that there are 137 records in ADSL dataset instead of 127 subjects screened. It is due to the fact that 10 subjects were screened twice in the study in one site (1578, Panama).

- 5 1st screening successful (iemetall=Y), but screened 2nd time and randomized;
- 2 1st screening failed (iemetall=N), but 2nd screening success and randomized;
- 3 failed at the screening at both 1st and 2nd times.

The numbers of subjects in each analysis population are listed in Table 8.

Table 8: Subject Counts for all Three Analysis Populations

Population	TDF	D4T_ZDV	Total
RAT	48	49	97
ITT	48	49	97
PP*	47	47	94

*: 3 subjects had protocol violation with HIV-1 RNA>400 at BSL and excluded from PP

3.2.2.3 Demographic and Baseline Characteristics

Overall, the demographic and baseline characteristics are balanced between two arms within.

There are 79% Hispanic/Latino enrolled in RAT population (Table 9). There are 51.5% male, with mean age of 7 years (range, 2 to 15 years, and 5 of them with age ≥12 years). The median body weight is 22.7 Kg, and the median Body Mass Index (BMI) is 16.68 kg/m^2.

Table 9: Demographic and Baseline Characteristics for Study GS-US-104-0352 (RAT)

Subgroup	TDF	d4t_ZDV	Total
As Randomized and Dosed (RT)			
N	48	49	97
Gender			
F	27(56.3%)	20(40.8%)	47(48.5%)
M	21(43.8%)	29(59.2%)	50(51.5%)
Race			
Black	13(27.1%)	6(12.2%)	19(19.6%)
White	3(6.3%)	6(12.2%)	9(9.3%)
American Indian	2(4.2%)	.(. %)	2(2.1%)
Asian	1(2.1%)	.(. %)	1(1.0%)
Other	29(60.4%)	37(75.5%)	66(68.0%)
Ethnicity			
Hispanic/Latino	35(72.9%)	42(85.7%)	77(79.4%)
Non-Hispanic/Latino	13(27.1%)	7(14.3%)	20(20.6%)
Age (Year)			
MEAN (SE)	7.19 (0.481)	7.20 (0.375)	7.20 (0.302)
median	7.00	7.00	7.00

Range	(2.00, 15.00)	(2.00, 14.00)	(2.00, 15.00)
std	3.330	2.622	2.978
Age Group			
2-<6 yrs	16(33.3%)	14(28.6%)	30(30.9%)
6-<12 yrs	28(58.3%)	34(69.4%)	62(63.9%)
12-<18 yrs	4(8.3%)	1(2.0%)	5(5.2%)
First Dose Form			
Capsule	.(. %)	8(16.3%)	8(8.2%)
Power	42(87.5%)	.(. %)	42(43.3%)
Solution	.(. %)	36(73.5%)	36(37.1%)
Tablet	6(12.5%)	5(10.2%)	11(11.3%)
Weight (Kg)			
MEAN (SE)	25.88 (1.737)	24.13 (1.110)	24.99 (1.025)
median	22.95	21.90	22.70
Range	(10.10, 63.30)	(10.20, 45.00)	(10.10, 63.30)
std	12.03	7.769	10.09
Height (CM)			
MEAN (SE)	118.3 (2.861)	119.2 (2.392)	118.7 (1.852)
median	118.0	120.0	118.0
Range	(78.00, 155.0)	(81.50, 152.0)	(78.00, 155.0)
std	19.82	16.74	18.24
Body Mass Index (kg/m^2)			
MEAN (SE)	17.59 (0.531)	16.59 (0.252)	17.08 (0.295)
median	16.52	16.75	16.68
Range	(12.38, 31.93)	(13.27, 20.92)	(12.38, 31.93)
std	3.680	1.762	2.905

3.2.3 Statistical Methodologies

The primary efficacy analysis will be conducted on the ITT population.

During the randomized phase, the number and percentage of subjects with HIV-1 RNA <400 copies/mL was descriptively summarized by visit and treatment group and compared between the 2 randomized treatment groups using missing = failure (M = F) and missing = excluded (M = E) methods.

A 2-sided 95% CI was constructed about the difference in response rates between the treatment groups (tenofovir DF group minus stavudine or zidovudine group) based on normal approximation methods for a binomial distribution. Treatment noninferiority was determined if the lower confidence bound of the difference between treatment groups was greater than −0.15. P-values were provided using Fisher's exact test.

The primary efficacy endpoint was also summarized using a US Food and Drug Administration (FDA)-requested snapshot analysis that was not defined in the study protocol.

The reviewer used two slightly different methods for 95% CI calculation for the rate difference.

- CMH method with adjustment of stratification factors to analyze the primary and key secondary efficacy endpoints. In this review, the number of subjects within each stratum was used as a weight to adjust the randomization strata in CMH method[3]. PROC Freq in SAS V9.2 was used to calculate the CMH test P-value for SVR rate difference.

- The exact confidence interval will be calculated using StatXact PORCs instead of normal approximation approach. Two 95% CIs using two one-sided score tests and one two-sided score test from PROC Binomial in PROC StatXact will be presented for between-treatment group difference in the observed proportions. Since both methods gave almost the same result in the analyses, the results from the two one-sided method will be used in text presentation although both results will be listed in tables.

Missing data handling

In the analysis of percentage of subjects with HIV-1 RNA concentrations <400 copies/mL or <50 copies/mL by visit, subjects with missing data will be included in the analysis for that visit as a failure (excluded from the number of subjects with viral load below the specified limit but included in the denominator for the percentage [Missing = Failure]).

3.2.4 Results and Conclusions

3.2.4.1 Summary of Applicant's Results

The primary efficacy analysis results of pre-specified approach and snapshot approach are listed in Table 10 and 11 separately, which are copied from CSR and ISE reports.

Table 10: The Primary Efficacy Results from the Sponsor

Table 5. GS-US-104-0352: Number and Percentage of Subjects with Plasma HIV-1 RNA < 400 copies/mL at Week 48 (ITT Analysis Set)

Subjects with Plasma HIV-1 RNA < 400 copies/mL at Week 48 (n, %)[a]	TDF (N = 48)	d4T or ZDV (N = 49)	p-value[b]	Difference (95% CI)[c, d]
Missing = Failure[e]				
At Week 48	40/48 (83.3%)	45/49 (91.8%)	0.23	–8.5% (–21.5% to 4.5%)
Missing = Excluded[f]				
At Week 48	40/44 (90.9%)	45/48 (93.8%)	0.71	–2.8% (–13.8% to 8.1%)

a Data collected after first dose of open-label tenofovir DF or last dose + 2 days (if terminated) excluded.
b p-values displayed to test for between group differences (randomized phase) are from a Fisher's exact test.
c The 95% CI for the percentage estimate for a treatment group is based on the exact method.
d The 95% CI on the difference in percentages between randomized treatment groups is based on normal approximation.
e Denominator (for %) is the number of ITT Subjects (subjects with missing HIV-1 RNA data counted as failures).
f Denominator (for %) is the number of ITT Subjects with nonmissing HIV-RNA data at the visit.
Source: m5.3.5.1, GS-US-104-0352 Week 48 Interim CSR, Section 12.1, Tables 13.1 and 52.1

Table 11: The Primary Efficacy Results Using Snapshot Approach from the Sponsor

Table 6. GS-US-104-0352: Number and Percentage of Subjects with HIV-1 RNA < 400 copies/mL at Week 48: Snapshot Analysis (ITT Analysis Set)

Virologic Response at Week 48 (n, %)[a]	TDF (N = 48)	d4T or ZDV (N = 49)	Difference (95% CI)[b]
Virologic Success	42 (87.5%)	43 (87.8%)	–0.3% (–13.4% to 12.9%)
Virologic Failure[c]	5 (10.4%)	5 (10.2%)	
No Virologic Data at Week 48 Window	1 (2.1%)	1 (2.0%)	
Discontinued Study Due to AE or Death[d]	0	0	
Discontinued Study for Other Reason[e]	1 (2.1%)	1 (2.0%)	
Missing Data during Window but on Study	0	0	

a Data collected up to the last randomized phase dose + 2 days were included.

b The 95% CI on the difference in percentages between randomized treatment groups is based on normal approximation.

c Virologic failure includes subjects with HIV-1 ≥ 400 copies/mL in the Week 48 window; subjects who discontinued for lack of efficacy and with no HIV-1 RNA data in the Week 48 window; subjects who changed antiretrovirals for reasons not permitted in the protocol; and subjects who discontinued for reasons other than AEs, death, and lack of efficacy and the last available HIV-1 RNA value before the start of the Week 48 window is ≥ 400 copies/mL.

d Category includes subjects who discontinued due to AE or death if this resulted in no virologic data on treatment during the Week 48 window.

e Category includes 1 subject from each treatment group who withdrew consent.

Source: Section 2.7.3.6.2, Table 1

3.2.4.2 The Reviewer's Results

Overall, the stat reviewer replicated the sponsor's results for the primary efficacy endpoint. There are some disagreements in terms of snapshot results. Since only about 3 of subjects dropped out ITT population and this will not change the conclusion of ITT results. PP analysis results will not be displayed here.

- **Primary Efficacy Analysis Results**

The primary efficacy endpoint is the percentage of subjects with HIV-1 RNA <400 copies/mL at Week 48. As you can see, the counts and percentages of two arms in the stat reviewer's in Table 12 are the same as Table 10 of the sponsor reported. The differences observed for 95% CI are due to the method used and it does not change any conclusion.

Table 12: The Primary Efficacy Endpoint (<400) Results for Study GS-US-104-0352 (ITT)

```
------------------------------------------------------------------------------------------------------
                                                  Rate
        TDF              D4T_ZDV                  Diff                 95% CI
-------------------------------------------------------------------------------
  Exact method of Rate Difference (TDF - D4T_ZDV)
    40/ 48 (83.3%)      45/ 49 (91.8%)            -8.5%        [-23.7%;     5.2%]

  CMH Weighted of Rate Difference (TDF - D4T_ZDV)
    40/ 48( 83.3)       45/ 49( 91.8)             -8.6%        [-22.2%;     5.1%]
------------------------------------------------------------------------------------------------------
```

The difference between the pre-specified analysis and the snapshot analysis (reported in ISE in Table 11) was due to two facts below:

First, some subjects had added new drug during the course of randomization phase, which will be counted as the failure according to the snapshot rule, even though the HIV-1 RNA was <400 copies/mL at Week 48 visit. According the pre-specified primary analysis in the protocol, these subjects were counted as the success. There are 3 subjects listed below (Table 13). Only subject 9062 was switched to as failure in the snapshot analysis.

Table 13: Subjects who Added New Drug during the Randomization Phase.

Subjid	First Dose Date	Last Dose Date	New ARV added Date	ARV Name	Treatment Arm	Results in the pre-specified primary analysis	Results in the snapshot analysis
9062[1]	2007-04-26	2008-03-27	2007-08-14	LPV/r	D4T_ZDV	Success	Failure
9092	2008-02-20	2008-03-03	2008-02-24	AZT	TDF	Failure	Failure
9093	2008-02-22	2008-04-03	2008-03-27	AZT	TDF	Failure	Failure
9044[2]	2007-02-07	2008-02-11	2007-06-08	LPV/r	TDF	Success	Failure
9054[2]	2007-02-14	2008-02-11	2007-06-12	LPV/r	D4T_ZDV	Success	Failure

[1]: Subject 9062 was counted as failure in Week 48 analysis dataset, ADEFFI since LPV/r drug name was not in the drug list when creating ADEFFI dataset, but was counted as failure in ADEFFI under ISE subfolder.
[2]: Please see the discussion regarding subjects 9044 and 9054 in Section 1, Key Statistical Issues, for details.

Second, some subjects had more than one HIV-1 RNA values within Week 48 visit window. The snapshot rule selects the last observation within target window while the original primary efficacy analysis method selects the record closest to the nominal day of the visit. As a result, 3 subjects changed the status due to this. Two subjects (subjid=9019 and 9033) in TDF arm changed to success from failure and one subject (subjid=9017) in D4T_ZDV arm changed to failure from success (Table 14, 15, and 16).

Overall, using snapshot rules, TDF arm got two more success and D4T_ZDV arm got two more failure and that is what you observed by comparing numbers in Table 10 and 11.

Table 14: The HIV-1 RNA Viral Load for Subject 9019 in the TDF arm

ANLVISC	SUBJID	TRTA	TRTPN	VISITNUM	VISIT	VISITTYP	LBDTN	CNVRESN	CNVRESC	EANLDY	ANLDY	ANLVISF	ANLVIS
BASE	9019	TDF	1	-10	SCREENING	S	2007-01-08	67	67	-21	-21		0
BASE	9019	TDF	1	0	BASELINE	S	2007-01-30	73	73	1	1	*	0
WEEK_2	9019	TDF	1	2	WEEK 2	S	2007-02-13	49	<50	15	15	*	2
WEEK_4	9019	TDF	1	4	WEEK 4	S	2007-02-28	49	<50	30	30	*	4
WEEK_8	9019	TDF	1	4	RETEST	U	2007-03-14	49	<50	44	44		8
WEEK_8	9019	TDF	1	8	WEEK 8	S	2007-03-27	73	73	57	57	*	8
WEEK_16	9019	TDF	1	16	WEEK 16	S	2007-05-23	49	<50	114	114	*	16
WEEK_24	9019	TDF	1	24	WEEK 24	S	2007-07-17	49	<50	169	169	*	24
WEEK_36	9019	TDF	1	36	WEEK 36	S	2007-10-09	8610	8610	253	253	*	36
WEEK_48	9019	TDF	1	48	WEEK 48	S	2008-01-02	25800	25800	338	338	*	48
WEEK_48	9019	TDF	1	100	EARLY DIS	U	2008-01-29	97	97	365	365		48
N/A	9019	TDF	1	300	30 DAY FO	U	2008-02-27	49	<50	394	394		-99
N/A	9019	TDF	1	300	30 DAY FO	U	2008-03-25	49	<50	421	421		-99

In old analysis, 25800 sampled on 2008-01-02 was used -- <400=No

In the snapshot analysis, 97 sample on 2008-01-29 was used -- <400=Yes.

Table 15: The HIV-1 RNA Viral Load for Subject 9033 in the TDF arm

ANLVISC	SUBJID	TRTA	TRTPN	VISITNUM	VISIT	VISITTYP	LBDTN	CNVRESN	CNVRESC	EANLDY	ANLDY	ANLVISF	ANLVIS
BASE	9033	TDF	1	-10	SCREENING	S	2007-01-15	49	<50	-21	-21		0
BASE	9033	TDF	1	0	BASELINE	S	2007-02-06	49	<50	1	1	*	0
WEEK_2	9033	TDF	1	2	WEEK 2	S	2007-02-14	49	<50	9	9	*	2
WEEK_4	9033	TDF	1	4	WEEK 4	S	2007-03-06	49	<50	29	29	*	4
WEEK_8	9033	TDF	1	8	WEEK 8	S	2007-04-02	49	<50	56	56	*	8
WEEK_16	9033	TDF	1	16	WEEK 16	S	2007-05-29	49	<50	113	113	*	16
WEEK_24	9033	TDF	1	24	WEEK 24	S	2007-07-24	49	<50	169	169	*	24
WEEK_36	9033	TDF	1	36	WEEK 36	S	2007-10-16	49	<50	253	253	*	36
WEEK_48	9033	TDF	1	48	WEEK 48	S	2008-01-08	4170	4170	337	337	*	48
WEEK_48	9033	TDF	1	52	WEEK 52	S	2008-02-07	167	167	367	367		48
N/A	9033	TDF	1	60	WEEK 60	S	2008-04-01	70	70	421	421		-99
N/A	9033	TDF	1	72	WEEK 72	S	2008-06-24	49	<50	505	505		-99
N/A	9033	TDF	1	84	WEEK 84	S	2008-09-16	49	<50	589	589		-99

In old analysis, 4170 sampled on 2008-01-08 was used -- <400=No

In the snapshot analysis, 167 sample on 2008-02-07 was used -- <400=Yes.

Table 16: The HIV-1 RNA Viral Load for Subject 9017 in the D4T_ZDV arm

ANLVISC	SUBJID	TRTA	TRTPN	VISITNUM	VISIT	VISITTYP	LBDTN	CNVRESN	CNVRESC	EANLDY	ANLDY	ANLVISF
BASE	9017	AZT	2	-10	SCREENING	S	2007-01-10	108	108	-383	-19	
BASE	9017	AZT	2	0	BASELINE	S	2007-01-30	51	51	-363	1	*
WEEK_2	9017	AZT	2	2	WEEK 2	S	2007-02-14	49	<50	-348	16	*
WEEK_4	9017	AZT	2	4	WEEK 4	S	2007-02-28	49	<50	-334	30	*
WEEK_8	9017	AZT	2	4	RETEST	U	2007-03-14	49	<50	-320	44	
WEEK_8	9017	AZT	2	8	WEEK 8	S	2007-03-27	49	<50	-307	57	*
WEEK_16	9017	AZT	2	16	WEEK 16	S	2007-05-23	49	<50	-250	114	*
WEEK_24	9017	AZT	2	24	WEEK 24	S	2007-07-17	64	64	-195	169	*
WEEK_36	9017	AZT	2	36	WEEK 36	S	2007-10-09	94	94	-111	253	*
WEEK_48	9017	AZT	2	48	WEEK 48	S	2008-01-02	196	196	-26	338	*
WEEK_48	9017	AZT	2	52	WEEK 52	S	2008-01-29	18300	18300	1	365	
N/A	9017	AZT	2	60	WEEK 60	S	2008-03-25	291	291	57	421	
N/A	9017	AZT	2	72	WEEK 72	S	2008-06-25	100	100	149	513	
N/A	9017	AZT	2	84	WEEK 84	S	2008-09-10	68	68	226	590	

In old analysis, 196 sampled on 2008-01-02 was used -- <400=Yes

In the snapshot analysis, 18300 sample on 2008-01-29 was used -- <400=No

- **Key Secondary Efficacy Analysis Results**

For the HIV-1 RNA <50 copies/mL analysis, the stat reviewer's results matched with the sponsor's results (Table 7-3 in Week 48 CSR) in terms counts and percentage. The difference between arms is wider than the primary efficacy endpoint (Table 17).

Table 17: HIV-1 RNA <50 copies/mL at Week 48 for Study GS-US-104-0352 (ITT)

TDF	D4T_ZDV	Rate Diff	95% CI
Exact method of Rate Difference (TDF - D4T_ZDV)			
34/ 48 (70.8%)	42/ 49 (85.7%)	-14.9%	[-31.5%; 2.0%]

```
Weighted MH method of Rate Difference (TDF - D4T_ZDV)
  34/ 48( 70.8%)     42/ 49( 85.7%)     -14.8%       [-31.2%;    1.6%]
-----------------------------------------------------------------------------------------------------------------------
```

Another secondary efficacy endpoint is the change from baseline CD4% at Week 48. The stat reviewer's results matched with the sponsor's results (Table 7-4 in Week 48 CSR). Two arms are similar in terms of CD% change from baseline (Table 18).

Table 18: Change from Baseline CD4% at Week 48 (M=E, completer analysis)

CD4 analysis parameters	TDF (N=48)	D4T_ZDV (N=49)	P-value[1]	Difference[2] (95% CI[1])
Baseline CD4 Count				
N	48	49		
Mean (SD)	1190.3 (541.65)	1143.6 (338.42)	0.63	46.7 (-143.9, 237.3)
Median	1061	1149		
Q1, Q3	880, 1371	868, 1362		
Min, Max	500, 3671	407, 2313		
Baseline CD4 %				
N	48	49		
Mean (SD)	33.9 (7.44)	33.0 (6.82)	0.51	0.96 (-1.92, 3.84)
Median	34	33		
Q1, Q3	28, 39.5	28, 37		
Min, Max	18, 48	17, 51		
CD 4 % change at Week 48 from Baseline[2]				
N	46	48		
Mean (SD)	0.3 (4.49)	1.1 (4.73)	0.40	-0.80 (-2.69, 1.09)
Median	0	1		
Q1, Q3	-3, 3	-2, 3.5		
Min, Max	-11, 11	-10, 20		

1: Satterthwaite, unequal variance method was used here for P-value and 95% CI.
2. the difference is TDF - D4T_ZDV.
3: Change is just numeric difference between CD4% at Week 48 - CD4 % at Baseline.

- **Week 96 Results:**

The stat reviewer did not validate the Week 96 results since all subjects got TDF after 48 weeks. The suppression rate (HIV-1 RNA <400 copies/mL) at Week 96 in all TDF population is 86.4% (57/66) with 95% CI of [75.7%, 93.6%].

3.3 Evaluation of Safety

Please see clinical review for details.

3.4 Benefit: Risk Assessment (Optional)

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Because the studies were not designed to detect these subgroup differences and the limitation of sample size within subgroup, be cautious in terms of the differences observed here.

4.1 Gender, Race, Age, and Geographic Region

No significant difference in the proportion of subjects with HIV-1 RNA <400 copies/mL at Week 48 was observed for gender, age, or location (US vs. non-US) in this study. There are some numeric differences some categories. The difference between two arms in female group seems wider than male group, the suppression rates in both arms for non-Hispanic/Latino seems lower than Hispanic/Latino group, and the difference between two arms in US seems smaller than non-us and overall (Table 19).

Table 19: The Summary Subgroup Analyses of Primary Efficacy Endpoint (<400) (ITT)

Efficacy Parameter	TDF	D4T_ZDV	Total
As Randomized and Dosed (ITT)			
N	40/ 48(83.3)	45/ 49(91.8)	85/ 97(87.6)
Gender			
F	20 / 27 (74.1)	19 / 20 (95.0)	39 / 47 (83.0)
M	20 / 21 (95.2)	26 / 29 (89.7)	46 / 50 (92.0)
Race			
American Indian	2 / 2 (100)	. / . (.)	2 / 2 (100)
Asian	. / 1 (0.00)	. / . (.)	. / . (.)
Black	10 / 13 (76.9)	6 / 6 (100)	16 / 19 (84.2)
Other	25 / 29 (86.2)	34 / 37 (91.9)	59 / 66 (89.4)
White	3 / 3 (100)	5 / 6 (83.3)	8 / 9 (88.9)
Ethic			
Hispanic/Latino	31 / 35 (88.6)	39 / 42 (92.9)	70 / 77 (90.9)
Non- Hispanic/Latino	9 / 13 (69.2)	6 / 7 (85.7)	15 / 20 (75.0)
Age Group			
2-<6 yrs	14 / 16 (87.5)	12 / 14 (85.7)	26 / 30 (86.7)
6-<12 yrs	23 / 28 (82.1)	32 / 34 (94.1)	55 / 62 (88.7)
12-<18 yrs	3 / 4 (75.0)	1 / 1 (100)	4 / 5 (80.0)
First Dose Form			
CAP	. / . (.)	7 / 8 (87.5)	7 / 8 (87.5)
Power	35 / 42 (83.3)	. / . (.)	35 / 42 (83.3)
SOL	. / . (.)	33 / 36 (91.7)	33 / 36 (91.7)
TAB	5 / 6 (83.3)	5 / 5 (100)	10 / 11 (90.9)
Country			
UNITED STATES	11 / 13 (84.6)	8 / 9 (88.9)	19 / 22 (86.4)
PANAMA	29 / 33 (87.9)	36 / 39 (92.3)	65 / 72 (90.3)
UNITED KINGDOM	. / 2 (0.00)	1 / 1 (100)	1 / 3 (33.3)

Region			
USA	11 / 13 (84.6)	8 / 9 (88.9)	19 / 22 (86.4)
Non-USA	29 / 35 (82.9)	37 / 40 (92.5)	66 / 75 (88.0)
Site ID			
1577	3 / 3 (100)	. / . (.)	3 / 3 (100)
1578	29 / 33 (87.9)	36 / 39 (92.3)	65 / 72 (90.3)
1800	1 / 2 (50.0)	3 / 3 (100)	4 / 5 (80.0)
2767	2 / 2 (100)	1 / 2 (50.0)	3 / 4 (75.0)
2827	2 / 2 (100)	. / . (.)	2 / 2 (100)
2880	2 / 3 (66.7)	1 / 1 (100)	3 / 4 (75.0)
3066	1 / 1 (100)	3 / 3 (100)	4 / 4 (100)
3105	. / . (.)	1 / 1 (100)	1 / 1 (100)
3106	. / 2 (0.00)	. / . (.)	. / . (.)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Some key statistical issues have already summarized in the executive summary at the beginning of the review.

5.2 Conclusions and Recommendations

There is only one phase 3 pediatric study submitted. The non-inferiority margin was set to -15%, which is a clinical margin since there is no appropriate way to establish statistical NI margin here.

The pre-defined primary efficacy analysis did not meet the pre-specified NI margin. The difference of the proportions of subjects with plasma HIV-1 RNA<400 Copies/mL at Week 48 between the TDF arm and the control arms is -8.5% with 95% CI of [-21.5%, 4.5%]. The post-hoc snapshot analysis of the primary efficacy endpoint is -0.3% with 95% CI of [-13.4%, 12.9%]. The snapshot analysis algorithm is currently recommended approach for the primary efficacy analysis for the HIV trials.

There are 5 subjects with age ≥12 and <16 enrolled into the study. If excluding these 5 subjects from the snapshot analysis, the suppression rate of the TDF arm was 88.6% (39/44), and 89.6% (43/48) for the control arm. The rate difference is -0.9% with 95% CI of [-13.7%, 11.8%].

Because of the efficacy results at Week 48, the Agency recommended the sponsor to extend the study to 96 weeks before the NDA submission with all subjects in the control arm switched to the TDF treatment after Week 48 visit. Ie, all subjects received TDF treatment after Week 48. The suppression rate at Week 96 for all subjects who received at least one dose of TDF was 86.4% (57/66) with the 95% CI of [75.7%, 93.6%].

APPENDICES

References

1. StatXact PROCs User Manual for SAS Users, Version 6, 2004, Cytel.
2. SAS Version 9.2, SAS Inc.
3. Koch, G.G., Carr, G.J., Amara, I.A., Stokes, M.E.. and Uryniak, T.J. (1989). Categorical Data Analysis. Chapter 13 in Berry, D.A. (ed.), Statistical Methodology in the pharmaceutical Sciences, Marcel Dekker, New York, pp. 414-421.

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