

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203100Orig1s000

STATISTICAL REVIEW(S)



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

The addendum to the STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number: 203-100 / S-0000

Drug Name: **Stribild**, A single-tablet regimen (STR) of the elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF, 150/150/200/300 mg, **E/C/F/T**)

Indication(s): a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults aged 18 years and over who are antiretroviral (ARV) naive or have no known substitutions associated with resistance to the individual components

Applicant: Gilead Science

Date(s): Submitted: October 26, 2011
Received: October 27, 2011
PDUFA Date: August 27, 2012
Addendum Date: July 17, 2012

Review Priority: Standard

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Keywords: HIV-1 Infected Subjects, Treatment naïve, EVG/COBI/FTC/TDF (E/C/F/T), single-tablet regimen (STR).

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1. Introduction

The CD4 change at Week 48 from baseline is one of secondary efficacy endpoints for the phase 3 studies, GS-US-236-0102 and GS-US-236-0103, reviewed in this NDA and will be presented in the label. In the original statistical review, the completer analysis and baseline observation carry forward (BOCF) approaches were used for analyzing CD4 change at Week 48 from baseline. Typically, the last observation carry forward (LOCF) approach was used for this type of analysis for the label even though the results are similar. The purpose of this addendum is to analyze the CD4 change at Week 48 from baseline using LOCF and mixed LOCF/BOCF approaches for validating the results used in the label.

2. Methods

LOCF: when a subject missed CD4 count at Week 48, the last available CD4 count for the subject will be used for the calculation of the CD4 change at Week 48 from baseline;

Mixture of LOCF/BOCF: when a subject missed CD4 count at Week 48, and if the subject discontinued the study, the BOCF approach will be used to impute the missing CD4 count. Otherwise, the LOCF approach will be used to impute the missing CD4 count for the calculation of the CD4 change at Week 48 from baseline;

3. Results

For the two phase 3 studies, GS-US-236-0102 and GS-US-236-0103, there are two ways to determine the subject discontinued or not. One is called the discontinuation from the study drug at Week 48, and other is called the discontinuation from the study at Week 48. The analysis results presented below will include both discontinuations from study drug and from study at Week 48 when imputing those missing CD4 count as Week 48.

3.1 Study GS-US-236-0102:

There are two subjects, "GS-US-236-0102-0659-6676" and "GS-US-236-0102-0744-6147", who did not have any CD4 observation after baseline, and the CD4 changes at Week 48 from baseline were imputed to ZERO using the LOCF.

The mean increase from baseline in CD4+ cell count at Week 48 was 239, 223, and **232** cells/mm³ for completer analysis, BOCF analysis, and **LOCF analysis** respectively in the E/C/F/T-treated subjects and 206, 184, and **197** cells per mm³ for completer analysis, BOCF analysis, and **LOCF analysis** respectively in the ATRIPLA-treated subjects (Table 1 and Table 34 of the original stat review).

Table 1: The CD4 Change at Week 48 from Baseline Using LOCF Approach for Study GS-US-236-0102 (ITT)

	E/C/F/T	ATR	Total
CD4 at Baseline			
n	348	352	700
Mean (SE)	390.8 (10.11)	381.7 (9.073)	386.2 (6.786)
Median	375.5	382.5	380.0
Range	(14.00, 1348)	(3.00, 1003)	(3.00, 1348)
std	188.6	170.2	179.5
CD4 at Week 48 (LOCF)			
n	347	351	698
Mean (SE)	623.7 (13.41)	579.7 (11.56)	601.6 (8.878)
Median	604.0	568.0	582.5
Range	(78.00, 1458)	(92.00, 1328)	(78.00, 1458)
std	249.8	216.5	234.6
CD4 Change at Week 48 from Baseline (LOCF)			
n	348	352	700
Mean (SE)	231.8 (8.983)	197.5 (8.114)	214.6 (6.079)
Median	217.5	181.0	201.0
Range	(-102, 882.0)	(-160, 844.0)	(-160, 882.0)
std	167.6	152.2	160.8

If using the study drug completion at Week 48 flag to determine completion, there are 83 subjects who did not complete the treatment at Week 48. Out of 83, 25 subjects did have CD4 count within Week 48 window, and there is no imputation. The rest of 58 subjects, who discontinued from study drug at Week 48 and did not have CD4 count within Week 48 window, will be imputed their missing Week 48 CD4 count by using BOCF approach. For subjects who completed study drug at Week 48 and missed CD4 count within Week 48 window, the LOCF approach will be used for the imputation.

If using the study completion at Week 48 flag to determine completion, there are 65 subjects who did not complete the study at Week 48. Out of 65, 7 subjects did have CD4 count within Week 48 window, and there is no imputation. The rest of 58 subjects, who discontinued from study at Week 48 and did not have CD4 count within Week 48 window, will be imputed their missing Week 48 CD4 count by using BOCF approach. For subjects who completed study at Week 48 and missed CD4 count within Week 48 window, the LOCF approach will be used for the imputation (Table 1 and Table 34 of the original stat review).

Results from both analyses are the same and are very close to the results from the BOCF (Table 2).

Table 2: The CD4 Change at Week 48 from Baseline Using LOCF/BOCF Approach for Study GS-US-236-0102 (ITT)

	E/C/F/T	ATR	Total

CD4 at Baseline			
n	348	352	700
Mean (SE)	390.8 (10.11)	381.7 (9.073)	386.2 (6.786)
Median	375.5	382.5	380.0
Range	(14.00, 1348)	(3.00, 1003)	(3.00, 1348)
std	188.6	170.2	179.5

--- Using LOCF+BOCF and Discontinuation of study drug at Week 48 ---			
CD4 at Week 48			
n	347	351	698
Mean (SE)	623.7 (13.41)	579.7 (11.56)	601.6 (8.878)
Median	604.0	568.0	582.5
Range	(78.00, 1458)	(92.00, 1328)	(78.00, 1458)
std	249.8	216.5	234.6
CD4 Change at Week 48 from Baseline			
n	348	352	700
Mean (SE)	223.2 (9.228)	184.1 (8.434)	203.6 (6.287)
Median	211.0	165.5	190.0
Range	(-102, 882.0)	(-160, 844.0)	(-160, 882.0)
std	172.2	158.2	166.3

--- Using LOCF+BOCF and Discontinuation of study at Week 48 ---			
CD4 at Week 48			
n	347	351	698
Mean (SE)	623.7 (13.41)	579.7 (11.56)	601.6 (8.878)
Median	604.0	568.0	582.5
Range	(78.00, 1458)	(92.00, 1328)	(78.00, 1458)
std	249.8	216.5	234.6
CD4 Change at Week 48 from Baseline			
n	348	352	700
Mean (SE)	223.2 (9.228)	184.1 (8.434)	203.6 (6.287)
Median	211.0	165.5	190.0
Range	(-102, 882.0)	(-160, 844.0)	(-160, 882.0)
std	172.2	158.2	166.3

3.2 Study GS-US-236-0103:

There are four subjects, "GS-US-236-0103-2191-7409" in E/C/F/T arm and "GS-US-236-0103-2675-7715", "GS-US-236-0103-5124-7374", "GS-US-236-0103-1407-7116" in ATR arm, who did not have any CD4 observation after baseline, and the CD4 changes at Week 48 from baseline were imputed to ZERO using the LOCF.

The mean increase from baseline in CD4+ cell count at Week 48 was 207, 196, and **200** cells/mm³ for completer analysis, BOCF analysis, and **LOCF analysis** respectively in the E/C/F/T-treated subjects, and 211, 191, and **204** cells per mm³ for completer analysis, BOCF analysis, and **LOCF analysis** respectively in the ATV/r + TRUVADA-treated subjects (Table 3 and Table 40 of the original stat review).

Table 3: The CD4 Change at Week 48 from Baseline Using LOCF Approach for Study GS-US-236-0103 (ITT)

	E/C/F/T		ATR		Total	
CD4 at Baseline						
n	353		355		708	
Mean (SE)	364.2	(9.613)	375.4	(8.436)	369.8	(6.392)
median	351.0		366.0		357.0	
Range	(5.00,	1132)	(10.00,	963.0)	(5.00,	1132)
std	180.6		158.9		170.1	
CD4 at Week 48 (LOCF)						
n	352		352		704	
Mean (SE)	565.3	(12.25)	582.2	(11.17)	573.7	(8.292)
median	535.5		557.0		551.5	
Range	(92.00,	1714)	(74.00,	1317)	(74.00,	1714)
std	229.9		209.6		220.0	
CD4 Change at Week 48 from Baseline (LOCF)						
n	353		355		708	
Mean (SE)	200.3	(9.006)	203.8	(8.354)	202.1	(6.137)
median	190.0		191.0		190.0	
Range	(-306,	1024)	(-276,	944.0)	(-306,	1024)
std	169.2		157.4		163.3	

If using the study drug completion at Week 48 flag to determine completion, there are 73 subjects who did not complete the treatment at Week 48. Out of 73, 23 subjects did have CD4 count within Week 48 window, and there is no imputation. The rest of 50 subjects, who discontinued from study drug at Week 48 and did not have CD4 count within Week 48 window, will be imputed their missing Week 48 CD4 count by using BOCF approach. For subjects who completed study drug at Week 48 and missed CD4 count within Week 48 window, the LOCF approach will be used for the imputation.

If using the study completion at Week 48 flag to determine completion, there are 53 subjects who did not complete the study at Week 48. Out of 53, 3 subjects did have CD4 count within

Week 48 window, and there is no imputation. The rest of 50 subjects, who discontinued from study at Week 48 and did not have CD4 count within Week 48 window, will be imputed their missing Week 48 CD4 count by using BOCF approach. For subjects who completed study at Week 48 and missed CD4 count within Week 48 window, the LOCF approach will be used for the imputation.

Results from both analyses are the same and are very close to the results from the BOCF (Table 4).

Table 4: The CD4 Change at Week 48 from Baseline Using LOCF/BOCF Approach for Study GS-US-236-0103 (ITT)

	E/C/F/T	ATR	Total

CD4 at Baseline			
n	353	355	708
Mean (SE)	364.2 (9.613)	375.4 (8.436)	369.8 (6.392)
Median	351.0	366.0	357.0
Range	(5.00, 1132)	(10.00, 963.0)	(5.00, 1132)
std	180.6	158.9	170.1

Using LOCF+BOCF and Discontinuation of study drug at Week 48 ---			
CD4 at Week 48			
n	352	352	704
Mean (SE)	565.3 (12.25)	582.2 (11.17)	573.7 (8.292)
median	535.5	557.0	551.5
Range	(92.00, 1714)	(74.00, 1317)	(74.00, 1714)
std	229.9	209.6	220.0
CD4 Change at Week 48 from Baseline			
n	353	355	708
Mean (SE)	195.6 (8.858)	192.3 (8.691)	194.0 (6.200)
median	182.0	184.0	183.0
Range	(-303, 1024)	(-276, 944.0)	(-303, 1024)
std	166.4	163.8	165.0

Using LOCF+BOCF and Discontinuation of study at Week 48 ---			
CD4 at Week 48			
n	352	352	704
Mean (SE)	565.3 (12.25)	582.2 (11.17)	573.7 (8.292)
Median	535.5	557.0	551.5
Range	(92.00, 1714)	(74.00, 1317)	(74.00, 1714)
std	229.9	209.6	220.0
CD4 Change at Week 48 from Baseline			
n	353	355	708
Mean (SE)	195.6 (8.858)	192.3 (8.691)	194.0 (6.200)
Median	182.0	184.0	183.0
Range	(-303, 1024)	(-276, 944.0)	(-303, 1024)
std	166.4	163.8	165.0

4. Summary

The medical division decided to use the LOCF approach in the **Stribild** label. Note that the applicant's CD4 changes at Week 48 from the baseline using the LOCF approach are little bit different from what I got above.

In GS-US-236-0102 study, the applicant got: 230 in Stribild arm and 193 in Atripla arm, and I got: 232 in Stribild arm and 197 in Atripla arm.

In GS-US-236-0103 study, the applicant got: 202 in Stribild arm and 201 in Atripla arm, and I got: 200 in Stribild arm and 204 in ATV/r + TVR arm.

Because the differences are very small and they are in alignment, and did not change any conclusions, we decided to use the applicant's results in the final label.

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/s/

WEN ZENG
07/19/2012

FRASER B SMITH
07/19/2012



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: 203-100 / S-0000

Drug Name: A single-tablet regimen (STR) of the elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF, 150/150/200/300 mg, **E/C/F/T**)

Indication(s): a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults aged 18 years and over who are antiretroviral (ARV) naive or have no known substitutions associated with resistance to the individual components

Applicant: Gilead Science

Date(s): Submitted: October 26, 2011
Received: October 27, 2011
PDUFA Date: August 27, 2012
Draft Review Completed: June 6, 2012
Final Review Completed: June 28, 2012

Review Priority: Standard

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Linda Lewis, M.D.; Medical Team Leader

Project Manager: Stacey Min, RPh. Regulatory Project Manager

Keywords: HIV-1 Infected Subjects, Treatment naïve, EVG/COBI/FTC/TDF (E/C/F/T), single-tablet regimen (STR).

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1. EXECUTIVE SUMMARY

Executive Summary (bottom-line)

The applicant submitted two randomized, active controlled, double-blinded, phase 3 clinical studies with the a fixed-dose combination of elvitegravir (EVG), cobicistat (COBI), emtricitabine (FTC, Emtriva®) and tenofovir disoproxil fumarate (TDF, Viread®): the EVG/COBI/FTC/TDF (150/150/200/300 mg) tablet (referred to as **E/C/F/T** throughout this document) compared to either Atripla (ATR) in study GS-US-236-0102 or Ritonavir-Boosted Atazanavir Plus Emtricitabine/Tenofovir Disoproxil Fumarate (ATV/r + TVD) in study GS-US-236-0103 in HIV-1 infected treatment naïve adult population.

The sponsor also submitted a phase 2 study, GS-US-236-0104, which will not be reviewed in this review because only 71 subjects were randomized in the study.

The primary objective of both phase 3 studies is to evaluate the efficacy of E/C/F/T versus a regimen containing ATR or ATV/r + TVD in HIV-1 infected ARV treatment-naïve adult subjects. The non-inferiority margin used in both studies was -12%, which is a clinical margin. The primary efficacy endpoint is the percentage of subjects with virologic success (ie, HIV-1 RNA < 50 copies/mL) at Week 48 using the FDA-defined snapshot analysis.

For study GS-US-236-0102, all subjects were enrolled from US sites, while there were only 46% of subjects from US sites for study GS-US-236-0103.

The virologic success rates for E/C/F/T arm were 87.6% (305/348) in GS-US-236-0102 and 89.5% (316/353) in GS-US-236-0103, comparing to the virologic success rates of 84.1% (296/352) in ATR arm and 86.8% (308/355) in ATV/r arm.

These two key phase 3 studies have demonstrated that the E/C/F/T STR was noninferior to ATR or ATV/r + TVD. The lower bound of the 2-sided 95% CI of the difference in virologic success rate was -1.6% for (E/C/F/T – ATR) and -1.9% for (E/C/F/T – (ATV/r + TVD)), which were greater than the pre-specified -12% noninferiority margin. The results are robust because the TLOVR analysis provided very similar results.

Key statistical issues:

1. Non-inferiority (NI) margin:

The NI margins used in these two pivotal studies, GS-US-236-0102 and GS-US-236-0103, were 12% in the treatment naïve population. For study GS-US-236-0102, it is E/C/F/T/ vs. Atripla (Efavirenz (EFV) + Truvada (FTC/TDF)), and E/C/F/T vs. Ritonavir-Boosted Atazanavir + Truvada (ATV/r + TVD) for study GS-US-236-0103. This NI margin is a clinical margin, so-called M2, not the M1 margin.

Normally when selecting a margin, the actual delta should be based on the contribution of the active comparator. Truvada or other two Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs) alone would give you zero, or maybe 1 or 2 percent undetectable rate after 48 weeks of treatment. Also, Truvada or other two NRTIS alone would never be ethical to be used as an intervention for HIV treatment these days. So, adding the third drug will have synergistic effects and the undetectable rate of 48 weeks of treatment could be around 80%. If using these data to calculate the M1, the NI margin will be huge. But the actual magnitude of what efavirenz and atazanavir, the third drug, is contributing to the overall regimen is actually unknown. Clinically the response that we would be willing to give up in terms of undetectable rate of 48 weeks of treatment in treatment-naïve population is about 12% (i.e., M2, the clinical margin).

2. Randomization for study GS-US-236-0103:

In the review of randomization files for study GS-US-236-0103 submitted, we identified a few potential issues:

- **Incorrect generation date:** which turned out to be the typographic error by the IVRS vendor in the programming code used to generate the PDF file according to the sponsor's response;
- **Local time vs. centralized time displayed in the randomization list:** when the sponsor provided randomization log file displayed in the local time, the treatment assignment order was not correct. If the local time was converted to the centralized time (e.g., the local time at the IVRS vendor), the order of randomization was correct;
- **Site changes:** 57 subjects changed their sites, ie, they were randomized at one site, and then they had switched to another site to continue the trial during the trial. Consequentially, the subjects who were in the randomization list provided the sponsor were not in the analysis datasets submitted due the change of site;

The following is the detailed information regarding these issues:

In this submission, there are 4 files for studies GS-US-236-0102 (phase 3), GS-US-236-0103 (phase 3), and GS-US-236-0104 (phase 2) each for randomization. They are:

1. List-based-randomization-req-v1-1-signed;
2. Dummy-randomization-list-approval-v1-signed;
3. Final-randlist-ver-1-1; (This final list should be generated before the first patient is randomized, according to the IVRS vendor's memo: "All FINAL randomization lists must be created and finalized before development may begin, and thus before the launch of the system").
4. Unblinded-randomization-19Oct2011;

Table 1: Randomization List Generation Information for Three Studies

Study	Event	Event Occurred Date	Source
0102	First Subject Screened	Mar. 16, 2010	CSR ¹ in S0000
	First Subject Randomized	Apr. 09, 2010	CSR in S0000
	Item 3 generated (RandDate)	Jan. 11, 2010	File ² in S0001
0103	First Subject Screened	Apr. 06, 2010	CSR in S0000
	First Subject Randomized	May. 20, 2010	CSR in S0000
	Item 3 generated (RandDate)	Dec. 08, 2010	File in S0001
	Last Subject Randomized	Sep. 30, 2010	CSR in S0000
	Treatment Unblinded	Sep. 16, 2011	CSR in S0000
0104	First Subject Screened	Mar. 30, 2009	CSR in S0000
	First Subject Randomized	Apr. 16, 2009	CSR in S0000
	Item 3 generated (RandDate)	Mar. 05, 2009	File in S0001

¹ CSR=Clinical Study Report

² File=gs-us-236-xxxx-final-randlist-ver-1.pdf. xxxx stands for the study number, 0102, 0103, or 0104.

There is one potential issue with the final randomization listed submitted in S0001 for study GS-US-236-0103. If RandDate is the generation date of final randomization list (Table 1 above), it indicates that the full randomization list for study GS-US-236-0103 was generated after the last subject was randomized, which contradicts the (b) (4) SOP-OP-002.

The sponsor's response is the following:

In the final Randomization list provided by (b) (4) (Gilead IVRS vendor), file name "gs-us-236-0103-final-randlist-ver-1.pdf", the field "randdate" is intended to define the date on which the list was generated. In this case, the date displayed in this field is incorrect due to typographic error in the programming code used to generate the PDF file. It should display 08 Jan 2010, but instead it incorrectly displays 08 Dec 2010. (b) (4) can provide the original copy of the final randomization list in .csv format if desired, which will provide evidence that the list was created on 08 Jan 2010. Once created on 08 Jan 2010, the randomization list was written to a secure read-only drive preventing alteration. (b) (4) has confirmed that the list was not altered after 08 Jan 2010. This error is a date/versioning error within the randomization list and had no functional impact on the system or randomization logic. All subjects were randomized after the creation of the list.

We did ask the sponsor to provide the original copy of the final randomization list in .csv format, and ask to clarify how the typographical error in the programming code used to generate the PDF file occurred. We also requested the sponsor to submit the programming code used to generate the PDF file as well as the IVRS log file in the original randomization order.

In the SAS program code submitted, there was a hard-coded line of code where randdate was set equal to "08DEC2010"d.

During our review of the PDF print out of the IVRS log file submitted, we noticed that the treatment assignment was not properly ordered by time of subject randomization on a particular date. If there was more than one subject randomized on the same date (identified by the variable 'RANDDT'), the treatment assignment order may not match the order by randomization time (identified by the variable 'RANDT') within the same stratum. For example, subject 7021 (randomized at RANDDT=3-Jun-10 and RANDT=9:10:00) received their treatment assignment in block 4 before subject 7022 (randomized at RANDDT=3-Jun-10 and RANDT=8:17:00) received the treatment assignment in block 5 and both in the same viral load stratum (“less than or equal to 100000 copies/mL”). Multiple occurrences like this have been noted (Table 2 below).

Table 2: Small Section of IVRS log File for Study GS-US-236-0103

RANDID	TREATNUM	TREATMNT	BLOCK	STRTNC	STRTNM	ASSIGNED	SITE	SUBJID	RANDDT	RANDT
13	1	Active EVG/F	4	1	Less than or equal to 100000 copies/mL	1	2475	7018	2-Jun-10	11:14:00
14	1	Active EVG/F	4	1	Less than or equal to 100000 copies/mL	1	2728	7019	2-Jun-10	10:04:00
15	2	Placebo EVC	4	1	Less than or equal to 100000 copies/mL	1	2728	7020	2-Jun-10	15:30:00
16	2	Placebo EVC	4	1	Less than or equal to 100000 copies/mL	1	637	7021	3-Jun-10	9:10:00
17	1	Active EVG/F	5	1	Less than or equal to 100000 copies/mL	1	765	7022	3-Jun-10	8:17:00
18	1	Active EVG/F	5	1	Less than or equal to 100000 copies/mL	1	302	7023	3-Jun-10	10:33:00
19	2	Placebo EVC	5	1	Less than or equal to 100000 copies/mL	1	1978	7024	3-Jun-10	8:51:00
20	2	Placebo EVC	5	1	Less than or equal to 100000 copies/mL	1	698	7026	4-Jun-10	7:52:00

We asked the sponsor to explain this and submit the IVRS log file in SAS data format, or in a .csv file.

The sponsor’s response is that the times in the PDF print out are local time.

In the newly submitted random.xpt file, the randdt and randt were updated to the centralized US west-coast time. In this file, the order of treatment assignment is correct. We did check a few subjects in terms of change of time, and they were correct (Table 3 below).

Table 3: Checking the Changes of RANDDT and RANDT between Local and Centralized Time for Study GS-US-236-0103

1	old local time zone data in S0018							new standard time zone in S0026					
2	randID	site	subjid	randdt	randt	Country	State	site	subjid	randdt	randt	site in the ADSL for the subject	
3	16	637	7021	3-Jun-10	9:10:00	US	NJ	637	7021	3-Jun-10	6:10:25		
4	17	765	7022	3-Jun-10	8:17:00	US	NY	765	7022	3-Jun-10	8:17:44	2728	US/CA
5	18	302	7023	3-Jun-10	10:33:00	US	TX	302	7023	3-Jun-10	8:33:27		
6	19	1978	7024	3-Jun-10	8:51:00	US	CA	1978	7024	3-Jun-10	8:51:33		
7													
8	899	5856	7474	3-Sep-10	8:14:00	France		5856	7474	2-Sep-10	11:14:19	2423	France
9													Note: site 5856 does not exist in the ADSL

However, when comparing the random.xpt file submitted April 3, 2012 to the ADSL dataset, we identified 57 subjects with discrepancies involving site. For example, subject 7022 was at site

765 in the random.xpt dataset but this subject did not appear in the ADSL dataset. A subject with subjid=2728-7022 was found in the ADSL which indicates that subject 7022 was at site 2728, not at site 765 (Table 3).

The sponsor's response is the following:

The discrepancies that the agency noticed were caused by subjects switching sites during the trial and by different approaches applied in capturing site numbers in raw and analysis datasets. For example, subject 7022 had switched from site 2728 to site 0765 when Gilead's IVRS vendor extracted the RANDOM.XPT dataset on 30 March 2012, so this subject was included in RANDOM.XPT dataset as 0765-7022. This subject was randomized at site 2728 and was included in the analysis dataset ADSL as 2728-7022.

Comparing ADSL and RANDOM.xpt datasets, the applicant confirmed that all the 57 discrepancies were caused by subjects switching sites during the trial.

The sponsor did provide the subject ID at randomization (for analysis datasets) and at data extraction on Mar. 30, 2012 in RANDOM.xpt, and the date of site switch for these 57 subjects.

At this moment, we asked the sponsor to provide the IVRS' SOP related to the site switch for review.

The sponsor's response is the following:

^{(b)(4)} *Gilead's IVRS vendor used to generate and manage treatment allocation codes for Study GS-US-236-0103, does not have a specific SOP related to site switch but does have SOPs which dictate the processing of data changes in the IVRS. While ^{(b)(4)} policies prevent them from distributing electronic copies of their SOPs outside of the company, they have provided a summary of the following relevant SOPs:*

- *SOP-DM-002: Data Changes*
- *SOP-DM-006: Data Change Impact Assessment and Change Methodology*
- *SOP-DM-007: Data Change Guide Creation*

The summary of the three SOPs governing data changes to transfer a subject from one site to another site is the following:

During the course of a trial, subjects may need to switch their site. In such an event, a data change form (DCF) is used to accomplish this transfer in the IxRS database. In the IxRS database, the site associated with a subject is updated to the new site, to allow the subject to continue recording visits and receiving drug at the new site. Both sites remain in the IxRS database, and the subject is disassociated from the first site, and associated to the second site. For example, in Gilead study GS-US-236-0103, subject 7022 transferred from site 2728 to site 0765 on 26-Jul-2010. The update was accomplished with a data change form.

If the Agency requires copies of the SOP for review, (b) (4) prefers that the Agency contact them directly at the telephone number and/or email address provided below.

After the statistical team went through the summary, we think it is reasonable. And there is no need for further action. That is, we think the randomization for study GS-US-236-0103 is OK based on the documents the sponsor provided.

3. FDA’s Snapshot Algorithm Used for the Primary Efficacy Analysis:

The sponsor did state that FDA’s snapshot algorithm was used for the primary efficacy analysis. By checking their snapshot analysis flowchart (Figure 1 below) presented in the SAP, however, it has been noticed that the non-study anti-retroviral (ARV) drug usage during the trial or the OBT change were not considered when they derived the primary efficacy endpoint (the percentage of <50 copies/mL in the week 48 window).

One possible reason is that this is a single-tablet regimen (STR), and subjects may not be able to change one of components in STR. But subjects can still add new ARV to the regimen. The drug changes during the trials have been examined by the stat reviewer in detail.

The final impact on the primary efficacy analysis of adding the ARV changes into snapshot algorithm is minimum for both studies, and there is no change on the final efficacy primary endpoint analysis. The detailed drug change information will be presented below by study.

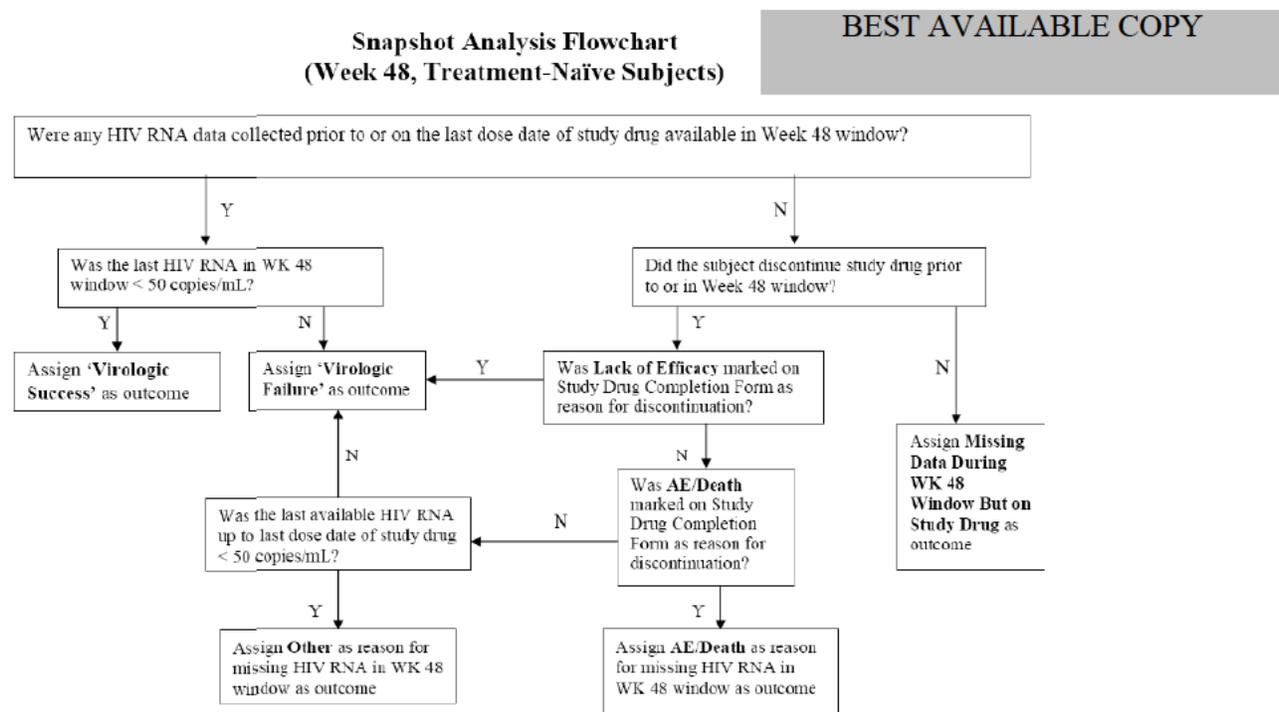


Figure 1: FDA’s Snapshot Analysis Flowchart Used in the Pivotal Studies

- ARV changes during the study GS-US-236-0102:

Overall, there were 84 records for 37 subjects, in which one of them was not in the ITT population, in the concomitant medication (CM) dataset. The majority of these 36 subjects who were in the ITT population and took other ARV drugs during the trial were already classified as non-responders by other reasons, such as discontinuation due to AE or death, etc. Only 5 out of these 36 subjects were classified as success in the sponsor's snapshot analysis.

The ARV drug usage information for these 5 subjects is listed in Table 4 below. As you can see, three subjects in E/C/F/T arm took other than randomized ARV drugs after the discontinuation of study drug, and the concomitant ARV medication started after the end of the Week 48 visit window. So, for the 48 week analysis it is OK to be classified as a responder as long as their HIV viral load was <50 copies/mL within the Week 48 visit window. One subject (2838-6437) in E/C/F/T arm took Atripla for one day within 48 weeks of treatment, and that could be an error. It seems OK here for this subject to be classified as a responder as long as their HIV viral load was <50 copies/mL within the Week 48 visit window.

But these subjects will be classified as non-responders for future analyses, like the Week 96 analysis.

One subject (1978-6117) in the ATR arm took Atripla within 48 weeks of treatment for 98 days. But the subject was randomized to receive Atripla. So, it is OK to be classified as a responder as long as their HIV viral load was <50 copies/mL within the Week 48 visit window.

Table 4: ARV Drug Usage Information for Subjects Who Took Other ARV Drug during the Trial and Classified as Success in Snapshot Analysis for Study GS-US-236-0102

Arm / Subjid	Study Drug Start/End date	ConMed	ConMed Start/End date	ConMed Starting Day	ConMed Duration
E/C/F/T					
0581-6471	6/25/10 -- 7/21/11	Atripla	7/23/11 -- ongoing	394	
0698-6222	5/13/10 -- 6/27/11	Epzicom (ABC+3TC), Rilpivirine	7/1/11 -- ongoing	415	
2480-6231	5/13/10 -- 7/14/11	Raltegravir, Truvada	7/15/11 -- ongoing	429	
2838-6437	6/18/10 -- 8/12/11	Atripla	4/8/11 -- 4/8/11	295	1 (compt trt*)
ATR					
1978-6117	4/29/10 -- 8/12/11	Atripla	1/11/11 -- 4/18/11	258	98 (compt trt)

*: compt trt: stands for complete the treatment.

- ARV changes during the study GS-US-236-0103:

Overall, there were 101 records for 40 subjects, in which one of them was not in the ITT population, in the CM dataset. The majority of these 39 subjects who were in the ITT population and took other ARV drugs during the trial were already classified as non-responders by other reasons, such as discontinuation due to AE or death, etc. Only 2 out of these 39 were classified as responders in the sponsor's snapshot analysis.

The ARV drug usage information for these 2 subjects is listed in Table 5 below. Note one subject (0959-7110) in E/C/F/T arm took ARV drug after the discontinuation of study drug, even though

the concomitant ARV medication started within the Week 48 visit window. So, for 48 week analysis it is OK to be classified as a responder as long as their HIV viral load is <50 copies/mL within the Week 48 visit window.

One subject (0369-7262) in ATV/r arm took ARV drug after the discontinuation of study drug, and the concomitant ARV medication started after the Week 48 visit window. So, for 48 week analysis it is OK to be classified as responder as long as their HIV viral load was <50 copies/mL within the Week 48 visit window.

Table 5: ARV Drug Usage Information for Subjects who took Other ARV Drug during the Trial and Classified as Success in Snapshot Analysis for Study GS-US-236-0103

Arm / Subjid	Study Drug Start/End date	ConMed	ConMed Start/End date	ConMed Starting Day	ConMed Duration
E/C/F/T					
0959-7110	7/5/10 -- 6/11/11	Abacavir + Lamivudine + Raltegravir	6/25/11 -- ongoing	356	Did not complete study trt
ATV/r					
0369-7262	8/10/10 -- 7/19/11	Combivir + Kaletra	7/19/05 -- 8/1/05		Completed study trt

2. INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

This NDA is being submitted to support for a single-tablet regimen (STR) that contains a fixed-dose combination of elvitegravir (EVG), cobicistat (COBI), emtricitabine (FTC, Emtriva®) and tenofovir disoproxil fumarate (TDF, Viread®): the EVG/COBI/FTC/TDF (150/150/200/300 mg) tablet (referred to as **E/C/F/T** throughout this document).

Elvitegravir is a new chemical entity that belongs to the new class of HIV-1 integrase strand-transfer inhibitors (INSTIs) that prevent integration of HIV-1 genetic material into the host-cell genome. According to the submitted document, Cobicistat is a new chemical entity and structural analogue of ritonavir (RTV, r) without ARV activity. It is a more specific, mechanism-based cytochrome P450 3A (CYP3A) inhibitor than RTV that enhances or “boosts” the exposure of CYP3A substrates, including EVG.

Gilead Sciences, Inc. (Gilead) has developed EVG and COBI for use within a new 4-drug fixed-dose combination tablet that also contains the current standard-of-care dual nucleoside/nucleotide reverse transcriptase inhibitor (NRTI/NtRTI) backbone FTC/TDF (Truvada® [TVD]).

Current treatment guidelines suggest that initial therapy for ARV treatment-naive HIV-1 infected patients consists of 2 NRTIs/NtRTIs and either a non-nucleoside reverse transcriptase inhibitor (NNRTI), usually efavirenz (EFV; Sustiva®), a boosted protease inhibitor (PI), or the INSTI raltegravir (RAL; Isentress®). Treatment guidelines list FTC and TDF as a preferred NRTI/NtRTI backbone in an ARV regimen for initial therapy.

The virologic response rates (HIV-1 ribonucleic acid [RNA] < 50 copies/mL) of these options from phase 3 studies are the following:

- EFV-plus-NRTI-containing regimens: approximately 80% at Week 48;
- RTV-boosted atazanavir (ATV, Reyataz®) (ATV/r)-plus-NRTI-containing regimens: about 78% at Week 48; and
- RAL in treatment-naive subjects: roughly 86 % at Week 48.

To date, there are 2 NNRTI/NRTI based-STRs approved for once-daily administration in the treatment of HIV-1 infection:

- Atripla® (EFV/FTC/TDF [ATR]; approved on 12 July 2006), and
- Complera™ ((FTC/rilpivirine [RPV]/TDF; approved on 10 August 2011)

This E/C/F/T STR provided the first a combination of an INSTI with an NRTI backbone, plus COBI which is an investigational pharmacoenhancer devoid of anti-HIV activity. This may

provide an alternative for patients who cannot tolerate boosted PIs or NNRTIs and for patients who wish to simplify their regimen through a lower pill burden.

The proposed indication for the E/C/F/T STR is for use once daily as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults aged 18 years and over who are antiretroviral (ARV) naive or have no known substitutions associated with resistance to the individual components.

2.1.2 History of Drug Development

There are two new agents, EVG and COBI. FTC and TDF are approved drugs. This NDA is supported by right of reference to applicable sections of following three products:

- Gilead's NDA 21,500, NDA 21,896, and IND 53,971 for FTC (Emtriva®);
- Gilead's NDA 21,356, NDA 22,577, and IND 52,849 for TDF (Viread®); and
- Gilead's NDA 21,752 and IND 67,671 for FTC/TDF (Truvada® [TVD]).

The efficacy and safety of FTC, TDF, and TVD as part of a regimen for the treatment of HIV-1 infection have been established through comprehensive programs of clinical studies with these medicinal products, as submitted in the original NDAs for Emtriva 200-mg hard capsules (approved on 02 July 2003) and Emtriva 10-mg/mL oral solution (approved on 28 September 2005); Viread 300-mg film-coated tablets (approved on 26 October 2001); and TVD film-coated tablets (approved on 02 August 2004). In addition, a variety of labeling and safety supplements have been submitted post approval to update the prescribing information with emergent data. Periodic safety update reports (PSURs) and annual reports have been submitted in accordance with local requirements.

At the time of this NDA submission, the principal clinical safety and efficacy data presented in this application are derived from two Phase 3 studies (GS-US-236-0102 and GS-US-236-0103) and one Phase 2 study (GS-US-236-0104) conducted with the E/C/F/T STR in ARV treatment-naive, HIV-1 infected subjects.

Only two phase 3 studies will be reviewed in this review. Study GS-US-236-0104 will not be fully reviewed in this review since only 71 subjects were randomized.

2.1.3 Studies Reviewed

The detailed description of two phase 3 studies and the phase 2 study is listed in Table 6. Study GS-US-236-0102 was conducted in US alone, and study GS-US-236-0103 was conducted in US as well as non-US countries, including AUSTRALIA, CANADA, THAILAND, GERMANY, FRANCE, UNITED KINGDOM, AUSTRIA, BELGIUM, ITALY, NETHERLANDS, PORTUGAL, DENMARK, SWITZERLAND, SWEDEN.

Both phase 3 studies are ongoing 192-week studies. The data submitted for this NDA are 48 week data. So there are additional data that will be available in the future.

Table 6: List of all studies included in analysis

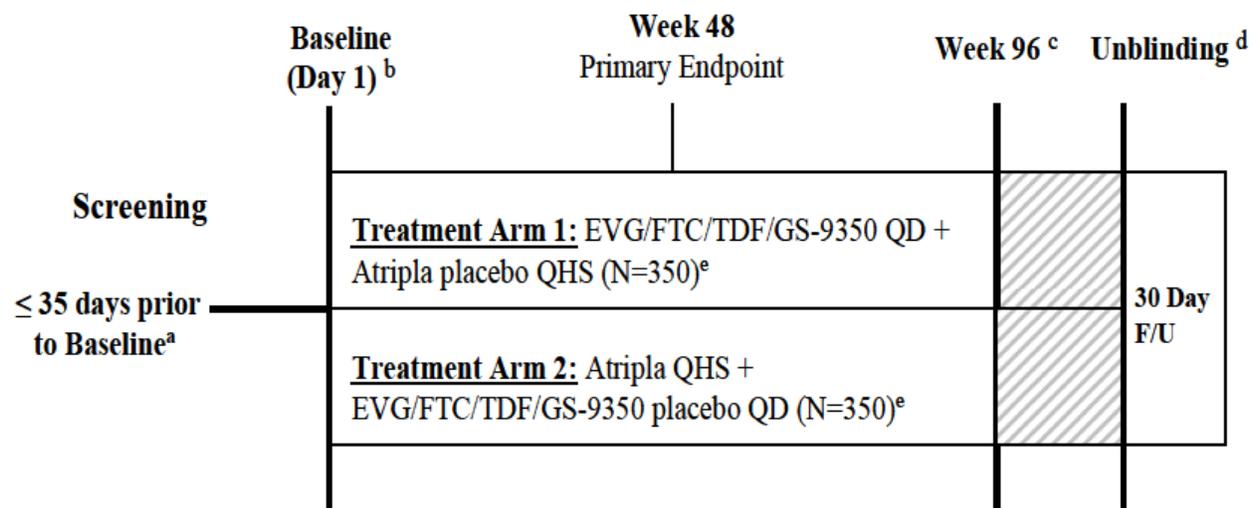
Study	Phase and Design	Objectives	Treatment Period	# of Subjects per Arm	Study Population
GS-US-236-0102	Phase 3, double-blind, Double - dummy, multicenter, randomized, active controlled study	Evaluate the efficacy of an STR containing EVG/COBI/FTC/TDF (E/C/F/T) versus an STR containing EFV/FTC/TDF (Atripla®; ATR) in HIV-1 infected, ARV treatment naive adult subjects, as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48	96 weeks of double-blind treatment. In this NDA, week 48 interim clinical study report was submitted for review	Randomized: 707 (353 E/C/F/T and 354 ATR) Subjects still on study treatment up to the Week 48 analysis data cut date: 617 (311 E/C/F/T and 306 ATR) Subjects still on study up to the Week 48 analysis data cut date: 635 (319 E/C/F/T and 316 ATR)	HIV-1 infected, ARV Treatment naive adults
GS-US-236-0103	Phase 3, double-blind, Double-dummy, multicenter, randomized, active controlled study	Evaluate the efficacy of an STR containing EVG/COBI/FTC/TDF (E/C/F/T) vs a regimen containing ATV/r plus TVD in HIV-1 infected, ARV treatment naive adult subjects, as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48	96 weeks of double-blind treatment. In this NDA, week 48 interim clinical study report was submitted for review	Randomized: 715 (357 E/C/F/T and 358 ATV/r +TVD group) Subjects still on study treatment up to the Week 48 analysis data cut date: 635 (320 E/C/F/T and 315 ATV/r +TVD group) Subjects still on study up to the Week 48 analysis data cut date: 655 (331 E/C/F/T and 324 ATV/rated group)	HIV-1 infected, ARV Treatment naive adults
GS-US-236-0104*	Phase 2, double-blind, double-dummy, multicenter, randomized, active-controlled study	Evaluate the efficacy of an STR containing EVG/COBI/FTC/TDF (E/C/F/T) vs an STR Containing EFV/FTC/TDF (Atripla®; ATR) in HIV-1 infected, ARV treatment-naive adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 24	60 weeks of double-blind treatment, followed by optional open-label E/C/F/T extension until study drug commercially available or study terminated by sponsor	Randomized: 71 (48 E/C/F/T and 23 ATR) Completed the randomized phase: 65 (45 E/C/F/T and 20 ATR) Entered open-label extension: 59 (45 E/C/F/T and 14 ATR)	HIV-1 infected, ARV Treatment naive adults

*: Study GS-US-236-0104 will not be reviewed in this review. It was listed here for completion purpose and information only.

The detailed design characteristics of two phase 3 studies were described below.

❖ **GS-US-236-0102, a phase 3 study for Treatment-naive HIV-1 subjects:**

Title: A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Emtricitabine/Tenofovir Disoproxil Fumarate/GS-9350 Versus Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Infected, Antiretroviral Treatment-Naive Adults



- a Screening window may be extended to up to 42 days prior to the Baseline visit for subjects who require repeat testing of the HIV-1 genotype.
- b Following the Baseline visit, subjects will return for study visits at Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48; and then every 12 weeks through Week 96.
- c Subjects will continue to attend visits every 12 weeks following Week 96 until treatment assignment is unblinded.
- d Once Gilead Sciences provides unblinded treatment assignments to the Investigators, all subjects will return to the clinic (preferably within 30 days) for an Unblinding Visit. At the Unblinding Visit all subjects will discontinue their blinded study drug and will be given an option to participate in an open-label rollover study. Subjects who do not wish to participate in the open-label rollover study will discontinue their blinded study drug and will return for a 30 Day Follow-up visit following the Unblinding Visit.
- e Subjects who have discontinued study drug prior to the Unblinding Visit will not be eligible for the open-label rollover study; these subjects will be asked to continue attending the scheduled study visits through the Unblinding Visit and discontinue the study after the Unblinding Visit.
- f The EVG/FTC/TDF/GS-9350 FDC tablet and matching placebo will be administered orally, one tablet, once daily with food at approximately the same time each day. ATR tablets and matching placebo will be administered orally, one tablet, once daily, on an empty stomach at preferably bedtime and at approximately the same time each day.

Figure 2: GS-US-236-0102 Study Design Diagram

*QHS stands for once daily at bedtime

A total of 707 subjects were randomized in a 1:1 ratio 1 of the following 2 treatment groups:

Treatment Group 1: STR containing EVG 150 mg/COBI 150 mg/FTC 200 mg/TDF 300 mg (E/C/F/T) once daily + placebo for Atripla (ATR) once daily prior to bedtime (**E/C/F/T arm**)

Treatment Group 2: STR containing EFV 600 mg/FTC 200 mg/TDF 300 mg (Atripla) once daily prior to bedtime + placebo for E/C/F/T once daily (**ATR arm**)

Randomization was stratified by HIV-1 RNA level ($\leq 100,000$ copies/mL or $> 100,000$ copies/mL) at screening. Block size 4 will be used for randomization.

Key Eligibility Criteria: HIV-1 infected subjects who meet the following criteria:

- Plasma HIV-1 RNA levels $\geq 5,000$ copies/mL at screening
- No prior use of any approved or experimental antiretroviral drug for any length of time
- Screening genotype report shows sensitivity to FTC, TDF, and EFV

During the double-blind treatment period, study visits occurred at Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48; and then every 12 weeks through Week 96. After Week 96, subjects will continue to take their blinded study drug and attend visits every 12 weeks until treatment assignments are unblinded. At the unblinding visit, subjects will be given the option to participate in an open-label rollover study in which all subjects will be treated with the E/C/F/T STR.

The double-blind phase of the study is ongoing; however, the 48-week primary endpoint has been analyzed.

The primary objective of this study is to evaluate the efficacy of an STR containing EVG/COBI/FTC/TDF (E/C/F/T) versus an STR containing EFV/FTC/TDF (ATR) in HIV-1 infected, ARV treatment-naive adult subjects.

Primary Efficacy Endpoint: The primary efficacy endpoint is the percentage of subjects with virologic success (ie, HIV-1 RNA < 50 copies/mL) at Week 48 using the FDA-defined snapshot analysis.

The percentage of subjects with virologic success at Week 48 was used to assess treatment noninferiority of the E/C/F/T STR compared with the ATR STR using a conventional 95% CI approach, with a noninferiority margin of 12%.

All primary and secondary efficacy analyses will be carried out using the two-sided stratum-adjusted Mantel Haenszel (MH) chi-square test (adjusted for the baseline stratification factors).

Sensitivity analysis for primary efficacy endpoint on ITT:

1. For the first sensitivity analysis, subjects who have no virologic data in the Week 48 analysis window due to discontinuation of study drug prior to or in the Week 48 analysis window for reasons other than lack of efficacy, AE or death and have the last available HIV-1 RNA on randomized treatment < 50 copies/mL will be excluded from both the numerator and denominator in the response rate computation. Additionally, for late discontinuation (ie, discontinuation of study drug due to reasons other than death in the Week 48 analysis window), all the HIV-1 RNA data in the Week 48 analysis window including data collected

after the last dose of study drug will be included in the evaluation of virologic response per FDA-defined snapshot algorithm.

2. As a second sensitivity analysis, subjects who have no virologic data in the Week 48 analysis window due to discontinuation of study drug prior to or in the Week 48 analysis window for reasons other than lack of efficacy, AE or death and have the last available HIV-1 RNA on randomized treatment < 50 copies/mL will be counted as success. Viral load collected after the last dose of study drug for late discontinuation will be handled in the same way as in the first sensitivity analysis.
3. The third sensitivity analysis is to assess whether the treatment effect is confounded by region and baseline plasma HIV-1 RNA level. The following analyses will be performed for the primary endpoint:
 - (1) Stratifying by region and not by baseline HIV-1 RNA, and
 - (2) Without any stratification factors. The results from these 2 analyses will be compared with primary analysis (ie, stratified by baseline HIV-1 RNA level). The stratified CMH analyses will be used to estimate the odds ratio, the corresponding 95% CI and to obtain p-values. A region is defined as multiple sites combined based on sites from neighboring states in the U.S. (Table 7 copied from its SAP)

The secondary objective of this study (evaluated beyond Week 48) is to evaluate the efficacy, safety, and tolerability of the 2 STRs through 96 weeks of treatment.

Secondary Endpoints:

- The percentage of subjects with virologic success (ie, HIV-1 RNA < 50 copies/mL) at Week 96 using the FDA-defined snapshot analysis.
- The achievement and maintenance of confirmed HIV-1 RNA <50 copies/mL through Weeks 48 and 96 as defined by the time-to-loss of virologic-response (TLOVR) algorithm.

The time-to-loss-of-virologic-response will be analyzed using the Kaplan-Meier estimates and the log rank test stratified by the baseline HIV-1 RNA level ($\leq 100,000$ copies/mL versus $> 100,000$ copies/mL).

Some Tertiary Efficacy Endpoints:

- The change from baseline in CD4 cell count and CD4% at Week 48 and 96.

The changes from baseline in \log_{10} HIV-1 RNA, CD4 cell count and CD4% at Weeks 48 and 96 will be summarized using descriptive statistics.

Table 7: Region Combination for Study GS-US-236-0102

Region	Country Name	State	No. of Randomized Subjects	Total No. of Randomized Subjects (N=707)	Total No. of ITT Subjects (N=700)
Region 1	United States	CA	148	167	164
		HI	3		
		WA	16		
Region 2	United States	FL	136	162	161
		PR	26		
Region 3	United States	AZ	10	82	81
		CO	8		
		NM	1		
		TX	63		
Region 4	United States	AL	6	51	51
		GA	45		
Region 5	United States	CT	3	81	80
		MA	11		
		NJ	22		
		NY	45		
Region 6	United States	DC	39	59	59
		MD	3		
		PA	8		
		VA	9		
Region 7	United States	NC	32	43	42
		SC	11		
Region 8	United States	AR	9	62	62
		IL	7		
		MI	14		
		MN	8		
		MO	10		
		OH	9		
		WI	5		

Note: Sites are combined according to geographic location to have n > 40 for each region.

Analysis Populations

- **Randomized:** includes subjects who were randomized into the study. This mainly is used for listing.
- **Intent-to-Treat (ITT):** includes all randomized subjects who received at least one dose of study drug. This is the primary analysis set for efficacy analyses.
- **Per Protocol (PP):** includes all subjects in ITT and have not committed any major protocol violation, including violation of key entry criteria. This is the secondary analysis set for efficacy analysis.

- **Safety analysis set:** includes all randomized subjects who received at least one dose of study drug. All the data collected up to 30 days after subjects permanently discontinue all study drugs will be included in the safety summaries. This is the primary analysis set for safety analysis.

For all efficacy analyses, subjects will be included in the treatment arm to which they are randomized. For all safety analyses, subjects will be included in the treatment arm corresponding to the study treatment they actually received.

Randomization was stratified by HIV-1 RNA level ($\leq 100,000$ copies/mL or $> 100,000$ copies/mL) at screening. HIV-1 RNA strata will be re-classified using baseline HIV-1 RNA level ($\leq 100,000$ copies/mL or $> 100,000$ copies/mL) for the primary efficacy statistical analysis. (There are some discrepancies that will be addressed in the analysis section.)

Interim analyses:

- **Week 12 Independent Data Monitoring Committee (IDMC) Analysis**
The Week 12 IDMC analysis has been conducted after the first 350 subjects either complete their Week 12 visit or prematurely discontinue study drug. The purpose of this interim analysis is to provide the IDMC with a statistical report for review.
- **Week 24 IDMC Analysis**
Same IDMC analysis was conducted after the last subject either completed their Week 24 visit or prematurely discontinue study drug.
- **Week 48 Analysis**
This analysis was conducted for the NDA submission.
- Other analyses include **Week 96 analysis** and **Final analysis**.

Multiplicity adjustment: there are two interim IDMC analyses performed at Week 12 (0.001) and 24 (0.001), and the alpha level at Week 48 analysis will be adjusted to 0.048. As a result, the 95% CI will be **95.2% CI** in order to preserve the overall type I error.

Data Handling Conventions and Transformations:

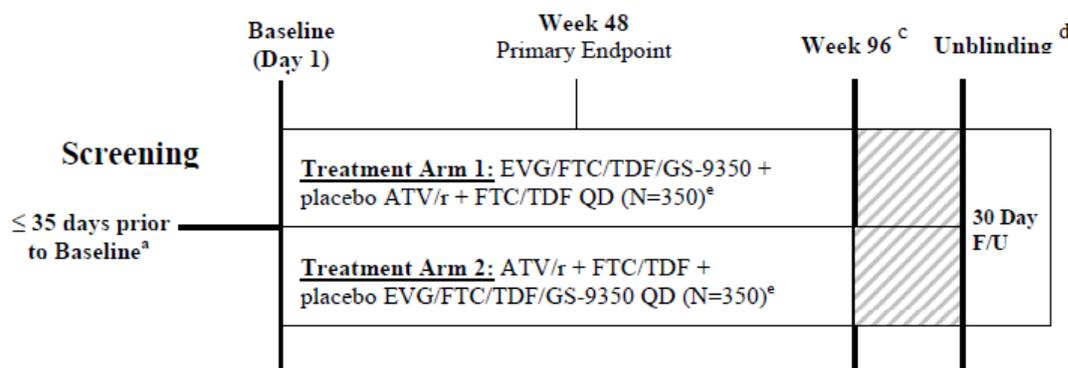
- Logarithm (base 10) will be used to transform HIV-1 RNA data.
- A value that is one unit less than the limit of quantification will be used for calculation of descriptive statistics if the datum is reported in the form of “< X”. For example, if the values are reported as < 50 and < 5.0, then values of 49 and 4.9 will be used for calculation of summary statistics, respectively.
- For serum Cystatin C, value of “<.10” is handled as a missing value in summary or in the calculation of eGFR.

Sample size calculation:

It is assumed that both treatment groups have a response rate of 0.795 (based on Gilead Study GS-01-934), that a noninferiority margin is 0.12, and that the significance level of the test is at a one-sided, 0.025 level, a total of 700 HIV-1 infected subjects, randomized in a 1:1 ratio to 2 groups (350 subjects per group) achieves at least 95% power to establish noninferiority in the Week 48 response (HIV-1 RNA < 50 copies/mL as defined by the Food and Drug Administration [FDA] snapshot analysis) rate difference between the 2 groups.

❖ GS-US-236-0103, a phase 3 study for Treatment-naive HIV-1 subjects:

Title: A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Emtricitabine/Tenofovir Disoproxil Fumarate/GS-9350 Versus Ritonavir-Boosted Atazanavir Plus Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Infected, Antiretroviral Treatment-Naive Adults.



- a Screening window may be extended to up to 42 days prior to the Baseline visit for subjects who require repeat testing of the HIV-1 genotype.
- b Following the Baseline visit, subjects will return for study visits at Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48; and then every 12 weeks through Week 96.
- c Subjects will continue to attend visits every 12 weeks following Week 96 until treatment assignment is unblinded.
- d Once Gilead Sciences provides unblinded treatment assignments to the Investigators, all subjects will return to the clinic (preferably within 30 days) for an Unblinding Visit. At the Unblinding Visit all subjects will discontinue their blinded study drug and will be given an option to participate in an open-label rollover study. Subjects who do not wish to participate in the open-label rollover study will discontinue their blinded study drug and will return for a 30 Day Follow-up visit following the Unblinding Visit.
Subjects who have discontinued study drug prior to the Unblinding Visit will not be eligible for the open-label rollover study; these subjects will be asked to continue attending the scheduled study visits through the Unblinding Visit and discontinue the study after the Unblinding Visit.
- e The EVG/FTC/TDF/GS-9350 FDC tablet and matching placebo will be administered orally, one tablet, once daily with food at approximately the same time each day. ATV/r plus FTC/TDF and matching placebos will be administered orally, once daily with food at approximately the same time each day.

Figure 3: GS-US-236-0103 Study Design Diagram

A total of 715 subjects were randomized in a 1:1 ratio to the following 2 treatment groups:

Treatment Group 1: STR containing EVG 150 mg/COBI 150 mg/FTC 200 mg/TDF 300 mg (E/C/F/T) once daily + placebos for RTV, ATV, and TVD once daily (n=350) (E/C/F/T arm)

Treatment Group 2: ATV 300 mg, RTV 100 mg, and FTC 200 mg/TDF 300 mg (TVD) once daily + placebo for E/C/F/T once daily (n=350) (ATV/r arm)

Randomization was stratified by HIV-1 RNA level ($\leq 100,000$ copies/mL or $> 100,000$ copies/mL) at screening. A block size of 4 was used for randomization.

Key Eligibility Criteria

HIV-1 infected adult subjects who meet the following criteria:

- Plasma HIV-1 RNA levels ≥ 5000 copies/mL at screening
- No prior use of any approved or experimental antiretroviral drug for any length of time
- Screening genotype report shows sensitivity to FTC, TDF and ATV

During the double-blind treatment period, study visits occurred at Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48; and then every 12 weeks through Week 96. After Week 96, subjects will continue to take their blinded study drug and attend visits every 12 weeks until treatment assignments are unblinded. At the unblinding visit, subjects will be given the option to participate in an open-label rollover study in which all subjects will be treated with the E/C/F/T STR.

The double-blind phase of the study is ongoing; however, the 48-week primary endpoint has been analyzed.

The primary objective of this study is to evaluate the efficacy of a STR containing EVG/COBI/FTC/TDF (E/C/F/T) versus a regimen containing ATV/r + TVD in HIV-1 infected, ARV treatment-naïve adult subjects, as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48.

Primary Efficacy Endpoint: The primary efficacy endpoint is the percentage of subjects with virologic success (ie, HIV-1 RNA < 50 copies/mL) at Week 48 using the FDA-defined snapshot analysis.

The percentage of subjects with virologic success at Week 48 was used to assess treatment noninferiority of the E/C/F/T STR compared with ATV/r + TVD using a conventional 95% CI approach, with a noninferiority margin of 12%.

The secondary objective (evaluated beyond Week 48) is to evaluate the efficacy, safety, and tolerability of the 2 treatment regimens through 96 weeks of treatment.

Secondary Endpoints:

- The percentage of subjects with virologic success (ie, HIV-1 RNA < 50 copies/mL) at Week 96 using the FDA-defined snapshot analysis.
- The achievement and maintenance of confirmed HIV-1 RNA <50 copies/mL through Weeks 48 and 96 as defined by the time-to-loss of virologic-response (TLOVR) algorithm.

The time-to-loss-of-virologic-response will be analyzed using the Kaplan-Meier estimates and the log rank test stratified by the baseline HIV-1 RNA level ($\leq 100,000$ copies/mL versus $> 100,000$ copies/mL).

Some Tertiary Efficacy Endpoints:

- The change from baseline in CD4 cell count and CD4% at Week 48 and 96.

The changes from baseline in \log_{10} HIV-1 RNA, CD4 cell count and CD4% at Weeks 48 and 96 will be summarized using descriptive statistics.

Analysis Populations

- **Randomized:** includes subjects who were randomized into the study. This mainly is used for listing.
- **Intent-to-Treat (ITT):** includes all randomized subjects who received at least one dose of study drug. This is the primary analysis set for efficacy analyses.
- **Per Protocol (PP):** includes all subjects in ITT and have not committed any major protocol violation, including violation of key entry criteria. This is the secondary analysis set for efficacy analysis.
- **Safety analysis set:** includes all randomized subjects who received at least one dose of study drug. All the data collected up to 30 days after subjects permanently discontinue all study drugs will be included in the safety summaries. This is the primary analysis set for safety analysis.

For all efficacy analyses, subjects will be included in the treatment arm to which they are randomized. For all safety analyses, subjects will be included in the treatment arm corresponding to the study treatment they actually received.

Randomization was stratified by HIV-1 RNA level ($\leq 100,000$ copies/mL or $> 100,000$ copies/mL) at screening. HIV-1 RNA strata will be re-classified using baseline HIV-1 RNA level ($\leq 100,000$ copies/mL or $> 100,000$ copies/mL) for statistical analysis including primary efficacy analysis.

Interim analyses:

- **Week 12 Independent Data Monitoring Committee (IDMC) Analysis**

The Week 12 IDMC analysis has been conducted after the first 350 subjects either complete their Week 12 visit or prematurely discontinue study drug. The purpose of this interim analysis is to provide the IDMC with a statistical report for review.

- **Week 24 IDMC Analysis**

Same IDMC analysis was conducted after last subject either complete the Week 24 visit or prematurely discontinue study drug.

- **Week 48 Analysis**

This analysis was conducted for the NDA submission.

- Other analyses include **Week 96 analysis** and **Final analysis**.

Multiplicity adjustment: there are two interim IDMC analyses performed at Week 12 (0.001) and 24 (0.001), and the alpha level at Week 48 analysis will be adjusted to 0.048. As a result, the 95% CI will be **95.2% CI** in order to preserve the overall type I error.

Data Handling Conventions and Transformations:

- Logarithm (base 10) will be used to transform HIV-1 RNA data.
- A value that is one unit less than the limit of quantification will be used for calculation of descriptive statistics if the datum is reported in the form of “< X”. For example, if the values are reported as < 50 and < 5.0, then values of 49 and 4.9 will be used for calculation of summary statistics, respectively.
- For serum Cystatin C, value of “<.10” is handled as a missing value in summary or in the calculation of eGFR.

Sample size calculation:

It is assumed that both treatment groups have a response rate of 0.795 (based on Gilead Study GS-01-934), that a noninferiority margin is 0.12, and that the significance level of the test is at a one-sided, 0.025 level, a total of 700 HIV-1 infected subjects, randomized in a 1:1 ratio to 2 groups (350 subjects per group) achieves at least 95% power to establish noninferiority in the Week 48 response (HIV-1 RNA < 50 copies/mL as defined by the Food and Drug Administration [FDA] snapshot analysis) rate difference between the 2 groups.

The region used in this study is listed Table 8 below (Copied from SAP):

Table 8: Region Combination for Study GS-US-236-0103

Region	Country Name	State	No. of Randomized Subjects (N=715)	Total No. of Randomized Subjects (N=715)	No. of ITT Subjects (N=708)	Total No. of ITT Subjects (N=708)
Region 1	AUSTRALIA		62	62	62	62
Region 2	CANADA		41	41	41	41
Region 3	THAILAND		11	11	11	11
Region 4	GERMANY		65	65	65	65
Region 5	FRANCE		47	74	46	72
	UNITED KINGDOM		27		26	
Region 6	AUSTRIA		20	70	20	70
	BELGIUM		21		21	
	ITALY		14		14	
	NETHERLANDS		6		6	
	PORTUGAL		3		3	
	DENMARK		3		3	
	SWITZERLAND		2		2	
	SWEDEN		1		1	
Region 7	UNITED STATES	CA	83	89	83	89
	UNITED STATES	WA	5		5	
	UNITED STATES	HI	1		1	
Region 8	UNITED STATES	FL	79	95	79	95
	UNITED STATES	PR	11		11	
	MEXICO		5		5	
	DOMINICAN REPUBLIC		0		0	
Region 9	UNITED STATES	TX	56	73	55	71
	UNITED STATES	CO	9		9	
	UNITED STATES	AZ	8		7	
Region 10	UNITED STATES	DC	24	52	24	50
	UNITED STATES	NC	13		12	
	UNITED STATES	VA	7		7	
	UNITED STATES	GA	4		4	
	UNITED STATES	SC	4		3	
Region 11	UNITED STATES	NY	20	44	20	44
	UNITED STATES	PA	9		9	
	UNITED STATES	NJ	8		8	
	UNITED STATES	MA	5		5	
	UNITED STATES	CT	2		2	
Region 12	UNITED STATES	MO	14	39	14	38
	UNITED STATES	MI	12		12	
	UNITED STATES	MN	6		6	
	UNITED STATES	OH	3		3	
	UNITED STATES	AR	2		1	
	UNITED STATES	IL	2		2	

2.2 Data Sources

The submission under NDA 203,100/S-0000 contains the efficacy, safety, and some genotyping results for subjects from 2 Phase III Studies GS-US-236-0102 and GS-US-236-0103, a Phase II Study GS-US-236-0104, and some other phase I/II studies. This reviewer conducted efficacy analyses to verify sponsor's results of two phase 3 studies, included the following two parts:

1. Reviewing protocols, statistical analysis plans, 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 2 Phase III Studies GS-US-236-0102 and GS-US-236-0103.
2. Converting SAS transportable files '*.xpt' in \analysis\datasets subfolder as analysis datasets, some of the raw datasets in \SDTM subfolder into SAS data files for verification based on the definitions in 'define.pdf', 'blankcrf.pdf', and Statistical Analysis Plan (SAP) in the CSR. In \analysis\datasets subfolder, there are 18 SAS transportable files for each of two phase studies. There are approximately 25 SAS transportable files which are the input datasets for creating efficacy/safety analysis datasets. These files are under CDER Electronic Document Room (EDR) directory of

<\\Cdsub1\evsprod\NDA203100\0000\m5\datasets\gs-us-236-0102>
and <\\Cdsub1\evsprod\NDA203100\0000\m5\datasets\gs-us-236-0103>

3. STATISTICAL EVALUATION

Two phase 3 studies, GS-US-236-0102 and GS-US-236-0103, will be reviewed separately under each of following section. All Tables and Figures are generated by the stat reviewer, otherwise the citation will be provided.

For study GS-US-236-0102, two arms will be notated as E/C/F/T and ATR and E/C/F/T and ATV/r for simplicity in the following sections.

3.1 Data and Analysis Quality

Overall, the reviewer can reproduce most variables in the primary analysis dataset, A_AdEff, for both studies using the datasets in subfolder named, \SDTM. Those supporting datasets are the raw datasets. Two other analysis datasets, A_Adsl and A_Adcm, are also checked for both studies.

The SAP and the comments in the SAS programs submitted are very helpful. The sponsor did not provide any other document, even though the stat reviewer would like to have some documents which provide some detailed information regarding the process of how to create analysis datasets and some detailed explanations for the algorithm used.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Both studies were randomized, multicenter, and double-blinded for boceprevir or placebo in combination with open-label PR, in adult subjects with HIV-1 infection.

Please see section 2.1.3 for the details in terms of study design, primary efficacy endpoint and analysis methods, analysis populations.

The **primary objective** of both studies is to demonstrate that the efficacy of a STR containing EVG/COBI/FTC/TDF (E/C/F/T) is non-inferior to a regimen containing EFV/FTC/TDF (ATR) (study GS-US-236-0102) and a regimen containing ATV/r + TVD (study GS-US-236-0103) in HIV-1 infected, ARV treatment-naive adult subjects, as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48.

Primary Efficacy Endpoint: The primary efficacy endpoint is the percentage of subjects with virologic success (ie, HIV-1 RNA < 50 copies/mL) at Week 48 using the FDA-defined snapshot analysis.

All primary and secondary efficacy analyses will be carried out using the two-sided stratum-adjusted Mantel Haenszel (MH) chi-square test (adjusted for the baseline stratification factors).

The **key secondary objective** of both studies is to evaluate the efficacy, safety, and tolerability of the 2 treatment regimens through 96 weeks of treatment.

Analysis Populations are the following:

Intent-To-Treat (ITT): all randomized subjects who received at least one dose of any study medication. Please see section 2.1.3 of study description in details.

Analysis Windows

In order to access the subject status at each scheduled visit (TW2, TW4, TW8, ..., TW48, ...), the pre-specified visit windows in terms of range of study days and days after end-of-treatment will be used to extract the HIV-1 RNA viral load for each visit as well as CD cell count, CD4%, hematology and chemistry laboratory tests.

For both studies, the **analysis windows** are listed in Table 9 below:

Table 9: The Analysis Windows Used in Both Studies GS-US-236-0102 & GS-US-236-0103

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 2	14	2	21
Week 4	28	22	42
Week 8	56	43	70
Week 12	84	71	98
Week 16	112	99	140
Week 24	168	141	196
Week 32	224	197	252
Week 40	280	253	308
Week 48	336	309	378
Week 60	420	379	462
Week 72	504	463	546
Week 84	588	547	630
Week 96	672	631	714
Week 108	756	715	798
Week 120	840	799	882
Week 132	924	883	966
Week 144	1008	967	1050

- **Study Day 1** is defined as the day when the first dose of study drug (ie, E/C/F/T or placebo or Atripla or placebo for study 0102 or ATV/r + TVD or placebo for study 0103) was taken, as recorded on the study drug administration eCRF form.

- **Study days** are calculated relative to Study Day 1. For events that occurred on and after Study Day 1 date, study days are calculated as (visit date minus date of the first dose plus 1). For events that occurred prior to Study Day 1, study days are calculated as (visit date minus date of the first dose date).
- **Last Dose Date** is defined as the maximum, non-missing end date of blinded study drug E/C/F/T or placebo or Atripla or placebo for study 0102 or ATV/r + TVD or placebo for study 0103, recorded on the Study Drug Administration form with the “Study Drug Permanently Discontinued” box checked for subjects who prematurely discontinued study drug or who completed study drug according to study drug completion eCRF.

If the date of last dose is missing (e.g., due to lost to follow-up) for subjects who prematurely discontinued study drug, use the maximum of non-missing study drug start dates and end dates, clinical visit dates, and laboratory visit dates excluding the date of 30-day follow-up visit to impute the last dose date.

- **Last Study Date** is the maximum of non-missing study drug start dates and end dates, clinic visit and laboratory visit dates, excluding the 30-day follow-up visit date for subjects who prematurely discontinued study or who completed study according to study completion eCRF.
- **Baseline value** is defined as the last non-missing value obtained on or prior to Study Day 1.

If multiple valid non-missing numeric observations exist in a window, then records will be chosen as follows:

- For efficacy data (ie, HIV-1 RNA level, CD4 cell count and CD4%), the latest record in the window will be selected.
- For other numeric observations, the record closest to the nominal day for that visit will be selected. If there are 2 records equidistant from the nominal day, the latest will be selected.
- If there is more than one record on the selected day, the average will be taken (geometric mean for HIV-1 RNA and arithmetic mean for others).

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

3.2.2.1 Randomization

Overall, the randomization stratification was OK for both studies. There are four variables created for either screening HIV viral load or baseline viral load either category or numeric value:

- ADSL.SRNACatN: 1 ($\leq 100K$ at screening), 2 ($> 100K$ at screening); (the label of the variable is “Screening HIV-1 RNA (copies/mL)”). If SRNACATN = 1 then R100KSCF = 'N'; Else if SRNACATN = 2 then R100KSCF = 'Y';
- SuppDS.Qval (when Qnam=”HIVRNA”): 1 or 2, (the label of the variable is “subject screening HIV RNA value”);
- ADSL.RNAScrn: numeric value of HIV viral load at screening visit;
- RNACat: classification using the baseline HIV viral load. There are four subjects who missed the baseline VL and screening HIV VL was used. (The primary efficacy analysis used this variable by the sponsor.)

Two things should be noted here:

- a) ADSL.SRNACatN and SuppDS.Qval should be the same theoretically. But for both studies, there were some difference.
- b) The randomization was stratified by the screening HIV VL, while the efficacy analysis used the baseline HIV VL category as the stratification factor in the CMH method. The consistency between these two was examined here as well.

The randomizations in two studies are examined separately in the following section.

❖ Study GS-US-236-0102

The numbers of subjects in each arm in each stratum classified by different variables are listed in Table 10. As you can see, there are 707 randomized subjects using both ADSL.SRCNCatN and SuppDS.Qval. Regardless the variable used, the difference between two arms within each stratum is less than or equal to 2 subjects. So, randomization stratification seems OK.

There were 700 subjects who were randomized and treated and the distribution of numbers of subjects in each arm and each stratum were listed in the bottom two rows in the Table 10 if using the HIV viral load value either at screening visit or baseline visit.

The discrepancy between two screening visit HIV viral load category variables is 15 in total (Table 11). The discrepancy between screening visit HIV viral load and baseline visit HIV viral load is 92 in total (Table 12).

Table 10: The Number of Subjects in each Arm in each Stratum Defined by Different Variables in Study GS-US-236-0102

	≤100,000 (1)		>100,000 (2)		
	E/C/F/T	ATR	E/C/F/T	ATR	
Treatment					
If using SRCNCatN	234	236	119	118	707
If using QVAL in SuppDs	233	234	120	120	707
By Screening HIV VL value	230	234	118	118	700
By Baseline HIV VL value	230	236	118	116	700

Table 11: The Relationship between two Screening HIV Viral Load Category Variables in Study GS-US-236-0102

Arm	E/C/F/T		ATR	
	Qval=1	Qval=2	Qval=1	Qval=2
SRCNCatN=1		3		6
SRCNCatN=2	2		4	

Table 12: The Relationship between Screening HIV Viral Load and Baseline HIV Viral Load in Study GS-US-236-0102

Arm	E/C/F/T		ATR	
	Baseline VL≤100K	Baseline VL>100K	Baseline VL≤100K	Baseline VL>100K
SRCNCatN=1 (≤100K)	210	20	209	25
SRCNCatN=2 (>100K)	20	98	27	91

❖ Study GS-US-236-0103

The numbers of subjects in each arm in each stratum classified by different variables are listed in Table 13. As you can see, there are 715 randomized subjects using both ADSL.SRCNCatN and SuppDS.Qval. Regardless the variable used, the difference between two arms within each stratum is less or equal 2 subjects. So, randomization stratification seems OK.

There were 708 subjects who were randomized and treated and the distribution of numbers of subjects in each arm and each stratum were listed in the bottom two rows in the Table 13 if using the HIV viral load value either at screening visit or baseline visit.

The discrepancy between two screening visit HIV viral load category variables is 13 in total (Table 14). The discrepancy between screening visit HIV viral load and baseline visit HIV viral load is 115 in total (Table 15).

Table 13: The Number of Subjects in each Arm in each Stratum Defined by Different Variables in Study GS-US-236-0103

	≤100,000 (1)		>100,000 (2)		
Treatment	E/C/F/T	ATV/r	E/C/F/T	ATV/r	
If using SRCNCatN	220	219	138	138	715
If using QVAL in SuppDs	224	224	134	133	715
By Screening HIV VL value	215	217	138	138	708
By Baseline HIV VL value	203	214	150	141	708

Table 14: The Relationship between two Screening HIV Viral Load Category Variables in Study GS-US-236-0103

	Qval=1	Qval=2
SRCNCatN=1	437	2
SRCNCatN=2	11	265

Table 15: The Relationship between Screening HIV Viral Load and Baseline HIV Viral Load in Study GS-US-236-0103

Arm	E/C/F/T		ATR/r	
	Baseline VL≤100K	Baseline VL>100K	Baseline VL≤100K	Baseline VL>100K
SRCNCatN=1 (≤100K)	181	34	186	31
SRCNCatN=2 (>100K)	22	116	28	110

The stat reviewer thought that SuppDS.Qval was the real variable used in the randomization stratification, even though the primary efficacy analysis used baseline HIV viral load category. In the efficacy analysis will using the sensitivity analysis to address this issue later.

3.2.2.2 Disposition

The stat reviewer can reproduce the disposition results the sponsor presented in the final study report (CSR) for randomized subjects for both studies. However, for both studies, the stat reviewer noted that there are a few more screening failure subjects in the ADSL datasets submitted than reported in the CSRs. The stat reviewer did not able to find the cause of it, and this did not affect the efficacy analyses.

❖ Study GS-US-236-0102

Out of 933 screened subjects, a total of 707 subjects were randomized, 700 subjects received at least one dose of study drug (Figure 4). In SCR, it reported that only 917 subjects screened and 707 randomized.

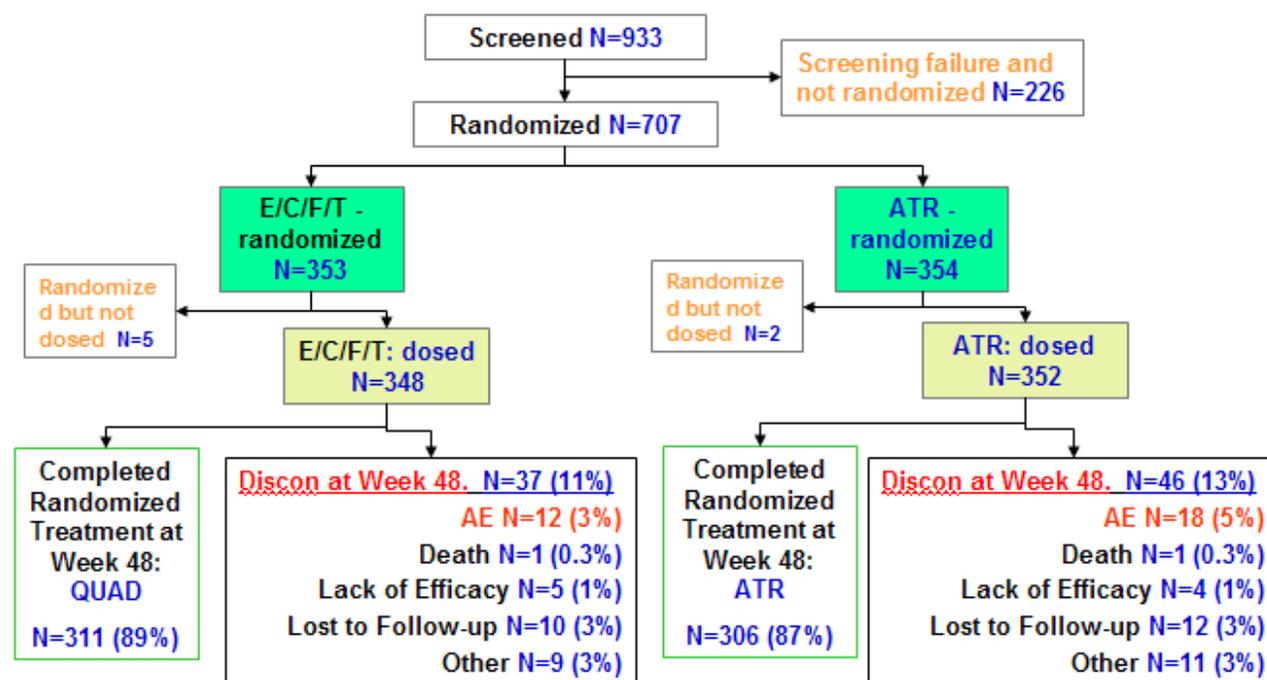
Seven subjects (5 in E/C/F/T arm and 2 in ATR arm) did not receive any study drug and will be excluded from the ITT and safety analysis population.

- 5 in E/C/F/T arm:
 - **1543-6418** with HIV-1 RNA at screening >100,000 copies/mL (had taken Atripla from 13AUG2010, randdt=16JUN2010.)
 - 1950-6581, 0754-6140, **0581-6688**, 0660-6386 ≤100,000 copies/mL
 - **0581-5588** was failed at screening but randomized.
- 2 in ATR arm:
 - 2840-6238, 0828-6508 with VL at screening ≤100,000 copies/mL

The 48 weeks of treatment completion rate (89%) in E/C/F/T arm is slightly higher than that in ATR arm (87%). The main reasons for treatment discontinuation for the first 48 weeks of treatment were discontinuation due to Adverse Events (AEs) (3% in E/C/F/T arm and 5% in ATR arm).

The two arms are pretty balanced in terms of other categories of discontinuation reason including death, lack of efficacy, lost to Follow-up, subject withdrew consent, non-compliance with study design, protocol violation, pregnancy, and physician decision (Table 16).

Note that the status of subject for study is also listed in the bottom of Table 14.



Other: includes non-compliance with study design, pregnancy, protocol violation, withdrawal by subject, and physician decision.

Figure 4: Patient Disposition at the End of Treatment Week 48 for Study GS-US-236-0102

Table 16: Subjects Disposition at 48 Weeks of Treatment for study GS-US-236-0102

Factor	E/C/F/T	ATR	Total
Completed Randomized Treatment at Week 48			
n	348	352	700
Y	311(89.4%)	306(86.9%)	617(88.1%)
N	37(10.6%)	46(13.1%)	83(11.9%)
Reasons of NOT completed treatment at Week 48			
ADVERSE EVENT	12(3.4%)	18(5.1%)	30(4.3%)
DEATH	1(0.3%)	1(0.3%)	2(0.3%)
LACK OF EFFICACY	5(1.4%)	4(1.1%)	9(1.3%)
LOST TO FOLLOW-UP	10(2.9%)	12(3.4%)	22(3.1%)
NON-COMPLIANCE WITH STUDY DESIGN	3(0.9%)	6(1.7%)	9(1.3%)
PHYSICIAN DECISION	1(0.3%)	.(. %)	1(0.1%)
PREGNANCY	1(0.3%)	.(. %)	1(0.1%)
PROTOCOL VIOLATION	1(0.3%)	.(. %)	1(0.1%)
WITHDRAWAL BY SUBJECT	3(0.9%)	5(1.4%)	8(1.1%)
on-going	311(89.4%)	306(86.9%)	617(88.1%)
Completed Study at Week 48			
n	348	352	700
Y	319(91.7%)	316(89.8%)	635(90.7%)
N	29(8.3%)	36(10.2%)	65(9.3%)
Reasons of NOT completed study at Week 48			
ADVERSE EVENT	6(1.7%)	12(3.4%)	18(2.6%)
DEATH	1(0.3%)	1(0.3%)	2(0.3%)
LACK OF EFFICACY	3(0.9%)	.(. %)	3(0.4%)
LOST TO FOLLOW-UP	10(2.9%)	12(3.4%)	22(3.1%)
NON-COMPLIANCE WITH STUDY DESIGN	2(0.6%)	6(1.7%)	8(1.1%)
PHYSICIAN DECISION	1(0.3%)	.(. %)	1(0.1%)
PROTOCOL VIOLATION	1(0.3%)	.(. %)	1(0.1%)
WITHDRAWAL BY SUBJECT	5(1.4%)	5(1.4%)	10(1.4%)
on-going	319(91.7%)	316(89.8%)	635(90.7%)

❖ Study GS-US-236-0103

Out of 1039 screened subjects, a total of 715 subjects were randomized, 708 subjects received at least one dose of study drug (Figure 5). In SCR, it reported that only 1017 subjects screened and 715 randomized.

Seven subjects (4 in E/C/F/T arm and 3 in ATV/r arm) did not receive any study drug and will be excluded from the ITT and safety analysis population.

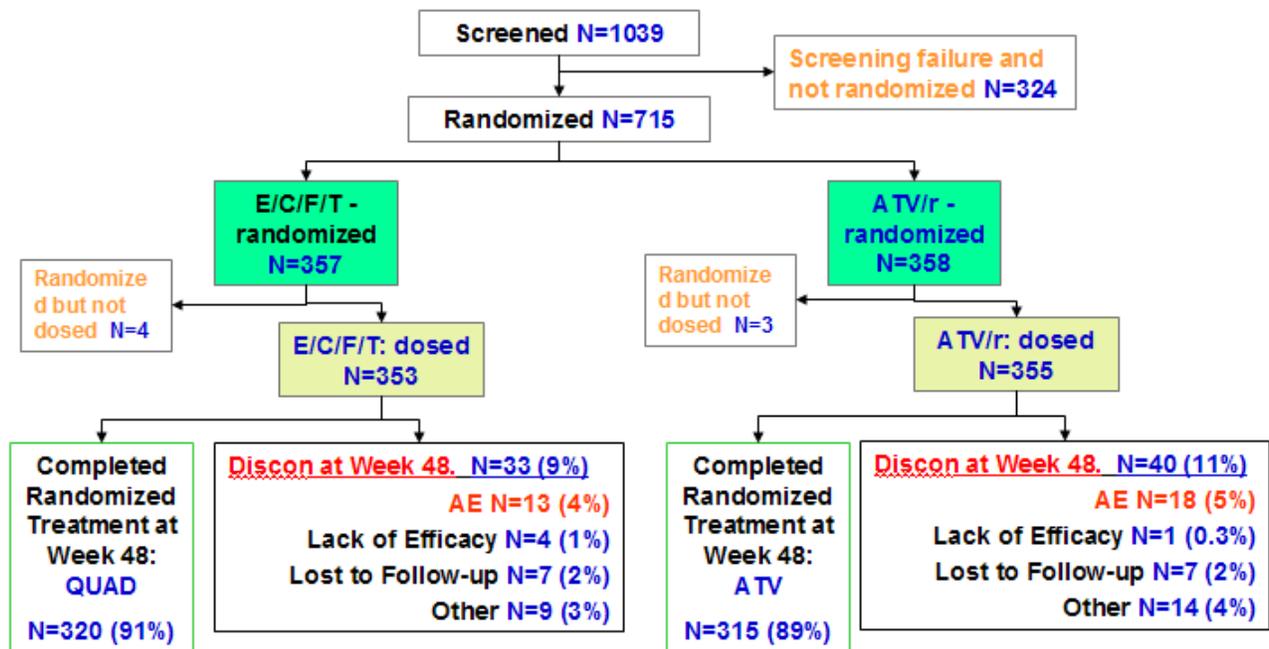
- 4 in E/C/F/T arm (all with VL at screening $\leq 100,000$ copies/mL):

- 3957-7362 (FRA), 2858-7661 (GBR), and 2003-7080 (AR)
- **0754-7028 (in AZ)** was failed at screening but randomized.
- 3 in ATR arm (all with VL at screening $\leq 100,000$ copies/mL in US)
 - 5221-7196, 0031-7099, and 2838-7157

The 48 weeks of treatment completion rate (91%) in E/C/F/T arm is slightly higher than that in ATV/r arm (89%). The main reasons for treatment discontinuation for the first 48 weeks of treatment were discontinuation due to Adverse Events (AEs) (4% in E/C/F/T arm and 5% in ATV/r arm).

The two arms are pretty balanced in terms of other category of discontinuation reason including death, lack of efficacy, lost to Follow-up, subject withdrew consent, non-compliance with study design, protocol violation, pregnancy, and physician decision (Table 17).

Note that the status of subject for study is also listed in the bottom of Table 15.



Other: includes non-compliance with study design, pregnancy, protocol violation, withdrawal by subject, and physician decision.

Figure 5: Patient Disposition at the End of Treatment Week 48 for Study GS-US-236-0103

Table 17: Subjects Disposition at 48 Weeks of Treatment for study GS-US-236-0103

Factor	E/C/F/T	ATV/r	Total
Subjects Randomized and Dosed	353	355	708
Completed Randomized Treatment at Week 48			
Y	320(90.7%)	315(88.7%)	635(89.7%)
N	33(9.3%)	40(11.3%)	73(10.3%)
Reasons of NOT completed treatment at Week 48			
ADVERSE EVENT	13(3.7%)	18(5.1%)	31(4.4%)
LACK OF EFFICACY	4(1.1%)	1(0.3%)	5(0.7%)
LOST TO FOLLOW-UP	7(2.0%)	7(2.0%)	14(2.0%)
NON-COMPLIANCE WITH STUDY D	5(1.4%)	5(1.4%)	10(1.4%)
PHYSICIAN DECISION	1(0.3%)	3(0.8%)	4(0.6%)
PREGNANCY	1(0.3%)	.(. %)	1(0.1%)
PROTOCOL VIOLATION	1(0.3%)	.(. %)	1(0.1%)
WITHDRAWAL BY SUBJECT	1(0.3%)	6(1.7%)	7(1.0%)
Completed Study at Week 48			
Y	331(93.8%)	324(91.3%)	655(92.5%)
N	22(6.2%)	31(8.7%)	53(7.5%)
Reasons of NOT completed study at Week 48			
ADVERSE EVENT	5(1.4%)	9(2.5%)	14(2.0%)
DEATH	.(. %)	3(0.8%)	3(0.4%)
LOST TO FOLLOW-UP	8(2.3%)	7(2.0%)	15(2.1%)
NON-COMPLIANCE WITH STUDY D	3(0.8%)	4(1.1%)	7(1.0%)
PHYSICIAN DECISION	1(0.3%)	2(0.6%)	3(0.4%)
PREGNANCY	1(0.3%)	.(. %)	1(0.1%)
PROTOCOL VIOLATION	1(0.3%)	.(. %)	1(0.1%)
WITHDRAWAL BY SUBJECT	3(0.8%)	6(1.7%)	9(1.3%)

3.2.2.3 Demographic and Baseline Characteristics

Overall, the demographic and baseline characteristics are balanced among three arms within both studies.

❖ Study GS-US-236-0102

All Subjects were from US (Table 18). There are 63% White, 28% Black, and 9% other enrolled. There is a much higher proportion of male (89%) than female (11%). The median age was 37 year old. Majority of subject (90%) had baseline HIV viral loads $\geq 10,000$ copies/mL. The median baseline CD4 count was 380 /uL, and the majority of subjects (86%) had baseline CD4 count greater than 200 /uL. Ninety-eight percent of subjects were HBV negative at baseline, and 95% HCV negative at baseline.

Table 18: Demographic and Baseline Characteristics for Study GS-US-236-0102 (ITT)

Factor	E/C/F/T	ATR	Total
As Randomized and Dosed (ITT)			
N	348	352	700
Gender			
F	41(11.8%)	36(10.2%)	77(11.0%)
M	307(88.2%)	316(89.8%)	623(89.0%)
Race			
AMERICAN INDIAN OR ALASKA NATIVE	2(0.6%)	4(1.1%)	6(0.9%)
ASIAN	6(1.7%)	10(2.8%)	16(2.3%)
BLACK OR AFRICAN	106(30.5%)	91(25.9%)	197(28.1%)
NATIVE HAWAIIAN OR PACIFIC ISLAND	4(1.1%)	1(0.3%)	5(0.7%)
OTHER	16(4.6%)	19(5.4%)	35(5.0%)
WHITE	214(61.5%)	227(64.5%)	441(63.0%)
Ethnicity			
HISPANIC/LATINO	82(23.6%)	85(24.1%)	167(23.9%)
NOT HISPANIC/LATINO	266(76.4%)	267(75.9%)	533(76.1%)
Age (Year)			
Mean (SE)	37.54 (0.556)	37.89 (0.566)	37.72 (0.397)
median	37.00	38.00	37.00
Range	(18.00, 63.00)	(18.00, 67.00)	(18.00, 67.00)
std	10.37	10.62	10.49
Screening HIV-1 RNA (Log10, copies/mL)			
Mean (SE)	4.75 (0.030)	4.77 (0.030)	4.76 (0.021)
median	4.71	4.76	4.73
Range	(3.72, 6.67)	(3.71, 6.54)	(3.71, 6.67)
std	0.560	0.560	0.560
Screening HIV-1 RNA Category (copies/mL)			
<= 100,000	230(66.1%)	234(66.5%)	464(66.3%)
> 100,000	118(33.9%)	118(33.5%)	236(33.7%)
Baseline HIV-1 RNA (Log10, copies/mL)			
Mean (SE)	4.73 (0.032)	4.78 (0.030)	4.76 (0.022)
median	4.75	4.78	4.76
Range	(2.64, 6.42)	(3.03, 6.54)	(2.64, 6.54)
std	0.602	0.564	0.583
Baseline HIV-1 RNA Category 1 (copies/mL)			
<= 100,000	230(66.1%)	236(67.0%)	466(66.6%)
> 100,000	118(33.9%)	116(33.0%)	234(33.4%)
Baseline HIV-1 RNA Category 2 (copies/mL)			
2<=, <3	1(0.3%)	.(. %)	1(0.1%)
3<=, <4	41(11.8%)	31(8.8%)	72(10.3%)
4<=, <5	188(54.0%)	204(58.0%)	392(56.0%)

5<=, <6	112(32.2%)	111(31.5%)	223(31.9%)
6<=, <7	6(1.7%)	6(1.7%)	12(1.7%)
Baseline CD4 Count (/uL)			
Mean (SE)	390.8 (10.11)	381.7 (9.073)	386.2 (6.786)
median	375.5	382.5	380.0
Range	(14.00, 1348)	(3.00, 1003)	(3.00, 1348)
std	188.6	170.2	179.5
Baseline CD4(%)			
Mean (SE)	23.15 (0.447)	22.75 (0.437)	22.95 (0.312)
median	22.60	22.75	22.65
Range	(1.90, 49.00)	(0.60, 50.60)	(0.60, 50.60)
std	8.340	8.203	8.268
Baseline CD4 Category (/uL)			
<= 50	7(2.0%)	6(1.7%)	13(1.9%)
51 to <= 200	36(10.3%)	45(12.8%)	81(11.6%)
201 to <= 350	112(32.2%)	96(27.3%)	208(29.7%)
351 to <= 500	113(32.5%)	136(38.6%)	249(35.6%)
> 500	80(23.0%)	69(19.6%)	149(21.3%)
Weight (Kg)			
Mean (SE)	81.59 (0.992)	81.03 (0.904)	81.31 (0.671)
median	78.50	78.20	78.45
Range	(47.10, 167.3)	(47.60, 163.7)	(47.10, 167.3)
std	18.51	16.97	17.74
Height (CM)			
Mean (SE)	174.9 (0.508)	176.1 (0.484)	175.5 (0.351)
median	176.3	177.8	177.8
Range	(132.0, 205.7)	(142.2, 198.1)	(132.0, 205.7)
std	9.484	9.074	9.291
Body Mass Index (kg/m^2)			
MSE	26.70 (0.318)	26.14 (0.277)	26.42 (0.211)
median	25.53	25.14	25.25
Range	(16.53, 53.17)	(16.51, 53.27)	(16.51, 53.27)
std	5.924	5.202	5.576
HIV status			
AIDS	28(8.0%)	24(6.8%)	52(7.4%)
Asymptomatic	290(83.3%)	295(83.8%)	585(83.6%)
Symptomatic HIV I	30(8.6%)	33(9.4%)	63(9.0%)
HBV status			
Negative	343(98.6%)	343(97.4%)	686(98.0%)
Positive	1(0.3%)	8(2.3%)	9(1.3%)
Positive, Confirm	4(1.1%)	1(0.3%)	5(0.7%)
HCV status			
Negative	331(95.1%)	337(95.7%)	668(95.4%)
Positive	17(4.9%)	15(4.3%)	32(4.6%)
Country			
USA	348(100.0%)	352(100.0%)	700(100.0%)

Region			
US	348(100.0%)	352(100.0%)	700(100.0%)
HIV Risk Factors			
Homosexual Sex	278(100.0%)	281(100.0%)	559(100.0%)
Heterosexual Sex	68(100.0%)	58(100.0%)	126(100.0%)
IV Drug Use	11(100.0%)	11(100.0%)	22(100.0%)
Transfusion	2(100.0%)	2(100.0%)	4(100.0%)
Vertical Transmission	.(. %)	.(. %)	.(. %)
Other	.(. %)	4(100.0%)	4(100.0%)
Unknown	7(100.0%)	11(100.0%)	18(100.0%)

For screening failure subjects, the demographic and baseline characteristics were summarized in Table 19 below. Overall, it is similar to the randomized subjects. There is a much higher proportion of male (88%) than female (12%). The median age was 38 years old.

Table 19: Demographic and Baseline Characteristics for Screening Failures in Study GS-US-236-0102 (Screening Failure)

Factor	Count (%)
Screening Failed and Not Dosed Subjects	
N	226
Gender	
F	27(11.9%)
M	199(88.1%)
Race	
WHITE	124(54.9%)
AMERICAN INDIAN/ALASKA NATIVE	2(0.9%)
ASIAN	3(1.3%)
BLACK OR AFRICAN AMERICAN	86(38.1%)
NATIVE HAWAIIAN OR OTHER PACIFIC	2(0.9%)
OTHER	9(4.0%)
Ethnicity	
HISPANIC OR LATINO	49(21.7%)
NOT HISPANIC OR LATINO	177(78.3%)
Age (Year)	
MEAN (SE)	37.65 (0.734)
median	38.00
Range	(18.00, 70.00)
std	11.04
Screening HIV-1 RNA (Log10, copies/mL)	
Mean (SE)	4.35 (0.069)
median	4.53
Range	(2.60, 7.75)
std	0.953

Screening HIV-1 RNA Category (copies/mL)	
<= 100,000 copies/mL	147(76.6%)
> 100,000 copies/mL	45(23.4%)
HIV status	
AIDS	19(8.4%)
Asymptomatic	184(81.4%)
Symptomatic HIV Infections	23(10.2%)
Country	
USA	226(100.0%)
HIV Risk Factors	
Homosexual Sex	172(100.0%)
Heterosexual Sex	48(100.0%)
IV Drug Use	6(100.0%)
Transfusion	.(. %)
Vertical Transmission	.(. %)
Other	6(100.0%)
Unknown	9(100.0%)

❖ Study GS--US-236-0103

Fifty-four percent (54%) of subjects were from US (Table 20). There are 74% White, 17% Black, and 9% other races enrolled. There were a much higher proportion of males (90%) than females (10%). The median age was 38 years old. A majority of subjects (90%) had baseline HIV viral loads $\geq 10,000$ copies/mL. The median baseline CD4 count was 357 /uL, and majority of subjects (87%) had baseline CD4 count greater than 200 /uL. Ninety-eight percent (98%) of subjects were HBV negative at baseline, and 96% were HCV negative at baseline.

Table 20: Demographic and Baseline Characteristics for Study GS-US-236-0103 (ITT)

Factor	E/C/F/T	ATV/r	Total
As Randomized and Dosed (ITT)			
N	353	355	708
Gender			
F	29(8.2%)	39(11.0%)	68(9.6%)
M	324(91.8%)	316(89.0%)	640(90.4%)
Race			
WHITE	250(70.8%)	277(78.0%)	527(74.4%)
AMERICAN INDIAN/ALASKA NATIVES	2(0.6%)	3(0.8%)	5(0.7%)
ASIAN	17(4.8%)	17(4.8%)	34(4.8%)
BLACK OR AFRICAN AMERICAN	72(20.4%)	47(13.2%)	119(16.8%)
NATIVE HAWAIIAN/OTHER PACIFIC	1(0.3%)	2(0.6%)	3(0.4%)

OTHER	11(3.1%)	9(2.5%)	20(2.8%)
Ethnicity			
HISPANIC/LATINO	64(18.1%)	47(13.2%)	111(15.7%)
NOT HISPANIC/LATINO	284(80.5%)	298(83.9%)	582(82.2%)
NOT REPORTED	5(1.4%)	10(2.8%)	15(2.1%)
Age (Year)			
Mean (SE)	37.58 (0.561)	38.70 (0.523)	38.14 (0.384)
median	37.00	39.00	38.00
Range	(19.00, 72.00)	(19.00, 69.00)	(19.00, 72.00)
std	10.54	9.849	10.21
Screening HIV-1 RNA (Log10, copies/mL)			
Mean (SE)	4.85 (0.030)	4.81 (0.031)	4.83 (0.021)
median	4.84	4.82	4.83
Range	(3.70, 6.38)	(3.70, 7.16)	(3.70, 7.16)
std	0.560	0.581	0.571
Screening HIV-1 RNA Category (copies/mL)			
<= 100,000 copies/mL	215(60.9%)	217(61.1%)	432(61.0%)
> 100,000 copies/mL	138(39.1%)	138(38.9%)	276(39.0%)
Baseline HIV-1 RNA (Log10, copies/mL)			
Mean (SE)	4.82 (0.032)	4.80 (0.033)	4.81 (0.023)
median	4.88	4.86	4.87
Range	(1.69, 6.58)	(2.98, 6.63)	(1.69, 6.63)
std	0.607	0.619	0.613
Baseline HIV-1 RNA Category 1 (copies/mL)			
<= 100,000 copies	203(57.5%)	214(60.3%)	417(58.9%)
> 100,000 copies/	150(42.5%)	141(39.7%)	291(41.1%)
Baseline HIV-1 RNA Category 2 (copies/mL)			
2<=, <3	.(. %)	1(0.3%)	1(0.1%)
3<=, <4	34(9.6%)	37(10.4%)	71(10.0%)
4<=, <5	167(47.3%)	175(49.3%)	342(48.3%)
5<=, <6	143(40.5%)	134(37.7%)	277(39.1%)
6<=, <7	8(2.3%)	8(2.3%)	16(2.3%)
<2	1(0.3%)	.(. %)	1(0.1%)
Baseline CD4 Count (/uL)			
Mean (SE)	364.2 (9.613)	375.4 (8.436)	369.8 (6.392)
median	351.0	366.0	357.0
Range	(5.00, 1132)	(10.00, 963.0)	(5.00, 1132)
std	180.6	158.9	170.1
Baseline CD4(%)			
Mean (SE)	21.05 (0.451)	21.75 (0.431)	21.40 (0.312)
median	20.20	21.30	20.75
Range	(0.50, 50.10)	(0.90, 46.10)	(0.50, 50.10)
std	8.468	8.113	8.294
Baseline CD4 Category (/uL)			
<= 50	12(3.4%)	5(1.4%)	17(2.4%)

51 to <= 200	42(11.9%)	34(9.6%)	76(10.7%)
201 to <= 350	122(34.6%)	124(34.9%)	246(34.7%)
351 to <= 500	122(34.6%)	122(34.4%)	244(34.5%)
> 500	55(15.6%)	70(19.7%)	125(17.7%)
Weight (Kg)			
Mean (SE)	79.16 (0.931)	79.71 (0.851)	79.43 (0.630)
median	76.60	77.50	77.10
Range	(42.00, 174.2)	(47.00, 153.3)	(42.00, 174.2)
std	17.49	16.04	16.77
Height (CM)			
Mean (SE)	176.4 (0.435)	175.7 (0.454)	176.1 (0.314)
median	177.0	176.0	177.0
Range	(149.9, 198.1)	(149.0, 200.0)	(149.0, 200.0)
std	8.167	8.554	8.366
Body Mass Index (kg/m^2)			
Mean (SE)	25.41 (0.281)	25.80 (0.255)	25.60 (0.190)
median	24.43	24.97	24.75
Range	(15.81, 53.23)	(17.82, 51.40)	(15.81, 53.23)
std	5.279	4.803	5.046
HIV status			
AIDS	32(9.1%)	24(6.8%)	56(7.9%)
Asymptomatic	285(80.7%)	293(82.5%)	578(81.6%)
Symptomatic HIV I	36(10.2%)	38(10.7%)	74(10.5%)
HBV status			
Negative	347(98.6%)	346(97.7%)	693(98.2%)
Positive	4(1.1%)	7(2.0%)	11(1.6%)
Positive, Confirm	1(0.3%)	.(. %)	1(0.1%)
Unable to confirm	.(. %)	1(0.3%)	1(0.1%)
HCV status			
Negative	335(94.9%)	344(97.2%)	679(96.0%)
Positive	18(5.1%)	10(2.8%)	28(4.0%)
Country			
AUS	30(8.5%)	32(9.0%)	62(8.8%)
AUT	12(3.4%)	8(2.3%)	20(2.8%)
BEL	9(2.5%)	12(3.4%)	21(3.0%)
CAN	19(5.4%)	22(6.2%)	41(5.8%)
CHE	.(. %)	2(0.6%)	2(0.3%)
DEU	29(8.2%)	36(10.1%)	65(9.2%)
DNK	1(0.3%)	2(0.6%)	3(0.4%)
FRA	23(6.5%)	23(6.5%)	46(6.5%)
GBR	11(3.1%)	15(4.2%)	26(3.7%)
ITA	9(2.5%)	5(1.4%)	14(2.0%)
MEX	3(0.8%)	2(0.6%)	5(0.7%)
NLD	2(0.6%)	4(1.1%)	6(0.8%)
PRT	1(0.3%)	2(0.6%)	3(0.4%)
SWE	.(. %)	1(0.3%)	1(0.1%)
THA	7(2.0%)	4(1.1%)	11(1.6%)
USA	197(55.8%)	185(52.1%)	382(54.0%)

Region			
Non-US	156(44.2%)	170(47.9%)	326(46.0%)
US	197(55.8%)	185(52.1%)	382(54.0%)
HIV Risk Factors			
Homosexual Sex	274(100.0%)	274(100.0%)	548(100.0%)
Heterosexual Sex	78(100.0%)	80(100.0%)	158(100.0%)
IV Drug Use	5(100.0%)	7(100.0%)	12(100.0%)
Transfusion	.(. %)	3(100.0%)	3(100.0%)
Vertical Transmission	.(. %)	.(. %)	.(. %)
Other	1(100.0%)	2(100.0%)	3(100.0%)
Unknown	11(100.0%)	9(100.0%)	20(100.0%)

For screening failure subjects, the demographic and baseline characteristics were summarized in Table 21 below. Overall, it is similar to the randomized subjects. There is a much higher proportion of male (78%) than female (22%). The median age was 37 years old.

Table 21: Demographic and Baseline Characteristics for Screening Failures in Study GS-US-236-0103 (Screening Failure)

Factors	Count (%)
Screening Failed and Not Dosed Subjects	
N	324
Gender	
F	71(22.0%)
M	252(78.0%)
Race	
WHITE	159(49.2%)
AMERICAN INDIAN/ALASKA NATIVES	1(0.3%)
ASIAN	41(12.7%)
BLACK OR AFRICAN AMERICAN	81(25.1%)
NATIVE HAWAIIAN OR OTHER PA	1(0.3%)
OTHER	40(12.4%)
Ethnicity	
HISPANIC OR LATINO	102(31.6%)
NOT HISPANIC OR LATINO	218(67.5%)
NOT REPORTED	3(0.9%)
Age (Year)	
Mean (SE)	37.0 (0.60)
median	36.0
Range	(19.0, 73.0)
std	10.7
Screening HIV-1 RNA (Log10, copies/mL)	
Mean (SE)	4.45 (0.064)
median	4.55
Range	(2.60, 7.16)
std	0.926

Screening HIV-1 RNA Category (copies/mL)	
<= 100,000 copies/mL	149(71.3%)
> 100,000 copies/mL	60(28.7%)
HIV status	
AIDS	30(9.3%)
Asymptomatic	262(80.9%)
Symptomatic HIV Infection	32(9.9%)
HIV Risk Factors	
Homosexual Sex	192(100.0%)
Heterosexual Sex	124(100.0%)
IV Drug Use	7(100.0%)
Transfusion	.(. %)
Vertical Transmission	.(. %)
Other	6(100.0%)
Unknown	11(100.0%)
Region	
US	172(53.1%)
Non-US	152(46.9%)
Country	
USA	172(53.1%)
AUS	13(4.0%)
AUT	7(2.2%)
BEL	5(1.5%)
CAN	10(3.1%)
CHE	1(0.3%)
DEU	6(1.9%)
DOM	39(12.0%)
FRA	6(1.9%)
GBR	7(2.2%)
MEX	26(8.0%)
PRT	3(0.9%)
THA	29(9.0%)

3.2.3 Statistical Methodologies

CMH method with adjustment of the stratification factor was used 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.

Missing data handling

The FDA-defined snapshot algorithm was used to derive the primary efficacy endpoint. The FDA-defined TLOVR algorithm was used as a secondary analysis.

For CD4 analysis, a completer analysis and baseline value carry forward approach were used.

3.2.4 Results and Conclusions

3.2.4.1 Summary of Applicant's Results

Note that the sponsor used the QUAD in their results to represent E/C/F/T arm which was used in the review by the stat reviewer.

The results of the sponsor's analyses on the primary efficacy for study GS-US-236-0102 are listed in Table 22. The applicant concluded that:

- Based on the Food and Drug Administration (FDA)-defined snapshot analysis, 87.6% of subjects (305 of 348) in the E/C/F/T group and 84.1% of subjects (296 of 352) in the ATR group had virologic success (intent-to-treat [ITT] analysis set). The baseline HIV-1 RNA stratum-weighted difference in the percentage of subjects with virologic success was 3.6% (95% confidence interval [CI]: -1.6% to 8.8%). Because the lower bound of the 2-sided 95% CI of the difference in response rate (E/C/F/T – ATR) was greater than the pre-specified -12% noninferiority margin, the E/C/F/T STR was determined to be noninferior to ATR. Sensitivity analyses supported the primary endpoint analysis using the ITT analysis set.
- The detailed classifications of snapshot results are listed in Table 23.

Table 22: The Primary Efficacy Results for GS--US-236-0102 from the Sponsor (ITT analysis set)

Treatment Outcomes	QUAD N = 348	ATR N = 352	QUAD vs ATR	
			P-value	Difference in Percentages (95% CI)
Virologic Success (HIV-1 RNA < 50 copies/mL) at Week 48 using Snapshot Analysis (n, %) ^a	305 (87.6%)	296 (84.1%)	0.17 ^b	3.6% (-1.6% to 8.8%) ^{c, d}
Virologic Responder (HIV-1 RNA < 50 copies/mL) at Week 48 using TLOVR Analysis (n, %) ^{a, e}	299 (85.9%)	293 (83.2%)	0.31 ^f	2.7% (-2.6% to 8.1%) ^g
Virologic Responder at Week 48 (HIV-1 < 50 copies/mL; M = F) (n, %) ^h	309 (88.8%)	301 (85.5%)	0.19 ^f	3.3% (-1.6% to 8.3%) ^g
Mean (SD) Change from Baseline in CD4 cell count at Week 48 (cells/ μ L)	239 (167.2)	206 (153.4)	0.009 ⁱ	33 (8, 58) ^j

a Week 48 window is between Day 309 and 378 (inclusive).

b P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by baseline HIV-1 RNA stratum.

c Difference in percentages of virologic success and its 95.2% CI were calculated based on baseline HIV-1 RNA stratum-adjusted Mantel-Haenszel (MH) proportion.

d At each of the 2 independent data monitoring committee (IDMC) meetings, an alpha penalty of 0.001 was applied; therefore, for the primary endpoint analysis, a 95.2% CI (corresponding to an alpha level of 0.048) was constructed to preserve the overall alpha level of 0.05. As such, the primary analysis CI is described as a 95% CI.

e Responder refers to subjects who achieved and maintained confirmed HIV-1 RNA <50 copies/mL through Week 48.

f P-value was from the CMH tests stratified by baseline HIV-1 RNA level (\leq 100,000 or $>$ 100,000 copies/mL).

g Difference in response rate (responder) and its 95% CI were from baseline HIV-1 RNA stratum-adjusted MH proportion.

h For the M = F analysis, denominator for percentage was the number of subjects in the ITT analysis set.

i P-values were obtained from ANOVA model adjusted for baseline HIV-1 RNA level.

j The difference (diff) in least-squares means (LSMs) and its 95% CI were computed adjusted for baseline HIV-1 RNA level.

Copied from 2.5 Clinical Overview Table 8.

Table 23: The Primary Efficacy Results for GS-US-236-0102 from the Sponsor With Detailed Categories of Failure in Snapshot Analysis (ITT analysis set)

HIV-1 RNA Category	QUAD (N=348)	ATR (N=352)	QUAD vs. ATR p-value ^a	Difference in Percentages (95.2% CI) ^{b, c}
Virologic Success at Week 48				
HIV-1 RNA < 50 copies/mL	305 (87.6%)	296 (84.1%)	0.17	3.6% (-1.6% to 8.8%)
Virologic Failure at Week 48				
HIV-1 RNA ≥ 50 copies/mL	25 (7.2%)	25 (7.1%)		
Discontinued Study Drug Due to Lack of Efficacy	4 (1.1%)	2 (0.6%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL ^d	8 (2.3%)	12 (3.4%)		
No Virologic Data in Week 48 Window^e				
Discontinued Study Drug Due to AE/Death	10 (2.9%)	19 (5.4%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL ^d	8 (2.3%)	11 (3.1%)		
Missing Data During Window but on Study Drug	0	1 (0.3%)		

a P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by baseline HIV-1 RNA stratum.

b Difference in percentages of virologic success and its 95.2% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.

c At each of the 2 IDMC meetings, an analysis of efficacy was performed at the alpha level of 0.001; therefore, for the primary endpoint analysis, a 95.2% CI (corresponding to an alpha level of 0.048) was constructed to preserve the overall alpha level of 0.05. As such, the primary analysis CI is described as a 95% CI.

d Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, subject noncompliance, protocol violation, and pregnancy.

e Week 48 window is between Day 309 and 378 (inclusive).

Copied from CSR Table 9-1.

The results of the sponsor's analysis on the primary efficacy for study GS-US-236-0103 are listed in Table 24. The applicant concluded that:

- Based on the snapshot analysis, 89.5% of subjects (316 of 353) in the E/C/F/T group and 86.8% of subjects (308 of 355) in the ATV/r + TVD group had virologic success (ITT analysis set). The baseline HIV-1 RNA stratum-weighted difference in the percentage of subjects with virologic success was 3.0% (95% CI: -1.9% to 7.8%). Because the lower bound of the 2-sided 95% CI of the difference in response rate (E/C/F/T – ATV/r + TVD)

was greater than the pre-specified –12% noninferiority margin, the E/C/F/T STR was determined to be noninferior to ATV/r + TVD. Sensitivity analyses supported the primary endpoint analysis using the ITT analysis set.

- The detailed classifications of snapshot results are listed in Table 25.

Table 24: The Primary Efficacy Results for GS--US-236-0103 from the Sponsor (ITT analysis set)

Treatment Outcomes	QUAD N = 353	ATV/r+TVD N = 355	QUAD vs ATV/r+TVD	
			p-value	Difference in Percentages (95% CI)
Virologic Success (HIV-1 RNA < 50 copies/mL) at Week 48 using Snapshot Analysis (n, %) ^a	316 (89.5%)	308 (86.8%)	0.22 ^b	3.0% (–1.9% to 7.8%) ^{c, d}
Virologic Responder (HIV-1 RNA < 50 copies/mL) at Week 48 using TLOVR Analysis (n, %) ^{a, e}	304 (86.1%)	301 (84.8%)	0.55 ^f	1.6% (–3.6% to 6.8%) ^g
Virologic Responder at Week 48 (HIV-1 < 50 copies/mL; M = F) (n, %) ^h	323 (91.5%)	313 (88.2%)	0.12 ^f	3.5% (–1.0% to 8.0%) ^g
Mean (SD) Change from Baseline in CD4 cell count at Week 48 (cells/ μ L)	207 (164.2)	211 (160.3)	0.61 ⁱ	–6 (–31 to 18) ^j

a Week 48 window is between Day 309 and 378 (inclusive).

b P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by baseline HIV-1 RNA stratum.

c Difference in percentages of virologic success and its 95.2% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.

d At each of the 2 IDMC meetings, an alpha penalty of 0.001 was applied; therefore, for the primary endpoint analysis, a 95.2% CI (corresponding to an alpha level of 0.048) was constructed to preserve the overall alpha level of 0.05. As such, the primary analysis CI is described as a 95% CI.

e Responder refers to subjects who achieved and maintained confirmed HIV-1 RNA <50 copies/mL through Week 48.

f P-value was from the CMH tests stratified by baseline HIV-1 RNA level (\leq 100,000 or $>$ 100,000 copies/mL).

g Difference in response rate (responder) and its 95% CI were from baseline HIV-1 RNA stratum-adjusted MH proportion.

h For the M = F analysis, denominator for percentage was the number of subjects in the ITT analysis set.

i P-values were obtained from ANOVA model including baseline HIV-1 RNA category (\leq 100,000 and $>$ 100,000 copies/mL) in the model.

j The difference (diff) in LSMs and its 95% CI were computed using ANOVA model, including baseline HIV-1 RNA category in the model.

Copied from 2.5 Clinical Overview Table 9.

Table 25: The Primary Efficacy Results for GS-US-236-0103 from the Sponsor with Detailed Categories of Failure in Snapshot Analysis (ITT analysis set)

HIV-1 RNA Category	QUAD (N=353)	ATV/r+TVD (N=355)	QUAD vs. ATV/r+TVD p-value ^a	Difference in Percentages (95.2% CI) ^{b,c}
Virologic Success at Week 48				
HIV-1 RNA < 50 copies/mL	316 (89.5%)	308 (86.8%)	0.22	3.0% (-1.9% to 7.8%)
Virologic Failure at Week 48	19 (5.4%)	19 (5.4%)		
HIV-1 RNA >= 50 copies/mL	7 (2.0%)	8 (2.3%)		
Discontinued Study Drug Due to Lack of Efficacy	4 (1.1%)	0		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL ^d	8 (2.3%)	11 (3.1%)		
No Virologic Data in Week 48 Window ^e	18 (5.1%)	28 (7.9%)		
Discontinued Study Drug Due to AE/Death	11 (3.1%)	18 (5.1%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL ^d	7 (2.0%)	9 (2.5%)		
Missing Data During Window but on Study Drug	0	1 (0.3%)		

- a P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by baseline HIV-1 RNA stratum.
- b Difference in percentages of virologic success and its 95.2% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.
- c At each of the 2 IDMC meetings, an alpha penalty of 0.001 was applied; therefore, for the primary endpoint analysis, a 95.2% CI (corresponding to an alpha level of 0.048) was constructed to preserve the overall alpha level of 0.05. As such, the primary analysis CI is described as a 95% CI.
- d Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, subject noncompliance, protocol violation, and pregnancy.
- e Week 48 window is between Day 309 and 378 (inclusive).

Copied from CSR Table 9-1.

3.2.4.2 Study GS-US-236-0102

Overall, the stat reviewer replicated the sponsor’s results for the primary efficacy endpoint.

The efficacy analysis is based on the ITT population, including subjects who randomized and had at least one dose of randomized study drug. There are only 7 randomized subjects excluded from the ITT due to not being dosed.

➤ Primary Efficacy Analysis Results

The primary efficacy endpoint is the percentage of subjects with virologic success (ie, HIV-1 RNA < 50 copies/mL) at Week 48 using the FDA-defined snapshot analysis based on the ITT population.

The virologic success rate was 87.6% of subjects (305/348) in the E/C/F/T arm and 84.1% of subjects (296/352) in the ATR arm. The baseline HIV-1 RNA stratum-weighted difference in the percentage of subjects with virologic success was 3.6% with 95.2% confidence interval [CI] of (-1.6%, 8.8%). If using the screening visit viral load for stratum-weighted adjustment, we have the same results (Table 26). Because of two interim analyses occurred before this analysis, this 95.2% CI is the 95% CI for this final analysis.

Because the lower bound of the 2-sided 95% CI of the difference in virologic success rate (E/C/F/T – ATR) was -1.6% greater than the pre-specified -12% noninferiority margin, the E/C/F/T STR was determined to be noninferior to ATR.

If just using normal approximation without stratification justification, the 95.2% CI is (-1.7%, 8.8%), and it leads to the same conclusion.

Table 26: The Primary Efficacy Endpoint (Virologic Success Rate (<50 copies/mL)) Results for Study GS-US-236-0102 (ITT)

(<50)	E/C/F/T	ATR	Rate Diff	95.2% CI
Normal approximation of Rate Difference (E/C/F/T - ATR)				
305/348 (87.6%)	296/352 (84.1%)		3.6%	[-1.7%; 8.8%]
CMH Weighted of Rate Difference by Baseline VL (E/C/F/T - ATR)				
305/348 (87.6%)	296/352 (84.1%)		3.6%	[-1.6%; 8.8%]
CMH Weighted of Rate Difference by Screening VL (E/C/F/T - ATR)				
305/348 (87.6%)	296/352 (84.1%)		3.6%	[-1.6%; 8.8%]

The virologic success rate by study visit and by treatment arm is listed in Figure 6 below. As you can see, E/C/F/T arm had a higher virologic success rate at the beginning and two arms were close at the end.

The virologic success rate results using <400 copies/mL are listed in Table 27. As you can see, there are 8 more responders (+2.3%) in E/C/F/T arm and 5 more responders (+1.4%) in ATR arm. The 95.2% CI of the rate difference between two arms is (-0.5%, 9.4%), which leads the same conclusion.

Table 27: The Primary Efficacy Endpoint (Virologic Success Rate (<400 copies/mL)) Results for Study GS-US-236-0102 (ITT)

(<400)	E/C/F/T	ATR	Rate Diff	95.2% CI
Normal approximation of Rate Difference (E/C/F/T - ATR)				
313/348 (89.9%)	301/352 (85.5%)	4.4%	[-0.5%;	9.4%]
CMH Weighted of Rate Difference by Baseline VL (E/C/F/T - ATR)				
313/348 (89.9%)	301/352 (85.5%)	4.5%	[-0.5%;	9.4%]
CMH Weighted of Rate Difference by Screening VL (E/C/F/T - ATR)				
313/348 (89.9%)	301/352 (85.5%)	4.4%	[-0.5%;	9.3%]

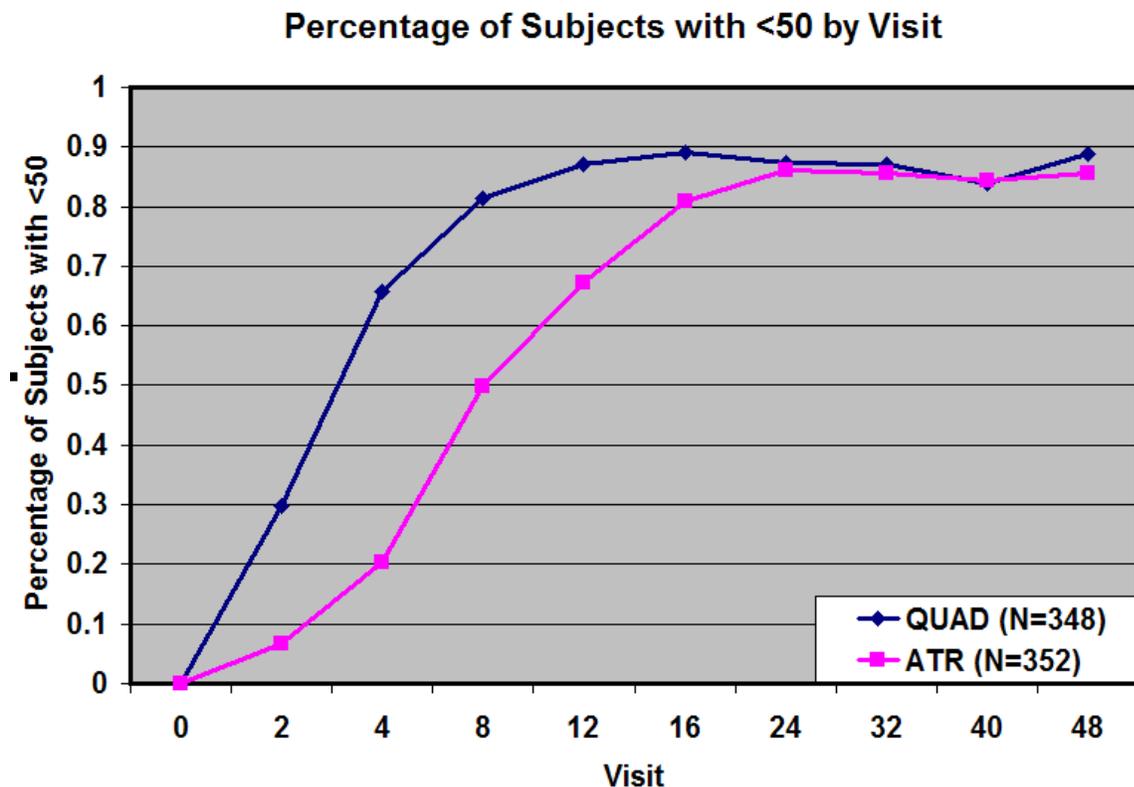


Figure 6: Proportion of Subjects Achieving Virologic Success (<50 copies/mL) by Study Visit and by Arm for Study GS-US-236-0102

The snapshot classifications are listed in Table 28 and 29 below for <50 copies/mL and <400 copies/mL respectively.

Table 28: The Snapshot Classification Results of the Primary Efficacy Endpoint (<50 copies/mL) for Study GS-US-236-0102 (ITT)

Snapshot Category (<50)	E/C/F/T (N=348)	ATR (N=352)	Total (N=700)
Virologic Success at Week 48	305(87.6%)	296(84.1%)	601(85.9%)
Overall Failure	43(12.4%)	56(15.9%)	99(14.1%)
2. Virologic Failure at Week 48	25(7.2%)	25(7.1%)	50(7.1%)
2a. HIV-1 RNA >= 50 copies/mL	13(3.7%)	11(3.1%)	24(3.4%)
2b. Discontinued Study Drug Due to Lack of Efficacy	4(1.1%)	2(0.6%)	6(0.9%)
2c. Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL	8(2.3%)	12(3.4%)	20(2.9%)
3. No Virologic Data in Week 48 Window	18(5.2%)	31(8.8%)	49(7.0%)
3a. Discontinued Study Drug Due to AE/Death	10(2.9%)	19(5.4%)	29(4.1%)
3b. Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL	8(2.3%)	11(3.1%)	19(2.7%)
3c. Missing Data During Window but on Study Drug	.(.%)	1(0.3%)	1(0.1%)

Table 29: The Snapshot Classification Results of the Virologic Success Rate (<400 copies/mL) for Study GS-US-236-0102 (ITT)

Snapshot Category (<400)	E/C/F/T (N=348)	ATR (N=352)	Total (N=700)
Virologic Success at Week 48	313(89.9%)	301(85.5%)	614(87.7%)
Overall Failure	35(10.1%)	51(14.5%)	86(12.3%)
2. Virologic Failure at Week 48	15(4.3%)	16(4.5%)	31(4.4%)
2a. HIV-1 RNA >= 400 copies/mL	5(1.4%)	6(1.7%)	11(1.6%)
2b. Discontinued Study Drug Due to Lack of Efficacy	4(1.1%)	2(0.6%)	6(0.9%)
2c. Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 400 copies/mL	6(1.7%)	8(2.3%)	14(2.0%)
3. No Virologic Data in Week 48 Window	20(5.7%)	35(9.9%)	55(7.9%)
3a. Discontinued Study Drug Due to AE/Death	10(2.9%)	19(5.4%)	29(4.1%)
3b. Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 400 copies/mL	10(2.9%)	15(4.3%)	25(3.6%)
3c. Missing Data During Window but on Study Drug	.(.%)	1(0.3%)	1(0.1%)

Note that these classifications depend on the order of data, such as treatment ending date, discontinuation date, viral load data within Week 48 visit window, etc, for each subject. For example, there are two subjects (0754-6242 and 0698-6012) who do not have viral load data

within Week 48 visit window before treatment ending date, even though they have viral load data after the treatment ending date within Week 48 visit window and it was after discontinuation date (Table 30). As a result, they were classified as discontinuations according to the snapshot rule.

There are two subjects (1549-6214 and 1950-6089) who had viral load data within Week 48 visit window before treatment ending date. Since they were still on-treatment, their viral load data were used for snapshot classification as either virologic success (1950-6089) or HIV-1 RNA ≥ 50 copies/mL, virologic failure at Week 48 (1549-6214) even though these two subjects were discontinued later (Table 30).

Table 30: The HIV Viral Load Profile by Visit for Four Subjects in Study GS-US-236-0102.

	USUBJID	ADT	ADY	AVISIT	AVAL	AVALC	BASE	RANFL	TRT01A	TRTSDT	TRTEDT	DISCDRUG
1	GS-US-236-0102-0754-6242	2010-05-18	1	Baseline	15200	15200	15200	Y	QUAD	2010-05-18	2011-04-05	ADVERSE EVENT
2	GS-US-236-0102-0754-6242	2010-06-01	15	Week 2	49	<50 HIV R	15200	Y	QUAD	2010-05-18	2011-04-05	ADVERSE EVENT
3	GS-US-236-0102-0754-6242	2010-06-15	29	Week 4	49	<50 HIV R	15200	Y	QUAD	2010-05-18	2011-04-05	ADVERSE EVENT
4	GS-US-236-0102-0754-6242	2010-07-08	52	Week 8	49	<50 No HI	15200	Y	QUAD	2010-05-18	2011-04-05	ADVERSE EVENT
5	GS-US-236-0102-0754-6242	2010-08-09	84	Week 12	49	<50 No HI	15200	Y	QUAD	2010-05-18	2011-04-05	ADVERSE EVENT
6	GS-US-236-0102-0754-6242	2010-09-07	113	Week 16	49	<50 No HI	15200	Y	QUAD	2010-05-18	2011-04-05	ADVERSE EVENT
7	GS-US-236-0102-0754-6242	2010-11-02	169	Week 24	49	<50 No HI	15200	Y	QUAD	2010-05-18	2011-04-05	ADVERSE EVENT
8	GS-US-236-0102-0754-6242	2010-12-27	224	Week 32	49	<50 No HI	15200	Y	QUAD	2010-05-18	2011-04-05	ADVERSE EVENT
9	GS-US-236-0102-0754-6242	2011-02-25	284	Week 40	49	<50 No HI	15200	Y	QUAD	2010-05-18	2011-04-05	ADVERSE EVENT
10	GS-US-236-0102-0754-6242	2011-05-05	353	Week 48	924	924	15200	Y	QUAD	2010-05-18	2011-04-05	ADVERSE EVENT
	USUBJID	ADT	ADY	AVISIT	AVAL	AVALC	BASE	RANFL	TRT01A	TRTSDT	TRTEDT	DISCDRUG
1	GS-US-236-0102-0698-6012	2010-04-14	1	Baseline	200000	200000	200000	Y	QUAD	2010-04-14	2011-03-31	LACK OF EFFICACY
2	GS-US-236-0102-0698-6012	2010-04-28	15	Week 2	60	60	200000	Y	QUAD	2010-04-14	2011-03-31	LACK OF EFFICACY
3	GS-US-236-0102-0698-6012	2010-05-10	27	Week 4	49	<50 HIV R	200000	Y	QUAD	2010-04-14	2011-03-31	LACK OF EFFICACY
4	GS-US-236-0102-0698-6012	2010-06-11	59	Week 8	49	<50 HIV R	200000	Y	QUAD	2010-04-14	2011-03-31	LACK OF EFFICACY
5	GS-US-236-0102-0698-6012	2010-07-09	87	Week 12	49	<50 No HI	200000	Y	QUAD	2010-04-14	2011-03-31	LACK OF EFFICACY
6	GS-US-236-0102-0698-6012	2010-08-04	113	Week 16	49	<50 No HI	200000	Y	QUAD	2010-04-14	2011-03-31	LACK OF EFFICACY
7	GS-US-236-0102-0698-6012	2010-09-29	169	Week 24	243	243	200000	Y	QUAD	2010-04-14	2011-03-31	LACK OF EFFICACY
8	GS-US-236-0102-0698-6012	2010-12-01	232	Week 32	2370	2370	200000	Y	QUAD	2010-04-14	2011-03-31	LACK OF EFFICACY
9	GS-US-236-0102-0698-6012	2011-02-03	296	Week 40	2770	2770	200000	Y	QUAD	2010-04-14	2011-03-31	LACK OF EFFICACY
10	GS-US-236-0102-0698-6012	2011-04-01	353	Week 48	3880	3880	200000	Y	QUAD	2010-04-14	2011-03-31	LACK OF EFFICACY
	USUBJID	ADT	ADY	AVISIT	AVAL	AVALC	BASE	ANLFL	TRT01A	TRTSDT	TRTEDT	DISCDRUG
1	GS-US-236-0102-1549-6214	2010-05-11	1	Baseline	23700	23700	23700	Y	ATR	2010-05-11	2011-05-06	LACK OF EFFICACY
2	GS-US-236-0102-1549-6214	2010-05-25	15	Week 2	286	286	23700	Y	ATR	2010-05-11	2011-05-06	LACK OF EFFICACY
3	GS-US-236-0102-1549-6214	2010-06-08	29	Week 4	49	<50 HIV	23700	Y	ATR	2010-05-11	2011-05-06	LACK OF EFFICACY
4	GS-US-236-0102-1549-6214	2010-07-06	57	Week 8	49	<50 HIV	23700	Y	ATR	2010-05-11	2011-05-06	LACK OF EFFICACY
5	GS-US-236-0102-1549-6214	2010-08-04	86	Week 12	49	<50 No H	23700	Y	ATR	2010-05-11	2011-05-06	LACK OF EFFICACY
6	GS-US-236-0102-1549-6214	2010-09-02	115	Week 16	49	<50 HIV	23700	Y	ATR	2010-05-11	2011-05-06	LACK OF EFFICACY
7	GS-US-236-0102-1549-6214	2010-10-27	170	Week 24	49	<50 HIV	23700	Y	ATR	2010-05-11	2011-05-06	LACK OF EFFICACY
8	GS-US-236-0102-1549-6214	2010-12-22	226	Week 32	6340	6340	23700	Y	ATR	2010-05-11	2011-05-06	LACK OF EFFICACY
9	GS-US-236-0102-1549-6214	2011-01-27	262	Week 40	8460	8460	23700	N	ATR	2010-05-11	2011-05-06	LACK OF EFFICACY
10	GS-US-236-0102-1549-6214	2011-04-13	338	Week 48	14100	14100	23700	Y	ATR	2010-05-11	2011-05-06	LACK OF EFFICACY
	USUBJID	ADT	ADY	AVISIT	AVAL	AVALC	BASE	ANLFL	TRT01A	TRTSDT	TRTEDT	DISCDRUG
1	GS-US-236-0102-1950-6089	2010-04-27	1	Baseline	5520	5520	5520	Y	QUAD	2010-04-27	2011-03-29	LOST TO FOLLOW-UP
2	GS-US-236-0102-1950-6089	2010-05-11	16	Week 2	49	<50 HIV	5520	Y	QUAD	2010-04-27	2011-03-29	LOST TO FOLLOW-UP
3	GS-US-236-0102-1950-6089	2010-05-25	29	Week 4	49	<50 No H	5520	Y	QUAD	2010-04-27	2011-03-29	LOST TO FOLLOW-UP
4	GS-US-236-0102-1950-6089	2010-06-22	57	Week 8	49	<50 HIV	5520	Y	QUAD	2010-04-27	2011-03-29	LOST TO FOLLOW-UP
5	GS-US-236-0102-1950-6089	2010-07-20	85	Week 12	49	<50 HIV	5520	Y	QUAD	2010-04-27	2011-03-29	LOST TO FOLLOW-UP
6	GS-US-236-0102-1950-6089	2010-08-18	114	Week 16	49	<50 No H	5520	Y	QUAD	2010-04-27	2011-03-29	LOST TO FOLLOW-UP
7	GS-US-236-0102-1950-6089	2010-10-12	169	Week 24	49	<50 HIV	5520	Y	QUAD	2010-04-27	2011-03-29	LOST TO FOLLOW-UP
8	GS-US-236-0102-1950-6089	2010-12-07	226	Week 32	49	<50 HIV	5520	Y	QUAD	2010-04-27	2011-03-29	LOST TO FOLLOW-UP
9	GS-US-236-0102-1950-6089	2011-02-28	308	Week 40	97100	97100	5520	Y	QUAD	2010-04-27	2011-03-29	LOST TO FOLLOW-UP
10	GS-US-236-0102-1950-6089	2011-03-29	337	Week 48	49	<50 No H	5520	Y	QUAD	2010-04-27	2011-03-29	LOST TO FOLLOW-UP

*ANLFL is the analysis week flag.

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➤ **Comparison between Snapshot analysis and TLOVR**

Also the FDA-defined snapshot results were compared to the TLOVR results. There are 12 difference listed in Table 31 below. The difference was caused by the algorithm itself, which decided which data should be used for analysis. For example, the subject 1951-6684 was called success in the snapshot analysis, but called never suppressed in the TLOVR analysis. This is because subject 1951-6684 was not suppressed at Week 44 visit and only suppressed at Week 48 visit (Table 32). Based on the Week 48 data, it was called success for snapshot analysis, but the TLOVR rule needs two conservative suppression visits in order to be called success. As a result, it was called never suppressed through Week 48 in TLOVR. Another example is subject 2825-6109, who was called a responder using the TLOVR algorithm, but called a virological failure (Table 33) using the snapshot algorithm because they had detectable HIV-1 viral load at the Week 48 visit after suppression from Week 4 to Week 44.

Table 31: The Difference between Snapshot and TLOVR Analysis Results for Study GS-US-236-0102 (ITT)

Snapshot	TLOVR	E/C/F/T	ATR
virologic success (HIV RNA <50 copies/mL)	Rebound	4735-6706 0660-6370 0364-6435 0698-6145 0661-6693	3317-6570 1534-6454 0947-6566
	Never Suppressed through Week 48	1951-6684	1534-6533
	Drug Discontinuation Due to Other Reasons	1950-6089	
missing data during the window but on study	Responder		2475-6103
virologic failure	Responder	2825-6109	

Table 32: The HIV Viral Load by Visit for Subject 1951-6684 in Study GS-US-236-0102.

	USUBJID	ADT	ADY	AVISIT	AVAL
1	GS-US-236-0102-1951-6684	2010-08-13	1	Baseline	5.5843312
2	GS-US-236-0102-1951-6684	2010-08-26	14	Week 2	2.9698816
3	GS-US-236-0102-1951-6684	2010-09-09	28	Week 4	2.5693739
4	GS-US-236-0102-1951-6684	2010-10-04	53	Week 8	1.7708520
5	GS-US-236-0102-1951-6684	2010-11-03	83	Week 12	1.6901960
6	GS-US-236-0102-1951-6684	2010-12-02	112	Week 16	1.8129133
7	GS-US-236-0102-1951-6684	2011-01-26	167	Week 24	2.1931245
8	GS-US-236-0102-1951-6684	2011-03-21	221	Week 32	1.6901960
9	GS-US-236-0102-1951-6684	2011-05-16	277	Week 40	1.7242758
10	GS-US-236-0102-1951-6684	2011-07-11	333	Week 48	1.6901960

Table 33: The HIV Viral Load by Visit for Subject 2825-6109 in Study GS-US-236-0102.

	USUBJID	ADT	ADY	AVISIT	AVAL
1	GS-US-236-0102-2825-6109	2010-04-30	1	Baseline	3.6998377
2	GS-US-236-0102-2825-6109	2010-05-13	14	Week 2	2.0086001
3	GS-US-236-0102-2825-6109	2010-05-26	27	Week 4	1.6901960
4	GS-US-236-0102-2825-6109	2010-06-24	56	Week 8	1.6901960
5	GS-US-236-0102-2825-6109	2010-07-26	88	Week 12	1.6901960
6	GS-US-236-0102-2825-6109	2010-08-24	117	Week 16	1.6901960
7	GS-US-236-0102-2825-6109	2010-10-12	166	Week 24	1.6901960
8	GS-US-236-0102-2825-6109	2010-12-08	223	Week 32	1.6901960
9	GS-US-236-0102-2825-6109	2011-02-01	278	Week 40	1.6901960
10	GS-US-236-0102-2825-6109	2011-03-31	336	Week 48	1.8450980

➤ **Secondary Efficacy Endpoint: CD4 Count Analysis**

The CD4 profile by visit and by treatment arm is listed in Figure 7 below (using the completer analysis). The simple statistical summary of CD4 count at baseline and Week 48 were listed in Table 34, so as the CD4 change from baseline to Week 48 by completer analysis or imputing missing at Week 48 to baseline analysis. As you can see, the mean increment of CD4 count in E/C/F/T arm (211) is slightly higher than that in the ATR arm (165).

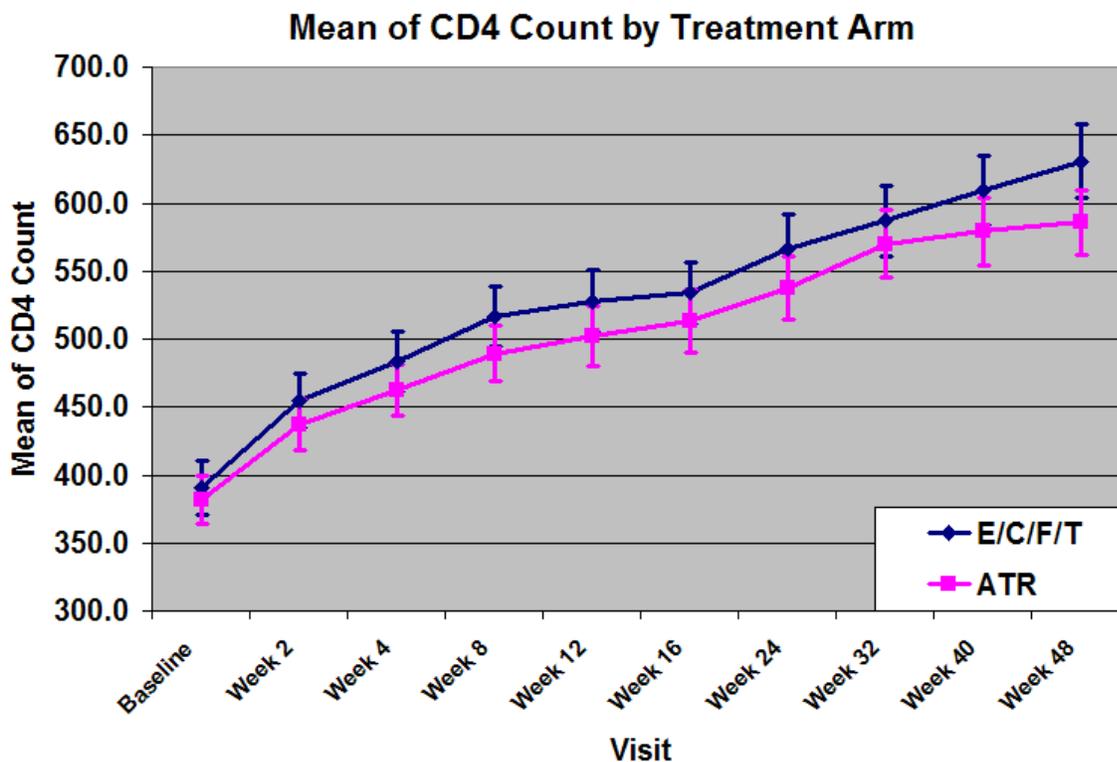


Figure 7: The CD4 Count by Study Visit and by Arm for Study GS-US-236-0102

Table 34: The CD4 Change from Baseline to Week 48 Analysis for Study GS-US-236-0102 (ITT)

	E/C/F/T	ATR	Total
CD4 at Baseline			
n	348	352	700
Mean (SE)	390.8 (10.11)	381.7 (9.073)	386.2 (6.786)
median	375.5	382.5	380.0
Range	(14.00, 1348)	(3.00, 1003)	(3.00, 1348)
std	188.6	170.2	179.5
CD4 at Week 48			
n	325	315	640
Mean (SE)	630.8 (13.82)	585.9 (12.05)	608.7 (9.223)
median	607.0	574.0	587.0
Range	(78.00, 1458)	(126.0, 1328)	(78.00, 1458)
std	249.1	213.9	233.3
--- Completer Analysis ---			
CD4 Change at Week 48 from Baseline (completer only)			
n	325	315	640
Mean (SE)	239.0 (9.274)	205.7 (8.643)	222.6 (6.376)
median	226.0	190.0	211.5
Range	(-102, 882.0)	(-160, 844.0)	(-160, 882.0)
std	167.2	153.4	161.3
--- Imputed missing to ZERO ---			
CD4 Change at Week 48 from Baseline (Missing=ZERO)			
n	348	352	700
Mean (SE)	223.2 (9.228)	184.1 (8.434)	203.5 (6.287)
median	211.0	165.5	190.0
Range	(-102, 882.0)	(-160, 844.0)	(-160, 882.0)
std	172.2	158.2	166.3

3.2.4.3 Study GS--US-236-0103

Overall, the stat reviewer replicated the sponsor's results for the primary efficacy endpoint. The efficacy analysis is based on the ITT population, including subjects who randomized and had at least one dose of randomized study drug. There are only 7 randomized subjects excluded from the ITT due to not being dosed.

➤ Primary Efficacy Analysis Results

The virologic success rate was 89.5% of subjects (316/353) in the E/C/F/T arm and 86.8% of subjects (308/355) in the ATV/r arm. The baseline HIV-1 RNA stratum-weighted difference in the percentage of subjects with virologic success was 3.0% with 95.2% confidence interval [CI] of (-1.8%, 7.8%). The 95.2% confidence interval [CI] is (-2.1%, 7.6%) using screening visit

viral load (Table 35). Because of two interim analyses occurred before this analysis, this 95.2% CI is the 95% CI for this final analysis.

Because the lower bound of the 2-sided 95% CI of the difference in virologic success rate (E/C/F/T – ATV/r) was –1.8% or –2.1% greater than the pre-specified –12% noninferiority margin, the E/C/F/T STR was determined to be noninferior to ATV/r.

If just using normal approximation without stratification justification, the 95.2% CI is (-2.1%, 7.7%), it leads to the same conclusion.

Table 35: The Primary Efficacy Endpoint (Virologic Success Rate (<50 copies/mL)) Results for Study GS-US-236-0103 (ITT)

<50	E/C/F/T	ATV/r	Rate Diff	95.2% CI
Normal approximation of Rate Difference (QUAD – ATV)				
	316/353 (89.5%)	308/355 (86.8%)	2.8%	[-2.1%; 7.7%]
CMH Weighted of Rate Difference by Baseline VL (QUAD – ATV)				
	316/353(89.5%)	308/355(86.8%)	3.0%	[-1.8%; 7.8%]
CMH Weighted of Rate Difference by Screening VL (QUAD – ATV)				
	316/353(89.5%)	308/355(86.8%)	2.8%	[-2.1%; 7.6%]

The virologic success rate by study visit and by treatment arm is listed in Figure 8 below. As you can see, E/C/F/T arm had a higher virologic success rate at the beginning and two arms were close at the end.

The virologic success rate results using <400 copies/mL are listed in Table 36. As you can see, there are 5 more responders (+1.4%) in E/C/F/T arm and 4 more responders (+1.1%) in ATV/r arm. The 95.2% CI of the rate difference between two arms is (-1.4%, 7.8%), which leads the same conclusion.

Table 36: The Primary Efficacy Endpoint (Virologic Success Rate (<400 copies/mL)) Results for Study GS-US-236-0103 (ITT)

<400	E/C/F/T	ATV/r	Rate Diff	95.2% CI
Normal approximation of Rate Difference (QUAD – ATV)				
	321/353 (90.9%)	312/355 (87.9%)	3.0%	[-1.6%; 7.7%]
CMH Weighted of Rate Difference by Baseline VL (QUAD – ATV)				
	321/353(90.9%)	312/355(87.9%)	3.2%	[-1.4%; 7.8%]
CMH Weighted of Rate Difference by Screening VL (QUAD – ATV)				
	321/353(90.9%)	312/355(87.9%)	3.1%	[-1.6%; 7.7%]

Note that one subject 0031-7076 in E/C/F/T arm had baseline HIV viral load <50 copies/mL and afterward without any ARV drug even though the HIV viral load at the screening visit was 23300 copies/mL (Table 37). The subject was counted as virologic success.

Table 37: The HIV Viral Load Profile for Subject 0031-7076 in Study GS-US-236-0103

	USUBJID	ADT	ADY	AVISITN	VISIT	AVAL	AVALC	BASE
1	GS-US-236-0103-0031-7076	2010-05-26	-35	0	Screening	23300	23300	49
2	GS-US-236-0103-0031-7076	2010-06-30	1	0	Baseline	49	<50 HIV R	49
3	GS-US-236-0103-0031-7076	2010-07-14	15	2	Week 2	49	<50 No HI	49
4	GS-US-236-0103-0031-7076	2010-07-27	28	4	Week 4	49	<50 No HI	49
5	GS-US-236-0103-0031-7076	2010-08-25	57	8	Week 8	49	<50 HIV R	49
6	GS-US-236-0103-0031-7076	2010-09-22	85	12	Week 12	49	<50 HIV R	49
7	GS-US-236-0103-0031-7076	2010-10-19	112	16	Week 16	49	<50 No HI	49
8	GS-US-236-0103-0031-7076	2010-12-16	170	24	Week 24	49	<50 No HI	49
9	GS-US-236-0103-0031-7076	2011-02-10	226	32	Week 32	49	<50 HIV R	49
10	GS-US-236-0103-0031-7076	2011-04-06	281	40	Week 40	49	<50 No HI	49
11	GS-US-236-0103-0031-7076	2011-06-01	337	48	Week 48	49	<50 No HI	49
12	GS-US-236-0103-0031-7076	2011-08-18	415	60	Week 60	49	<50 No HI	49

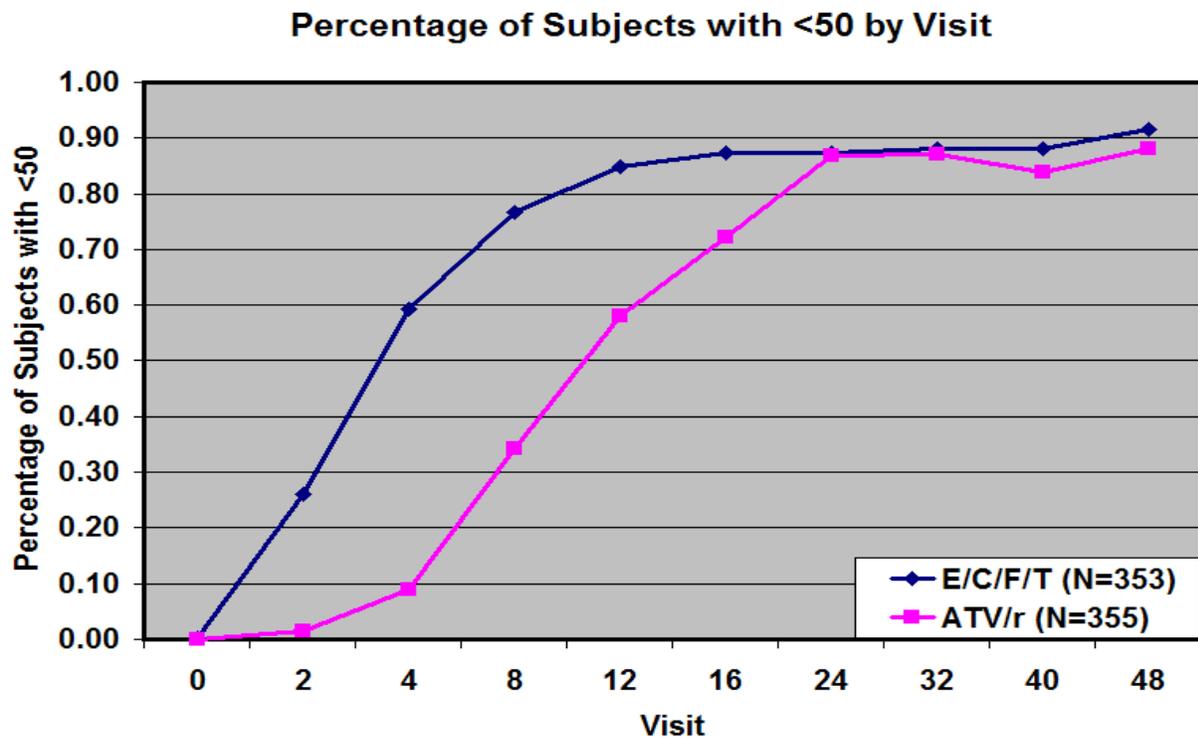


Figure 8: Proportion of Subjects Achieving Virologic Success (<50 copies/mL) by Study Visit and by Arm for Study GS-US-236-0103

The snapshot classifications are listed in Table 38 and 39 below for <50 copies/mL and <400 copies/mL respectively.

Table 38: The Snapshot Classification Results of the Primary Efficacy Endpoint (<50 copies/mL) for Study GS-US-236-0103 (ITT)

Snapshot Category (<50)	E/C/F/T (N=353)	ATV/r (N=355)	Total (N=708)
Virologic Success at Week 48	316(89.5%)	308(86.8%)	624(88.1%)
Overall Failure	37(10.5%)	47(13.2%)	84(11.9%)
2. Virologic Failure at Week 48	19(5.4%)	19(5.4%)	38(5.4%)
2a. HIV-1 RNA >= 50 copies/mL	7(2.0%)	8(2.3%)	15(2.1%)
2b. Discontinued Study Drug Due to Lack of Efficacy	4(1.1%)	.	4(0.6%)
2c. Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL	8(2.3%)	11(3.1%)	19(2.7%)
3. No Virologic Data in Week 48 Window	18(5.1%)	28(7.9%)	46(6.5%)
3a. Discontinued Study Drug Due to AE/Death	11(3.1%)	18(5.1%)	29(4.1%)
3b. Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL	7(2.0%)	9(2.5%)	16(2.3%)
3c. Missing Data During Window but on Study Drug	.	1(0.3%)	1(0.1%)

Table 39: The Snapshot Classification Results of the Virologic Success Rate (<400 copies/mL) for Study GS-US-236-0103 (ITT)

Snapshot Category (<400)	E/C/F/T (N=353)	ATV/r (N=355)	Total (N=708)
Virologic Success at Week 48	321(90.9%)	312(87.9%)	633(89.4%)
Overall Failure	32(9.1%)	43(12.1%)	75(10.6%)
2. Virologic Failure at Week 48	10(2.8%)	8(2.3%)	18(5.4%)
2a. HIV-1 RNA >= 400 copies/mL	2(0.6%)	4(1.1%)	6(0.6%)
2b. Discontinued Study Drug Due to Lack of Efficacy	4(1.1%)	.	4(0.6%)
2c. Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 400 copies/mL	4(1.1%)	4(1.1%)	8(1.1%)
3. No Virologic Data in Week 48 Window	22(6.2%)	35(9.9%)	57(8.1%)
3a. Discontinued Study Drug Due to AE/Death	11(3.1%)	18(5.1%)	29(4.1%)
3b. Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 400 copies/mL	11(3.1%)	16(4.5%)	27(3.8%)
3c. Missing Data During Window but on Study Drug	.	1(0.3%)	1(0.1%)

➤ **Comparison between Snapshot analysis and TLOVR**

Also the FDA-defined snapshot results were compared to the TLOVR results. There are 23 differences listed in Table 40 below. The difference was caused by the algorithm itself, which decided which data should be used for analysis.

Table 40: The Difference between Snapshot and TLOVR Analysis Results for Study GS-US-236-0103 (ITT)

Snapshot	TLOVR	E/C/F/T	ATV/r
virologic success (HIV RNA <50 copies/mL)	Rebound	3976-7260	0121-7015
		3976-7315	2475-7545
		1994-7301	2728-7450
		0457-7514	
		2480-7057	
		2475-7035	
	Never Suppressed through Week 48	1708-7419	3947-7656
		2817-7492	3714-7666
		5215-7639	5130-7674
		0315-7354	0554-7495
			0698-7456
	Drug Discontinuation Due to AEs	0959-7110	
		1021-7348	
	Drug Discontinuation Due to Other Reasons		5083-7237
missing data during the window but on study	Responder		4143-7687
virologic failure			2135-7574

➤ **Secondary Efficacy Endpoint: CD4 Count Analysis**

The CD4 profile by visit and by treatment arm is listed in Figure 9 below (this is a completer analysis). The simple statistical summary of CD4 count at baseline and Week 48 is listed in Table 41, as is the CD4 change from baseline to Week 48 by completer analysis or imputing missing at Week 48 to baseline analysis. As you can see, the mean increment of CD4 count in E/C/F/T arm (196) is the almost same as that in the ATV/r arm (191).

Table 41: The CD4 Change from Baseline to Week 48 Analysis for Study GS-US-236-0103 (ITT)

Subgroup	E/C/F/T	ATV/r	Total
CD4 at Baseline			
n	353	355	708
Mean (SE)	364.2 (9.613)	375.4 (8.436)	369.8 (6.392)
median	351.0	366.0	357.0
Range	(5.00, 1132)	(10.00, 963.0)	(5.00, 1132)
std	180.6	158.9	170.1
CD4 at Week 48			
n	334	321	655
Mean (SE)	567.7 (12.58)	584.8 (11.77)	576.1 (8.629)
median	535.5	557.0	553.0
Range	(92.00, 1714)	(74.00, 1317)	(74.00, 1714)
std	230.0	210.9	220.8
--- Completer Analysis ---			
CD4 Change at Week 48 from Baseline (completer only)			
n	334	321	655
Mean (SE)	206.8 (8.986)	211.4 (8.944)	209.0 (6.337)
median	195.0	204.0	196.0
Range	(-303, 1024)	(-276, 944.0)	(-303, 1024)
std	164.2	160.3	162.2
--- Imputed missing to ZERO ---			
CD4 Change at Week 48 from Baseline (Missing=ZERO)			
n	353	355	708
Mean (SE)	195.6 (8.858)	191.1 (8.736)	193.4 (6.217)
median	182.0	182.0	182.0
Range	(-303, 1024)	(-276, 944.0)	(-303, 1024)
std	166.4	164.6	165.4

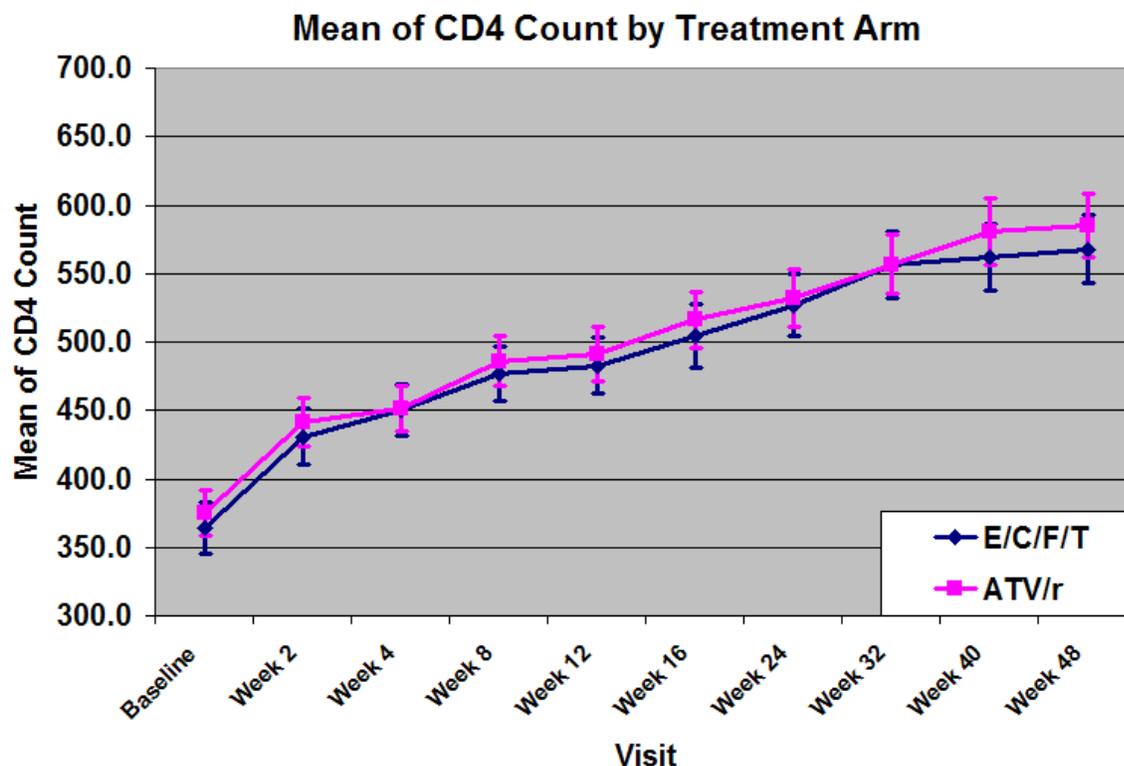


Figure 9: The CD4 Count by Study Visit and by Arm for Study GS-US-236-0103

3.3 Evaluation of Safety

3.4 Benefit: Risk Assessment (Optional)

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

No significant differences in virologic success rates were observed for gender, age, or location (US vs. non-US) between E/C/F/T arm and active control arm (ATR or ATV/r). Only about 10% of the subjects are female in both studies, so the virologic success rates estimations for females may not be stable.

In both studies, the virologic success rates in subjects who had HIV viral load $\leq 100,000$ copies/mL at baseline are higher than that in subject who had HIV viral load $>100,000$ copies/mL at baseline. The virologic success rates in subjects who had CD4 counts > 200 cells/uL at baseline are higher than that in subject who had CD4 counts ≤ 200 cells/uL at baseline.

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

❖ Study GS--US-236-0102

For study GS-US-236-0102, the virologic success rates in white subjects (89% in E/C/F/T arm and 88% in ATR arm) were slightly higher than that in non-white subjects (85% in E/C/F/T arm and 78% in ATR arm) (Table 42).

In study GS-US-236-0102, all subjects were from US. There were 102 sites involved in the study and there is not trend due to small sample sizes at each site. The virologic success rates by site and by arm are listed at the bottom of the Table 42 for reference.

Table 42: The Summary Subgroup Analyses of Virologic Success Rate (HIV VL<50 copies/mL) at Week 48 for Study GS-US-236-0102 (ITT)

Efficacy Parameter	E/C/F/T	ATR	Total

As Randomized and Dosed (ITT)			
N	305/348 (87.6)	296/352 (84.1)	601/700 (85.9)
Gender			
F	35 / 41 (85.4)	30 / 36 (83.3)	65 / 77 (84.4)
M	270 /307 (87.9)	266 /316 (84.2)	536 /623 (86.0)
Race			
Non-White	114 /134 (85.1)	97 /125 (77.6)	211 /259 (81.5)
WHITE	191 /214 (89.3)	199 /227 (87.7)	390 /441 (88.4)
Ethnic			
HISPANIC/LATINO	73 / 82 (89.0)	72 / 85 (84.7)	145 /167 (86.8)
NOT HISPANIC/LATINO	232 /266 (87.2)	224 /267 (83.9)	456 /533 (85.6)
Age Group			
<37 yrs	136 /162 (84.0)	140 /166 (84.3)	276 /328 (84.1)
37<=, <60 yrs	164 /180 (91.1)	146 /175 (83.4)	310 /355 (87.3)
60<= yrs	5 / 6 (83.3)	10 / 11 (90.9)	15 / 17 (88.2)
Age Group 2			
<=40 yrs	179 /208 (86.1)	179 /209 (85.6)	358 /417 (85.9)
>40 yrs	126 /140 (90.0)	117 /143 (81.8)	243 /283 (85.9)
Site ID			
0031	3 / 4 (75.0)	2 / 2 (100)	5 / 6 (83.3)
0033	4 / 4 (100)	8 / 8 (100)	12 / 12 (100)
0085	. / . (.)	1 / 1 (100)	1 / 1 (100)
0121	9 / 9 (100)	6 / 7 (85.7)	15 / 16 (93.8)
0255	3 / 4 (75.0)	4 / 5 (80.0)	7 / 9 (77.8)
0302	4 / 4 (100)	6 / 6 (100)	10 / 10 (100)
0310	2 / 4 (50.0)	3 / 5 (60.0)	5 / 9 (55.6)
0315	4 / 5 (80.0)	2 / 5 (40.0)	6 / 10 (60.0)
0352	. / 1 (0.00)	3 / 4 (75.0)	3 / 5 (60.0)
0354	2 / 2 (100)	2 / 2 (100)	4 / 4 (100)
0359	1 / 1 (100)	1 / 1 (100)	2 / 2 (100)

0360	1 / 1 (100)	1 / 1 (100)	2 / 2 (100)
0364	5 / 5 (100)	7 / 7 (100)	12 / 12 (100)
0365	2 / 2 (100)	1 / 1 (100)	3 / 3 (100)
0407	6 / 7 (85.7)	6 / 6 (100)	12 / 13 (92.3)
0444	1 / 1 (100)	2 / 2 (100)	3 / 3 (100)
0446	2 / 2 (100)	3 / 4 (75.0)	5 / 6 (83.3)
0524	1 / 1 (100)	3 / 3 (100)	4 / 4 (100)
0550	7 / 7 (100)	2 / 2 (100)	9 / 9 (100)
0566	1 / 1 (100)	. / . (.)	1 / 1 (100)
0581	4 / 4 (100)	2 / 3 (66.7)	6 / 7 (85.7)
0589	1 / 1 (100)	3 / 4 (75.0)	4 / 5 (80.0)
0597	4 / 4 (100)	. / 1 (0.00)	4 / 5 (80.0)
0598	6 / 6 (100)	3 / 5 (60.0)	9 / 11 (81.8)
0608	. / . (.)	3 / 3 (100)	3 / 3 (100)
0637	3 / 4 (75.0)	1 / 1 (100)	4 / 5 (80.0)
0651	2 / 2 (100)	. / . (.)	2 / 2 (100)
0652	1 / 2 (50.0)	. / 1 (0.00)	1 / 3 (33.3)
0659	4 / 5 (80.0)	2 / 3 (66.7)	6 / 8 (75.0)
0660	5 / 5 (100)	1 / 1 (100)	6 / 6 (100)
0661	8 / 8 (100)	8 / 9 (88.9)	16 / 17 (94.1)
0663	6 / 8 (75.0)	1 / 2 (50.0)	7 / 10 (70.0)
0698	12 / 15 (80.0)	20 / 21 (95.2)	32 / 36 (88.9)
0708	2 / 3 (66.7)	1 / 1 (100)	3 / 4 (75.0)
0729	1 / 1 (100)	3 / 3 (100)	4 / 4 (100)
0744	5 / 6 (83.3)	4 / 5 (80.0)	9 / 11 (81.8)
0754	5 / 6 (83.3)	3 / 3 (100)	8 / 9 (88.9)
0765	1 / 1 (100)	1 / 1 (100)	2 / 2 (100)
0783	2 / 2 (100)	. / . (.)	2 / 2 (100)
0828	1 / 1 (100)	1 / 1 (100)	2 / 2 (100)
0947	2 / 3 (66.7)	1 / 1 (100)	3 / 4 (75.0)
0989	2 / 2 (100)	2 / 2 (100)	4 / 4 (100)
0991	5 / 6 (83.3)	5 / 5 (100)	10 / 11 (90.9)
0994	2 / 3 (66.7)	1 / 2 (50.0)	3 / 5 (60.0)
0995	. / . (.)	. / 1 (0.00)	. / . (.)
1236	1 / 1 (100)	5 / 6 (83.3)	6 / 7 (85.7)
1407	6 / 6 (100)	7 / 7 (100)	13 / 13 (100)
1534	3 / 3 (100)	4 / 4 (100)	7 / 7 (100)
1536	5 / 5 (100)	6 / 6 (100)	11 / 11 (100)
1537	2 / 2 (100)	4 / 4 (100)	6 / 6 (100)
1541	7 / 7 (100)	1 / 1 (100)	8 / 8 (100)
1543	5 / 5 (100)	3 / 4 (75.0)	8 / 9 (88.9)
1549	1 / 1 (100)	2 / 3 (66.7)	3 / 4 (75.0)
1560	3 / 3 (100)	2 / 2 (100)	5 / 5 (100)
1598	4 / 5 (80.0)	11 / 11 (100)	15 / 16 (93.8)
1602	1 / 2 (50.0)	. / . (.)	1 / 2 (50.0)
1603	5 / 5 (100)	1 / 3 (33.3)	6 / 8 (75.0)
1609	3 / 3 (100)	7 / 8 (87.5)	10 / 11 (90.9)
1634	. / . (.)	2 / 2 (100)	2 / 2 (100)
1668	1 / 1 (100)	. / . (.)	1 / 1 (100)
1729	2 / 2 (100)	1 / 2 (50.0)	3 / 4 (75.0)
1808	4 / 4 (100)	3 / 3 (100)	7 / 7 (100)
1912	2 / 2 (100)	. / . (.)	2 / 2 (100)
1925	. / 2 (0.00)	2 / 2 (100)	2 / 4 (50.0)
1950	3 / 4 (75.0)	1 / 1 (100)	4 / 5 (80.0)
1951	1 / 1 (100)	1 / 2 (50.0)	2 / 3 (66.7)
1961	2 / 2 (100)	2 / 2 (100)	4 / 4 (100)

1965	4 / 4 (100)	3 / 3 (100)	7 / 7 (100)
1966	2 / 2 (100)	1 / 1 (100)	3 / 3 (100)
1967	2 / 2 (100)	3 / 3 (100)	5 / 5 (100)
1978	4 / 5 (80.0)	8 / 8 (100)	12 / 13 (92.3)
1990	. / . (.)	1 / 1 (100)	1 / 1 (100)
1993	2 / 3 (66.7)	6 / 6 (100)	8 / 9 (88.9)
2003	3 / 4 (75.0)	3 / 5 (60.0)	6 / 9 (66.7)
2058	4 / 4 (100)	3 / 4 (75.0)	7 / 8 (87.5)
2124	2 / 2 (100)	. / . (.)	2 / 2 (100)
2135	1 / 1 (100)	. / . (.)	1 / 1 (100)
2140	4 / 7 (57.1)	3 / 5 (60.0)	7 / 12 (58.3)
2154	4 / 6 (66.7)	5 / 6 (83.3)	9 / 12 (75.0)
2191	1 / 1 (100)	1 / 2 (50.0)	2 / 3 (66.7)
2475	7 / 8 (87.5)	4 / 7 (57.1)	11 / 15 (73.3)
2480	7 / 8 (87.5)	3 / 3 (100)	10 / 11 (90.9)
2493	2 / 3 (66.7)	4 / 4 (100)	6 / 7 (85.7)
2675	6 / 6 (100)	11 / 13 (84.6)	17 / 19 (89.5)
2728	7 / 7 (100)	15 / 15 (100)	22 / 22 (100)
2734	1 / 2 (50.0)	2 / 4 (50.0)	3 / 6 (50.0)
2824	5 / 5 (100)	. / . (.)	5 / 5 (100)
2825	. / 1 (0.00)	. / 1 (0.00)	. / . (.)
2838	5 / 6 (83.3)	4 / 5 (80.0)	9 / 11 (81.8)
2840	3 / 4 (75.0)	3 / 5 (60.0)	6 / 9 (66.7)
2843	4 / 4 (100)	5 / 7 (71.4)	9 / 11 (81.8)
2873	1 / 1 (100)	1 / 1 (100)	2 / 2 (100)
3317	1 / 1 (100)	1 / 3 (33.3)	2 / 4 (50.0)
3612	2 / 2 (100)	. / . (.)	2 / 2 (100)
3947	2 / 2 (100)	2 / 3 (66.7)	4 / 5 (80.0)
4039	1 / 1 (100)	1 / 1 (100)	2 / 2 (100)
4140	4 / 6 (66.7)	3 / 3 (100)	7 / 9 (77.8)
4170	3 / 3 (100)	2 / 2 (100)	5 / 5 (100)
4555	. / . (.)	1 / 1 (100)	1 / 1 (100)
4735	3 / 3 (100)	. / 2 (0.00)	3 / 5 (60.0)
5083	3 / 3 (100)	1 / 1 (100)	4 / 4 (100)
5221	2 / 2 (100)	2 / 3 (66.7)	4 / 5 (80.0)

❖ Study GS--US-236-0103

For study GS-US-236-0103, the virologic success rates in white subjects (90% in E/C/F/T arm and 87% in ATV/r arm) were similar to that in non-white subjects (88% in E/C/F/T arm and 87% in ATV/r arm) (Table 43).

In study GS-US-236-0103, 46% of subjects were from US. The virologic success rates in US is 87% in E/C/F/T arm and 84% in ATV/r arm, which is about 5% lower than that in non-US subjects (92% in E/C/F/T arm and 90% in ATV/r arm) (Table 42). The virologic success rates by Country and by arm and by State in US are listed at the bottom of the Table 43 for reference.

Table 43: The Summary Subgroup Analyses of Virologic Success Rate (HIV VL<50 copies/mL) at Week 48 for Study GS-US-236-0103 (ITT)

Efficacy Parameter	E/C/F/T	ATV/r	Total
As Randomized and Dosed (ITT)			
N	316/353 (89.5)	308/355 (86.8)	624/708 (88.1)
Gender			
F	24 / 29 (82.8)	32 / 39 (82.1)	56 / 68 (82.4)
M	292 /324 (90.1)	276 /316 (87.3)	568 /640 (88.8)
Race			
Non-White	91 /103 (88.3)	68 / 78 (87.2)	159 /181 (87.8)
WHITE	225 /250 (90.0)	240 /277 (86.6)	465 /527 (88.2)
Ethnic			
HISPANIC/LATINO	57 / 64 (89.1)	39 / 47 (83.0)	96 /111 (86.5)
NOT HISPANIC/LATINO	255 /284 (89.8)	262 /298 (87.9)	517 /582 (88.8)
NOT REPORTED	4 / 5 (80.0)	7 / 10 (70.0)	11 / 15 (73.3)
Age Group			
<38 yrs	163 /186 (87.6)	142 /167 (85.0)	305 /353 (86.4)
38<=, <60 yrs	145 /156 (92.9)	158 /180 (87.8)	303 /336 (90.2)
60<= yrs	8 / 11 (72.7)	8 / 8 (100)	16 / 19 (84.2)
Age Group 2			
<=40 yrs	191 /216 (88.4)	173 /205 (84.4)	364 /421 (86.5)
>40 yrs	125 /137 (91.2)	135 /150 (90.0)	260 /287 (90.6)
Region			
Non-USA	144 /156 (92.3)	153 /170 (90.0)	297 /326 (91.1)
USA	172 /197 (87.3)	155 /185 (83.8)	327 /382 (85.6)
Country			
AUS	29 / 30 (96.7)	32 / 32 (100)	61 / 62 (98.4)
AUT	10 / 12 (83.3)	6 / 8 (75.0)	16 / 20 (80.0)
BEL	8 / 9 (88.9)	11 / 12 (91.7)	19 / 21 (90.5)
CAN	19 / 19 (100)	22 / 22 (100)	41 / 41 (100)
CHE	. / . (.)	1 / 2 (50.0)	1 / 2 (50.0)
DEU	27 / 29 (93.1)	28 / 36 (77.8)	55 / 65 (84.6)
DNK	. / 1 (0.00)	2 / 2 (100)	2 / 3 (66.7)
FRA	21 / 23 (91.3)	22 / 23 (95.7)	43 / 46 (93.5)
GBR	10 / 11 (90.9)	12 / 15 (80.0)	22 / 26 (84.6)
ITA	7 / 9 (77.8)	5 / 5 (100)	12 / 14 (85.7)
MEX	3 / 3 (100)	2 / 2 (100)	5 / 5 (100)
NLD	2 / 2 (100)	4 / 4 (100)	6 / 6 (100)
PRT	1 / 1 (100)	2 / 2 (100)	3 / 3 (100)
SWE	. / . (.)	1 / 1 (100)	1 / 1 (100)
THA	7 / 7 (100)	3 / 4 (75.0)	10 / 11 (90.9)
USA	172 /197 (87.3)	155 /185 (83.8)	327 /382 (85.6)
State in US			
AR	. / . (.)	1 / 1 (100)	1 / 1 (100)
AZ	4 / 4 (100)	3 / 3 (100)	7 / 7 (100)

CA	43 / 45 (95.6)	31 / 38 (81.6)	74 / 83 (89.2)
CO	3 / 4 (75.0)	4 / 5 (80.0)	7 / 9 (77.8)
CT	1 / 1 (100)	1 / 1 (100)	2 / 2 (100)
DC	11 / 13 (84.6)	11 / 11 (100)	22 / 24 (91.7)
FL	29 / 33 (87.9)	36 / 46 (78.3)	65 / 79 (82.3)
GA	3 / 3 (100)	1 / 1 (100)	4 / 4 (100)
HI	. / . (.)	1 / 1 (100)	1 / 1 (100)
IL	2 / 2 (100)	. / . (.)	2 / 2 (100)
MA	2 / 4 (50.0)	1 / 1 (100)	3 / 5 (60.0)
MI	7 / 7 (100)	5 / 5 (100)	12 / 12 (100)
MN	4 / 4 (100)	1 / 2 (50.0)	5 / 6 (83.3)
MO	5 / 6 (83.3)	8 / 8 (100)	13 / 14 (92.9)
NC	6 / 6 (100)	4 / 6 (66.7)	10 / 12 (83.3)
NJ	4 / 5 (80.0)	2 / 3 (66.7)	6 / 8 (75.0)
NY	14 / 16 (87.5)	3 / 4 (75.0)	17 / 20 (85.0)
OH	. / . (.)	3 / 3 (100)	3 / 3 (100)
PA	1 / 3 (33.3)	6 / 6 (100)	7 / 9 (77.8)
PR	5 / 7 (71.4)	3 / 4 (75.0)	8 / 11 (72.7)
SC	1 / 2 (50.0)	1 / 1 (100)	2 / 3 (66.7)
TX	22 / 26 (84.6)	24 / 29 (82.8)	46 / 55 (83.6)
VA	4 / 5 (80.0)	2 / 2 (100)	6 / 7 (85.7)
WA	1 / 1 (100)	3 / 4 (75.0)	4 / 5 (80.0)

4.2 Other Special/Subgroup Populations

The subgroup analysis for some baseline covariates will be presented below for two studies separately.

4.2.1 Other Baseline Covariates

In both studies, as expected the virologic success rates in subjects who had HIV viral load \leq 100,000 copies/mL at baseline are higher than that in subject who had HIV viral load $>$ 100,000 copies/mL at baseline. The virologic success rates in subjects who had CD4 counts $>$ 200 cells/uL at baseline are higher than that in subject who had CD4 counts \leq 200 cells/uL at baseline (Table 44 for study GS-US-236-0102 and Table 45 for study GS-US-236-0103).

Table 44: The Baseline Covariates Subgroup Analyses of Virologic Success Rate (HIV VL<50 copies/mL) at Week 48 for Study GS-US-236-0102 (ITT)

Efficacy Parameter	E/C/F/T	ATR	Total
As Randomized and Dosed (ITT)			
N	305/348 (87.6)	296/352 (84.1)	601/700 (85.9)
Baseline HIV-1 RNA Category - 2			
2<=, <3	1 / 1 (100)	. / . (.)	1 / 1 (100)
3<=, <4	36 / 41 (87.8)	30 / 31 (96.8)	66 / 72 (91.7)
4<=, <5	169 /188 (89.9)	170 /204 (83.3)	339 /392 (86.5)
5<=, <6	96 /112 (85.7)	91 /111 (82.0)	187 /223 (83.9)
6<=, <7	3 / 6 (50.0)	5 / 6 (83.3)	8 / 12 (66.7)
Baseline HIV-1 RNA Category - 1			
<= 100,000 copies/mL	206 /230 (89.6)	201 /236 (85.2)	407 /466 (87.3)
> 100,000 copies/mL	99 /118 (83.9)	95 /116 (81.9)	194 /234 (82.9)
Screening HIV-1 RNA Category			
<= 100,000 copies/mL	208 /230 (90.4)	194 /234 (82.9)	402 /464 (86.6)
> 100,000 copies/mL	97 /118 (82.2)	102 /118 (86.4)	199 /236 (84.3)
Baseline CD4 Count Category - 1			
<= 50	3 / 7 (42.9)	5 / 6 (83.3)	8 / 13 (61.5)
51 to <= 200	29 / 36 (80.6)	37 / 45 (82.2)	66 / 81 (81.5)
201 to <= 350	97 /112 (86.6)	81 / 96 (84.4)	178 /208 (85.6)
351 to <= 500	104 /113 (92.0)	115 /136 (84.6)	219 /249 (88.0)
> 500	72 / 80 (90.0)	58 / 69 (84.1)	130 /149 (87.2)
Baseline CD4 Count Category - 2			
<= 200	32 / 43 (74.4)	42 / 51 (82.3)	74 / 94 (78.7)
> 200	273 /305 (89.5)	254 /301 (84.3)	527 /606 (87.0)

Table 45: The Baseline Covariates Subgroup Analyses of Virologic Success Rate (HIV VL<50 copies/mL) at Week 48 for Study GS-US-236-0103 (ITT)

Efficacy Parameter	E/C/F/T	ATV/r	Total
As Randomized and Dosed (ITT)			
N	316/353(89.5)	308/355(86.8)	624/708(88.1)
Baseline HIV-1 RNA Category - 2			
<2	1 / 1 (100)	. / . (.)	1 / 1 (100)
2<=, <3	. / . (.)	1 / 1 (100)	1 / 1 (100)
3<=, <4	32 / 34 (94.1)	33 / 37 (89.2)	65 / 71 (91.5)
4<=, <5	154 /167 (92.2)	157 /175 (89.7)	311 /342 (90.9)
5<=, <6	123 /143 (86.0)	109 /134 (81.3)	232 /277 (83.8)
6<=, <7	6 / 8 (75.0)	8 / 8 (100)	14 / 16 (87.5)
Baseline HIV-1 RNA Category - 1			
<= 100,000 copies/mL	188 /203 (92.6)	192 /214 (89.7)	380 /417 (91.1)
> 100,000 copies/mL	128 /150 (85.3)	116 /141 (82.3)	244 /291 (83.8)
Screening HIV-1 RNA Category			
<= 100,000 copies/mL	195 /215 (90.7)	192 /217 (88.5)	387 /432 (89.6)
> 100,000 copies/mL	121 /138 (87.7)	116 /138 (84.1)	237 /276 (85.9)
Baseline CD4 Count Category - 1			
<= 50	8 / 12 (66.7)	5 / 5 (100)	13 / 17 (76.5)
51 to <= 200	35 / 42 (83.3)	28 / 34 (82.4)	63 / 76 (82.9)
201 to <= 350	114 /122 (93.4)	110 /124 (88.7)	224 /246 (91.1)
351 to <= 500	113 /122 (92.6)	105 /122 (86.1)	218 /244 (89.3)
> 500	46 / 55 (83.6)	60 / 70 (85.7)	106 /125 (84.8)
Baseline CD4 Count Category - 2			
<= 200	43 / 54 (79.6)	33 / 39 (84.6)	76 / 93 (81.7)
> 200	273 /299 (91.3)	275 /316 (87.0)	548 /615 (89.1)

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. Here will present some additional statistical considerations.

5.1.1 Randomization Stratification

Even though the randomization stratification used screening visit HIV viral load, the primary efficacy analysis used baseline HIV viral load to do the adjustment in CMH method. The impact of this on the primary efficacy endpoint analysis using CMH method is minimal as both cases

have been shown to have almost identical results. Please see section 3.2.4.2 and 3.2.4.3 for details.

5.2 Conclusions and Recommendations

These two key phase 3 studies have demonstrated that the E/C/F/T STR was noninferior to ATR or ATV/r + TVD. The lower bound of the 2-sided 95% CI of the difference in virologic success rate was -1.6% for (E/C/F/T – ATR) and -1.9% for (E/C/F/T – (ATV/r+TVD)), which are greater than the pre-specified -12% noninferiority margin. The results are robust as the TLOVR analysis provided the very similar results.

The virologic success rates for E/C/F/T arm were 87.6% (305/348) in GS-US-236-0102 and 89.5% (316/353) in GS-US-236-0103, compared to the virologic success rates of 84.1% (296/352) in ATR arm and 86.8% (308/355) in ATV/r+TVD arm.

APPENDICES

References

1. StatXact PROCs User Manual for SAS Users, Version 6, 2004, Cytel.
2. SAS Version 9.2, SAS Inc.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WEN ZENG
06/29/2012

FRASER B SMITH
06/29/2012



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

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number: NDA 20-3100

Drug Name: GS-9137 with or without Ritonavir

Applicant: Sponsor: Gilead Sciences, Inc. 333 Lakeside Drive Foster City,
California USA 94404

Test Facility: [REDACTED] (b) (4)

Documents Reviewed: Electronic data submitted on October 31, 2011.

Review Priority: Standard

Biometrics Division: Division of Biometrics -6

Statistical Reviewer: Min Min, Ph.D.

Concurring Reviewer: Karl Lin, Ph.D.

Medical Division: Division of Antiviral Products

Reviewing Pharmacologist: Pritam S Verma, Ph.D.

Project Manager:

Keywords: Carcinogenicity, Dose response

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1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. The purpose of rat study was to investigate the carcinogenic potential of GS-9137 following daily oral administration by gavage to Crl:CD(SD) rats for a minimum of 104 consecutive weeks. However, because the number of surviving animals in the control groups reached 20 earlier than expected, males were dosed for a minimum of 88 weeks and females were dosed for a minimum of 90 weeks. The purpose of mouse study was to investigate the carcinogenic potential of GS-9137 with or without Ritonavir following daily oral administration by gavage to Crl:CD1 (ICR) mice for a minimum of 104 consecutive weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Verma.

2. Rat Study

Two separate experiments were conducted, one in males and one in females. Male and female Crl:CD(SD) rats were assigned to 4 groups (60/sex/group) and received either the vehicle (0.5% methyl cellulose), or 100, 300, and 2000 mg/kg/day GS-9137 in vehicle at a dose volume of 10 mL/kg. Satellite animals were used for toxicokinetic (TK) evaluation on Days 4, 178 (Week 26), and 360 (Week 52). The following table contains the information about the study design:

Animals were randomized into the following groups:

Group Number Identification	Dose (mg/kg/day)	Animal Numbers			
		Main Study		Toxicokinetic Study ^b	
		Males	Females	Males	Females
1/ Vehicle Article	0	60	60	6	6
2/ GS-9137 ^a	100	60	60	9	9
3/ GS-9137	300	60	60	9	9
4/ GS-9137	2000	60	60	9	9
5/ Health Screen	-	10	10	-	-

^a One animal in Group 2 (Animal No. 2020) swallowed a gavage needle on Day 28 and was replaced by a spare animals (which became Animal No. 2070).

^b Toxicokinetic population included 3 additional dosed animals, which were used as replacements, as required.

The following were collected: clinical signs (weekly, including the examination for the presence of palpable masses starting Week 26), body weight (weekly), food consumption (weekly for the first fourteen weeks and monthly thereafter), ophthalmology (predose, Week 52), hematology (red blood cell count and total and differential white blood cell counts, including blood cell morphology, at Months 12, 18 and at necropsy), TK, macroscopic observations at necropsy, and histopathology.

All animals were observed twice daily (once on the day of arrival) for mortality and signs of ill health and/or reaction to treatment throughout the study. In addition, a detailed examination was performed at least once prior to the start of treatment and weekly throughout the treatment period on the main study animals only. In addition, from Week 26 onwards, all main study animals were examined for the presence of palpable

masses during the detailed examination. The site, size, and appearance of these masses were recorded when first detected and, following this initial description, the presence or disappearance of these masses was monitored. Any mass borne by an animal was given a numerical designation (e.g. M1, M2, etc.) according to order of appearance. Death and observed clinical signs were individually recorded. All main study animals found dead during the study were subjected to necropsy and tissue samples were preserved. Prior to necropsy, the carcasses were stored and refrigerated (set to maintain 4°C).

2.1. Sponsor's analyses

2.1.1. Survival analysis

The statistical analyses for mortality data were performed for each sex separately. The survival function of each group was estimated using the Kaplan Meier product limit method applied on daily intervals. Any animal with accidental injury that caused its death or its unscheduled sacrifice was censored in the estimation. In addition, all animals still alive at the end of the experimental period were censored at the following day.

The log rank test was applied to the four groups to assess the significance of the overall group effect on the mortality data. When the log rank test revealed significant differences among groups ($p \leq 0.05$), then the significance of a dose related trend in mortality across the considered groups was evaluated using the method of Tarone. Using the Multtest procedure of the SAS/STAT module, Tarone's test was implemented as a Peto two-sided test with all uncensored deaths coded as 2 and all censored deaths coded as 0. The arithmetic dose level score (0, 100, 300 and 2000) was used to perform this overall trend test. In addition to the trend test, each test article treated group was compared against the control group. These pairwise comparisons were implemented with Peto's one tailed trend test, which were done in the direction indicated by the sign of the statistic of the overall trend test. When performing a pairwise comparison, only the two compared groups were included in the data set submitted to statistical analysis. For each trend test and pairwise group comparison of interest, significance was reported at the 0.05, 0.01 and 0.001 levels.

Sponsor's findings: For both male and female datasets, the log rank test revealed no significance at all among four groups. Consequently, for both sexes, no post-hoc testing was done, that is neither Tarone's trend test nor the pairwise comparisons were performed.

Table 1 Survival of Rats

Group 1 - Vehicle Article

Group 3 - GS-9137 300 mg/kg/day

Group 2 - GS-9137 100 mg/kg/day

Group 4 - GS-9137 2000 mg/kg/day

Males								Sex Group Week	Females							
1		2		3		4			1		2		3		4	
S	%	S	%	S	%	S	%		S	%	S	%	S	%	S	%
60	100	60	100	60	100	60	100	1 - 4	60	100	60	100	60	100	60	100
60	100	60	100	60	100	60	100	5 - 8	60	100	60	100	59	98	60	100
60	100	60	100	60	100	59	98	9 - 12	60	100	60	100	59	98	60	100
59	98	60	100	60	100	59	98	13 - 16	60	100	60	100	59	98	60	100
59	98	60	100	59	98	59	98	17 - 20	60	100	60	100	59	98	60	100
58	97	60	100	59	98	59	98	21 - 24	60	100	60	100	59	98	60	100
58	97	60	100	59	98	59	98	25 - 28	59	98	60	100	59	98	60	100
58	97	60	100	58	97	59	98	29 - 32	59	98	60	100	59	98	60	100
58	97	59	98	57	95	59	98	33 - 36	58	97	59	98	59	98	60	100
58	97	58	97	56	93	59	98	37 - 40	58	97	59	98	59	98	60	100
57	95	58	97	56	93	58	97	41 - 44	58	97	59	98	59	98	59	98
55	92	56	93	54	90	57	95	45 - 48	58	97	59	98	59	98	58	97
54	90	56	93	51	85	54	90	49 - 52	55	92	58	97	59	98	58	97
53	88	55	92	50	83	54	90	53 - 56	52	87	58	97	59	98	56	93
50	83	54	90	49	82	51	85	57 - 60	47	78	55	92	58	97	54	90
48	80	51	85	47	78	49	82	61 - 64	44	73	53	88	51	85	53	88
45	75	50	83	44	73	46	77	65 - 68	42	70	49	82	49	82	48	80
42	70	48	80	40	67	40	67	69 - 72	37	62	44	73	43	72	44	73
36	60	45	75	37	62	33	55	73 - 76	30	50	41	68	40	67	39	65
28	47	41	68	33	55	28	47	77 - 80	27	45	34	57	38	63	37	62
24	40	34	57	31	52	28	47	81 - 84	23	38	31	52	37	62	31	52
20	33	29	48	27	45	24	40	85 - End	20	33	24	40	29	48	26	43

S: number of the animals alive.

Figure 1 Survival Curves (%) - Males

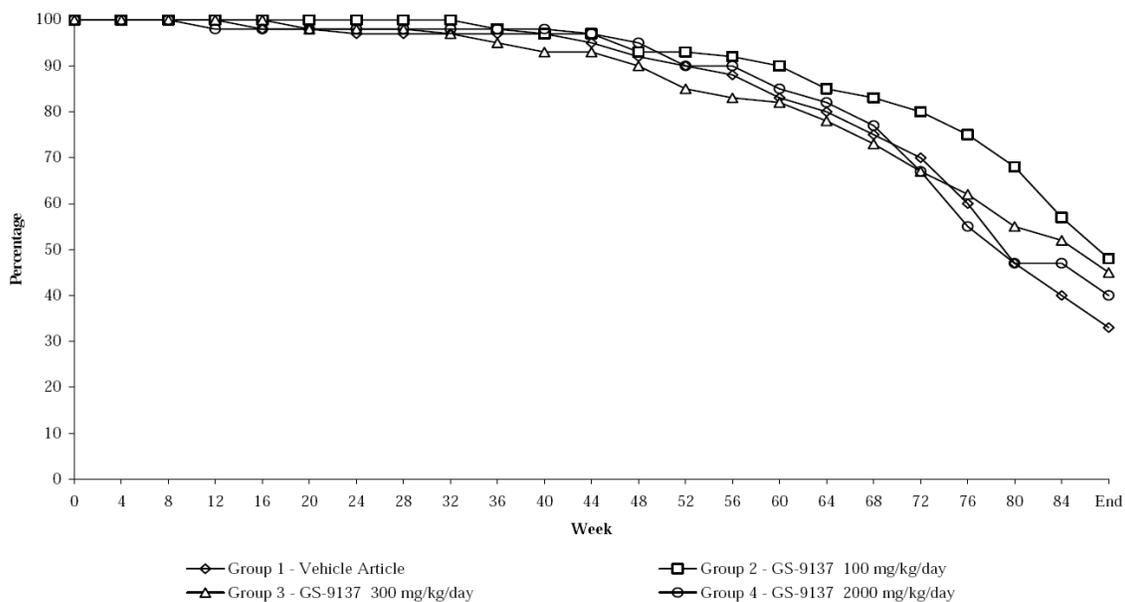
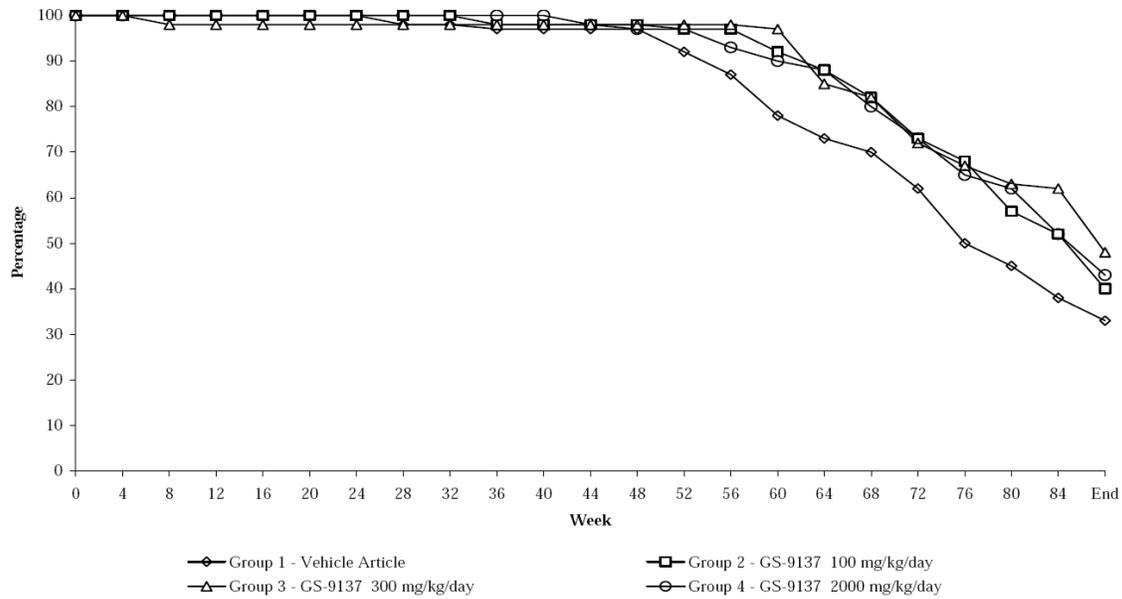


Figure 2 Survival Curves (%) - Females



2.1.2. Tumor data analysis

The statistical evaluation of tumor data was done using the Multtest procedure of the SAS/STAT module and was limited to non-metastasis tumors. The statistical evaluation was restricted to neoplastic lesions that were found in tissues for which it was decided, as per protocol, to systematically examine all animals histopathologically.

In addition to the analysis of tumor data from individual tissue sites, identical neoplastic lesions were combined across selected tissues. The combinations of selected tissue sites were the protocol-required skin with the miscellaneous skin and the subcutaneous tissue; the protocol-required skeletal muscle(s) with the miscellaneous skeletal muscle; the protocol-required bone(s) with the miscellaneous bone. The analysis of each combination of tissues was based on the number of animals from which at least one of the tissues in the combination was examined.

Systemic neoplasms tabulated under hemolymphoreticular tissue, such as lymphosarcomas (malignant lymphomas), histiocytic sarcomas, leukemias and mast cell tumors, were evaluated using the total number of examined animals in each group. Hemangiosarcomas were evaluated for each tissue site systematically examined as well as combined across all tissue sites (including those neoplasms found at sites which were not planned to be examined in all animals).

Clinically palpable neoplasms from the skin, subcutaneous tissue and other superficial glands (mammary, preputial, clitoral and Zymbal's) were analyzed in a "mortality independent" context according to Peto's onset rate method. More precisely, the time of first palpation was used as the estimate of the tumor onset time for each palpable lesion detected/identified during the in-life experimental period. Also, any lesion categorized as palpable but detected/identified only after the in-life period was included in the statistical analysis by setting the onset time as being the animal death time. For the purpose of the statistical analysis with Proc Multtest, each considered palpable tumor was processed as being fatal but with a "death" time equal to the onset time. If an analysis had to be performed on a combination of tumors that were all categorized as palpable, the earliest onset time among the combined tumors was used in the analysis. If an

analysis had to be performed on a combination of lesions including both palpable and non-palpable tumors, the animal death time was used for the analysis and the tumor combination was analyzed using the “mortality dependent” method described hereafter for non-palpable tumors.

The results show significance only for the male dataset corresponding to adenoma c-cell listed under thyroid, with p -value=0.0161. Based on Lin and Rahman (1998) recommendations, the overall dose-related increase in tumor incidence corresponding to the male thyroid adenoma c-cell is considered to be statistically significant only if this tumor is classified as rare. The statistical results of the pairwise comparisons revealed no significance for all datasets in both sexes (p -value > 0.05).

2.2. Reviewer's analyses

To verify sponsor's analyses and to perform the additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

2.2.1. Survival analysis

The survival distributions of animals in all four treatment groups (three treated groups and the control group) were estimated by the Kaplan-Meier product limit method. The dose response relationship and homogeneity of survival distributions were tested using the Cox test (Cox, 1972). The inter-current mortality data are given in Tables 1A1 and 1B in the appendix for males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A1 and 1B in the appendix for males and females, respectively. Results for the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A1 and 2B in the appendix for males and females, respectively.

Reviewer's findings: The test results showed no statistically significant dose-response relationship and statistically significant difference in mortality in either sex when compared with the control group. There were some differences between reviewer's and sponsor's survival rates and the differences may be caused by the different dates of starting the terminal killing.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships and pair-wise comparisons of the control group with each of the treated groups were performed using the Poly-k method described in the paper of Bailer and Portier (1988), and Bieler and Williams (1993). One critical point for Poly-k test is the choice of the appropriate value of k . For long term 104 week standard rat and mouse studies, a value of $k=3$ is suggested in the literature. For short term study of 26 weeks no such suggestion is available, in the mouse tumor data analysis we chose $k=3$ here. For the calculation of p -values the exact permutation method was used. The tumor rates and the p -values of the tested tumor types are listed in Tables 3A and 3B in the appendix for males and females, respectively.

As suggested by the reviewing pharmacologist Dr. Verma, this reviewer did the analysis of the combinations of all organ/tumors as the following:

- **Rat:** Hemangiosarcoma from all sites; C-cell adenoma and carcinoma from Thyroid gland; Follicular

- **Mouse:** Hemangioma, Hemangiosarcoma and combined hemangioma and hemangiosarcoma from all sites; Adenoma and carcinoma from liver; adenoma and carcinoma from lung; For female mice: leiomyoma and leioma from uterus.

Multiple testing adjustment: Adjustment for the multiple dose response relationship testing was done using the criteria developed by Lin and Rahman (1998). The criteria recommend the use of a significance level $\alpha=0.025$ for rare tumors and $\alpha=0.005$ for common tumors for a submission with two species, and a significance level $\alpha=0.05$ for rare tumors and $\alpha=0.01$ for common tumors for a submission with only one species study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the spontaneous tumor rate is less than 1%. The adjustment for multiple pair-wise comparisons was done using the criteria developed by Haseman (1983) that recommends the use of a significance level $\alpha=0.05$ for rare tumors and $\alpha=0.01$ for common tumors, in order to keep the false-positive rate at the nominal level of approximately 10%.

It should be noted that the recommended test levels by Lin and Rahman for the adjustment of multiple testing were originally based on the result of a simulation and an empirical study using the Peto method for dose response relationship analysis. However, some later simulation results by Rahman and Lin (2008) indicate that the criteria apply equally well to the analysis using the poly-3 test.

Reviewer’s findings: Following tumor types showed p-values less than or equal to 0.05 either tests for dose response relationship and/or pair-wise comparisons between control and each of individual treated groups.

Tumor Types with P-Values \leq 0.05 for Dose Response Relationship or Pair-wise Comparisons

Organ Name	Tumor Name	Cont N=60	Low N=60	Med N=60	High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Male	THYROID ADENOMA, C-cell	1	4	1	6	0.033	0.225	0.759	0.058
	ADENOMA+CARCINOMA C-cell	1	4	2	6	0.040	0.225	0.509	0.058

Based on the criteria of adjustment for multiple testing of trends by Lin and Rahman, the incidence of none of the above or any other tested tumor types in either sex was considered to have a statistically significant positive dose response relationship. Also based on the criteria of Haseman, none of the pair-wise comparisons of treated groups with the control was considered to be statistically significant in either sex for increased tumor incidence in the treated group.

3. Mouse Study

Male and female Crl:CD1 (ICR) mice were assigned to 7 groups (70/sex/group). The animals received either the vehicle for GS-9137 (0.5% methylcellulose [MC]), 200, 600 and 2000 mg/kg/day GS-9137 alone, 25 mg/kg/day ritonavir alone, the vehicles for GS-9137 and ritonavir (0.5% MC and 43:15:42 ethanol: water:

propylene glycol), or 2000/25 mg/kg/day GS-9137/ritonavir. GS-9137 and ritonavir were formulated separately and were given in sequential gavages to the 2000/25 mg/kg/day GS-9137/ritonavir animals. Satellite animals (6/sex/vehicle groups and 21/sex/toxicity groups) were used for toxicokinetic evaluation on Weeks 1 and 26. The following table contains the information about the study design:

Animals were randomized into the following groups:

Group Number/ Identification	Dose (mg/kg/day)	Animal Numbers			
		Main Study		Toxicokinetic Study ^c	
		Males	Females	Males	Females
1/ Control Article ^a	0	70	70	6	6
2/ Vehicle Articles ^b	0/0	70	70	6	6
3/ ritonavir	25	70	70	21	21
4/ GS-9137	200	70	70	21	21
5/ GS-9137	600	70	70	21	21
6/ GS-9137	2000	70	70	21	21
7/ GS-9137/ ritonavir	2000/25	70	70	21	21
8 Health Screen	-	10	10	-	-

^a The control article was 0.5% methylcellulose

^b The vehicle articles were 43:15:42 ethanol water:PG and 0.5% methylcellulose. They were formulated separately and dosed as 2 sequential gavages

^c The toxicokinetic population included 3 additional dosed animals per sex per group to be used as possible

3.1. Sponsor's analyses

3.1.1. Survival analysis

Survival data from the mouse study were analyzed by the sponsor using the same statistical methodologies that were used to analyze the survival data from the rat study. Since there are 7 groups in mouse study, there were two phases in the testing procedure. The first phase will consist of comparing the vehicle control (Group 2) and the 0.5% methylcellulose control (Group 1) together, and the second phase consisted of analysing two possible datasets. The first dataset included Groups 2, 4, 5, and 6, and the second dataset will include Groups 1, 4, 5, and 6. The tests involved in the first and the second phase were performed using the method of Tarone. Using the Multtest procedure of the SAS/STAT module, Tarone's test was implemented as a Peto two-sided test with all uncensored deaths coded as 2 and all censored deaths coded as 0. If the test performed in the first phase revealed no significant difference between Groups 1 and 2, then only the analysis of the first dataset (Groups 2, 4, 5, and 6) was undertaken. More precisely, the significance of a dose-related trend in mortality across Groups 2, 4, 5, and 6 was evaluated using Peto's two-sided test. Otherwise, in addition to the analysis of the first dataset, the analysis of the second dataset (Groups 1, 4, 5, and 6) was considered. That is, the significance of a dose-related trend in mortality across Groups 1, 4, 5, and 6 was also evaluated using Peto's two-sided test. The arithmetic dose level scores (0, 200, 600, and 2000) were used to perform these overall trend tests.

Table 1 Survival of Mice

Group 1 - Control Article
Group 2 - Vehicle Articles

Group 3 - ritonavir 25 mg/kg/day

Group 4 - GS-9137 200 mg/kg/day

Group 5 - GS-9137 600 mg/kg/day

Group 6 - GS-9137 2000 mg/kg/day

Group 7 - GS-9137/ ritonavir 2000/25 mg/kg/day

Sex Group	Males													
	1		2		3		4		5		6		7	
	S	%	S	%	S	%	S	%	S	%	S	%	S	%
Week														
1 - 4	70	100	70	100	70	100	70	100	70	100	70	100	70	100
5 - 8	70	100	70	100	70	100	70	100	70	100	70	100	70	100
9 - 12	70	100	70	100	70	100	70	100	70	100	70	100	70	100
13 - 16	70	100	70	100	70	100	70	100	70	100	70	100	70	100
17 - 20	70	100	70	100	70	100	70	100	70	100	70	100	68	97
21 - 24	69	99	68	97	69	99	70	100	70	100	70	100	67	96
25 - 28	69	99	68	97	68	97	70	100	70	100	68	97	64	91
29 - 32	68	97	65	93	68	97	70	100	70	100	68	97	64	91
33 - 36	68	97	65	93	65	93	69	99	70	100	66	94	63	90
37 - 40	67	96	64	91	62	89	69	99	64	91	65	93	62	89
41 - 44	65	93	64	91	62	89	67	96	62	89	64	91	58	83
45 - 48	64	91	64	91	62	89	67	96	61	87	64	91	57	81
49 - 52	63	90	62	89	57	81	66	94	60	86	61	87	48	69

% Percent of the original group size

S Number of Survivors

Table 1 Survival of Mice

Group 1 - Control Article
Group 2 - Vehicle Articles

Group 3 - ritonavir 25 mg/kg/day

Group 4 - GS-9137 200 mg/kg/day

Group 5 - GS-9137 600 mg/kg/day

Group 6 - GS-9137 2000 mg/kg/day

Group 7 - GS-9137/ ritonavir 2000/25 mg/kg/day

Sex Group	Males													
	1		2		3		4		5		6		7	
	S	%	S	%	S	%	S	%	S	%	S	%	S	%
Week														
53 - 56	63	90	58	83	56	80	66	94	59	84	60	86	47	67
57 - 60	62	89	57	81	56	80	66	94	57	81	57	81	44	63
61 - 64	61	87	54	77	53	76	65	93	54	77	55	79	43	61
65 - 68	60	86	51	73	48	69	64	91	52	74	51	73	40	57
69 - 72	59	84	49	70	45	64	62	89	50	71	44	63	39	56
73 - 76	57	81	47	67	40	57	59	84	46	66	40	57	39	56
77 - 80	54	77	44	63	37	53	56	80	41	59	39	56	38	54
81 - 84	49	70	44	63	34	49	53	76	37	53	36	51	36	51
85 - 88	48	69	40	57	34	49	51	73	37	53	34	49	33	47
89 - 92	48	69	39	56	34	49	46	66	35	50	33	47	30	43
93 - 96	45	64	36	51	33	47	41	59	34	49	31	44	26	37
97 - 100	42	60	35	50	29	41	39	56	33	47	28	40	23	33
101 - 104	37	53	32	46	26	37	38	54	31	44	26	37	21	30

% Percent of the original group size

S Number of Survivors

Table 1 Survival of Mice

Group 1 - Control Article

Group 2 - Vehicle Articles

Group 3 - ritonavir 25 mg/kg/day

Group 4 - GS-9137 200 mg/kg/day

Group 5 - GS-9137 600 mg/kg/day

Group 6 - GS-9137 2000 mg/kg/day

Group 7 - GS-9137/ ritonavir 2000/25 mg/kg/day

Sex Group	Females													
	1		2		3		4		5		6		7	
Week	S	%	S	%	S	%	S	%	S	%	S	%	S	%
1 - 4	70	100	70	100	70	100	70	100	70	100	70	100	70	100
5 - 8	70	100	70	100	70	100	70	100	70	100	70	100	69	99
9 - 12	70	100	70	100	70	100	70	100	70	100	70	100	69	99
13 - 16	70	100	70	100	69	99	70	100	70	100	70	100	67	96
17 - 20	70	100	69	99	69	99	70	100	70	100	70	100	66	94
21 - 24	70	100	69	99	68	97	70	100	70	100	69	99	63	90
25 - 28	70	100	68	97	68	97	70	100	70	100	66	94	63	90
29 - 32	70	100	66	94	67	96	69	99	70	100	66	94	61	87
33 - 36	68	97	66	94	65	93	68	97	69	99	65	93	56	80
37 - 40	68	97	64	91	64	91	68	97	69	99	65	93	54	77
41 - 44	66	94	64	91	64	91	68	97	69	99	64	91	54	77
45 - 48	66	94	60	86	61	87	67	96	68	97	64	91	54	77
49 - 52	66	94	53	76	61	87	67	96	68	97	64	91	52	74

% Percent of the original group size

S Number of Survivors

Table 1 Survival of Mice

Group 1 - Control Article

Group 2 - Vehicle Articles

Group 3 - ritonavir 25 mg/kg/day

Group 4 - GS-9137 200 mg/kg/day

Group 5 - GS-9137 600 mg/kg/day

Group 6 - GS-9137 2000 mg/kg/day

Group 7 - GS-9137/ ritonavir 2000/25 mg/kg/day

Sex Group	Females													
	1		2		3		4		5		6		7	
Week	S	%	S	%	S	%	S	%	S	%	S	%	S	%
53 - 56	64	91	51	73	60	86	66	94	68	97	64	91	52	74
57 - 60	63	90	49	70	60	86	66	94	66	94	64	91	51	73
61 - 64	61	87	48	69	59	84	65	93	65	93	63	90	51	73
65 - 68	58	83	45	64	56	80	64	91	65	93	61	87	48	69
69 - 72	56	80	43	61	55	79	62	89	60	86	61	87	47	67
73 - 76	52	74	40	57	54	77	59	84	56	80	60	86	45	64
77 - 80	46	66	36	51	51	73	59	84	51	73	55	79	43	61
81 - 84	44	63	33	47	48	69	53	76	45	64	49	70	42	60
85 - 88	41	59	32	46	44	63	44	63	43	61	45	64	39	56
89 - 92	36	51	29	41	42	60	40	57	37	53	35	50	37	53
93 - 96	35	50	25	36	35	50	39	56	34	49	32	46	32	46
97 - 100	34	49	23	33	28	40	36	51	30	43	29	41	25	36
101 - End†	33	47	20	29	23	33	32	46	27	39	26	37	22	31

% Percent of the original group size

S Number of Survivors

† End of study Week 103

Figure 1 Survival Curves (%) - Males

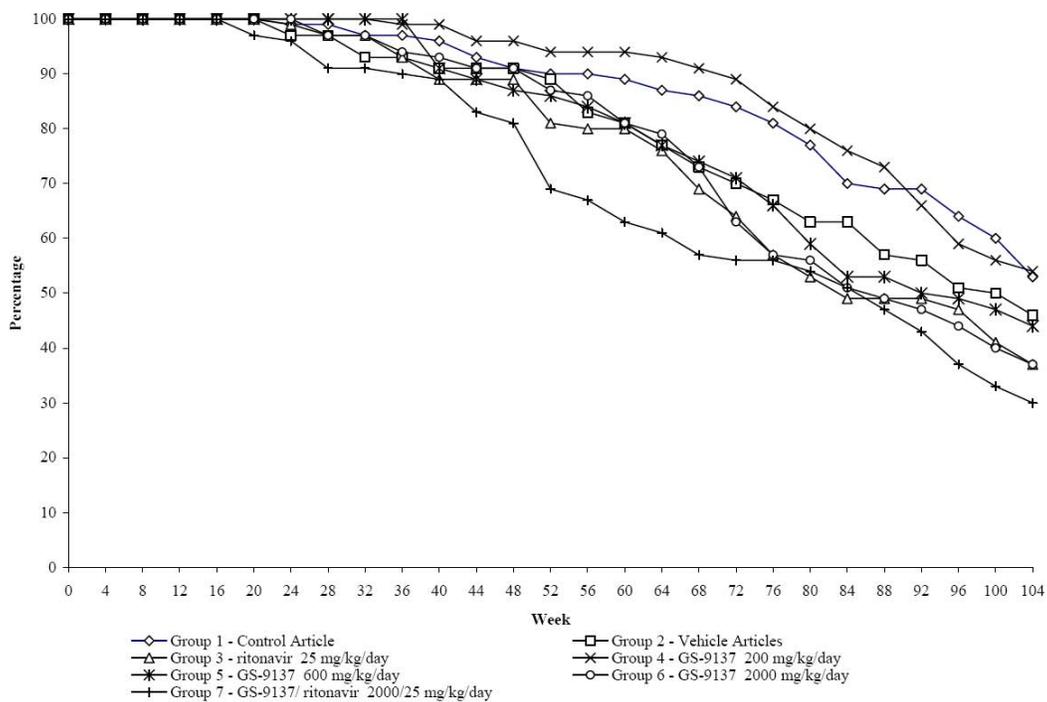
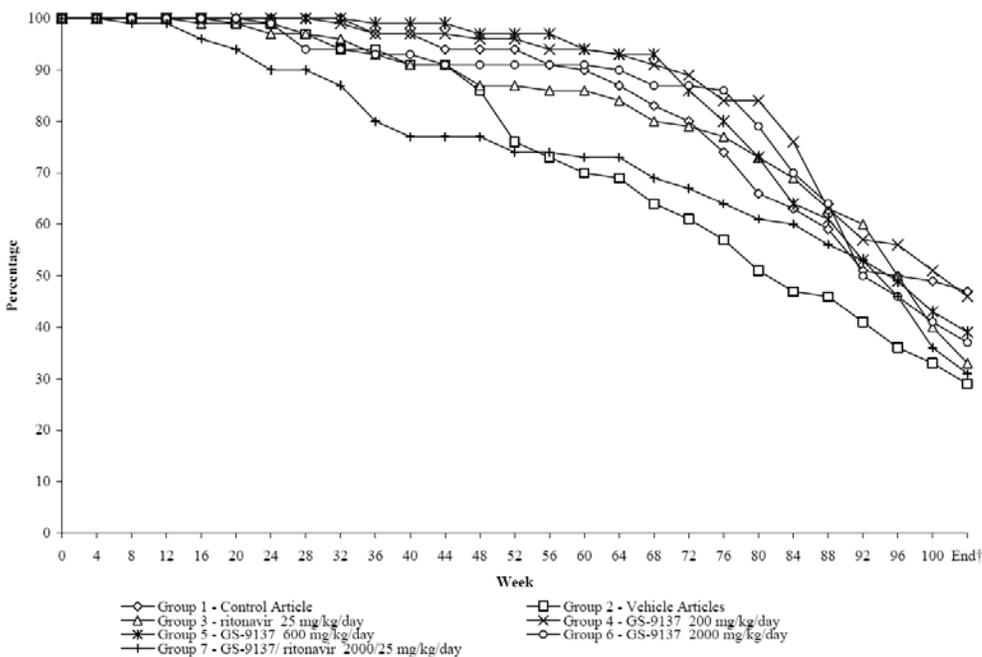


Figure 2 Survival Curves (%) - Females



Sponsor's findings: For the females, the log rank test was found to be not significant (p-value > 0.05). However, for the males, this test revealed significant group differences in mortality rates p=0.0039.

Consequently, the dose-related trend tests and the pairwise comparisons were done for the males only. The trend test results revealed a significant dose-related response only for Groups 2, 4, 5, 6 and 7. In addition to the overall dose-related trend tests, pairwise comparisons of mortality rates in males were performed to compare Group 3 and Group 7, and to compare Group 2 with each of Groups 1, 4, 5, 6 and 7. A significant difference in mortality rates was observed only between Groups 2 and 7, with $p=0.0191$.

3.1.2. Tumor data analysis

Tumor data from the mouse study were also analyzed by the sponsor using the same statistical methodologies that were used to analyze the tumor data from the rat study.

Sponsor's findings:

Both trend tests aimed to assess the significance of an overall linear dose-related increase in tumor occurrence rates across groups; more precisely across Groups 2, 4, 5, 6 and 7 for the first trend test and across Groups 2, 4, 5 and 6 for the second trend test. The one-sided overall trend test provides a $p\text{-value} \leq 0.05$ for the following cases.

Sex	Organ Name	Including Group 7	Tumor Name	Trend Test P-Value
Male	Liver	Yes	Adenoma: hepatocellular	0.0076
Male	Lung	Yes	Carcinoma: alveolar/bronchiolar	0.0137
Female	Uterus	Yes	Sarcoma: endometrial stromal	0.0188
Female	Uterus	No	Leiomyosarcoma	0.0147

Based on Lin and Rahman (1998) criteria, each of the above listed trend test results is considered to be statistically significant only if these tumors are classified as rare (since the p -values are less than 0.025 but greater than 0.005).

The following table presents the pairwise comparisons with the $p\text{-value} \leq 0.05$.

Sex	Organ Name	Tumor Name	Comparison	P-Value
Male	Lung	Carcinoma: alveolar/bronchiolar	3 vs 7	0.0388

Based on Lin and Rahman (1998) criteria, the increased incidence of Carcinoma: alveolar/bronchiolar in Lungs of Group 7 animals, relative to Group 3, is considered statistically significant only if this neoplastic lesion is classified as rare since the associated p -value is between 0.05 and 0.01.

3.2. Reviewer's analyses

To verify sponsor's analyses and to perform the additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Since there are seven groups with two testing

drugs: GS-9137 with or without Ritonavir, the reviewing pharmacologist suggested to do four sets of analyses: Goups 1, 4, 5, 6; Goups 2, 3; Groups 6, 7 and Group 2, 7 (refer to the study design table on page 9).

3.2.1. Survival analysis

The intercurrent mortality data are given in Tables 4A and 4B in the appendix for all seven groups of males and females, respectively. The Kaplan-Meier curves for death rate are given in Figures 2A and 2B in the appendix for all the seven groups of males and females, respectively. Results for the tests for dose response relationship and homogeneity of survivals, are given in Tables 5A1, 5A2, 5A3, 5A4, 5B1, 5B2, 5B3 and 5B4 in the appendix for three sets of groupings in males and females, respectively.

Reviewer’s findings: The tests showed a statistically significant dose response relationship and a statistically significant pair-wise difference between high dose group and the control group in survivals in males using groups 1, 4, 5 and 6. Also the tests showed a statistically significant pair-wise difference between high dose group and the control group in survivals in males using groups 2 and 7. There were few differences between reviewer’s and sponsor’s survival rates and the differences may be caused by the different dates of starting the terminal killing.

3.2.2. Tumor data analysis

The tumor rates and the p-values of the tumor types tested for dose response relationship and pair-wise comparisons of the control group and treated groups are given in Table 6A1, 6A2, 6A3, 6A4 and 6B1, 6B2, 6B3 6B4 in the appendix for three sets of groupings in males and females, respectively.

Reviewer’s findings: Following tumor types showed p-values less than or equal to 0.05 either tests for dose response relationship or pair-wise comparisons between control and each of individual treated groups.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pair-wise Comparisons

Sex	Organ Name	Tumor Name	Cont 0mg N=70	Low 200mg N=70	Med 600mg N=70	High 2000mg N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Male	TESTIS	Adenoma: interstitia	0	0	1	2	0.042	.	0.454	0.193
□										
Sex	Organ Name	Tumor Name	High1 2000mg N=70	High2 200mg/25mg N=70	P_Value					
Male	LIVER	ADENOMA+CARCINOMA	9	18	0.015					
		Carcinoma: hepatocel	0	4	0.047					
	LUNG	Carcinoma: alveolar/	3	10	0.024					

Based on the criteria of adjustment for multiple testing of trends by Lin and Rahman, the incidence of none of the above or any other tested tumor types in either sex was considered to have a statistically significant positive dose response relationship. Also based on the criteria of Haseman, none of the pair-wise comparisons of treated groups with the control was considered to be statistically significant in either sex for

4. Evaluation of validity of the designs of the rat and mouse studies

As has been noted, the tumor data analyses from rat and mouse studies showed no statistically significant dose-response relationship in any tested single tumor type. Before drawing any conclusion regarding the carcinogenic or non-carcinogenic potential of the drug in mice and rats, it is important to look into the following two issues, pointed out in the paper by Haseman (1984).

- (i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumors?
- (ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group. The following are some rules of thumb regarding these two issues as suggested by experts in this field:

Haseman (1985) did an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3F1 mice conducted at the National Toxicology Program (NTP). It was found that, on the average, approximately 50% of the animals in the high dose group survived the two-year study period. Also, in a personal communication with Dr. Karl Lin of Division of Biometrics-6, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals or 20 to 30 animals still alive in the high dose group, between weeks 80-90, would be considered as a sufficient number and adequate exposure. In addition Chu, Cueto and Ward (1981), suggested that "to be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted based on the toxicity endpoints approach that the high dose should be close to the maximum tolerated dose (MTD). In the paper of Chu, Cueto and Ward (1981), the following criteria are mentioned for dose adequacy. A high dose is considered as close to MTD if any of the criteria is met.

- (i) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."
- (ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."
- (iii) "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

We will now investigate the validity of the GS-9137 in rat and mouse carcinogenicity studies with or without ritonavir in the light of the above guidelines.

4.1. Rat Study

The following table contains the summary of survival data of rats in the high dose groups:

Percentage of survival in the high dose group at the end of Weeks 52 and 79

	Percentage of survival	
	End of 52 weeks	End of 79 weeks
Male	85.0%	60.0%
Female	98.3%	66.7%

Based on the survival criterion Haseman proposed, it could be concluded that there were enough rats in both genders that were exposed to the high dose for a sufficient amount of time.

The following table shows the percent differences in mean body weight gain of treated groups when compared with the concurrent control. The percent difference is defined as

$$\text{Percent difference} = \frac{(\text{Final BW} - \text{Baseline BW})_{\text{Treated}} - (\text{Final BW} - \text{Baseline BW})_{\text{Control}}}{(\text{Final BW} - \text{Baseline BW})_{\text{Control}}} \times 100$$

Percent Difference in Mean body Weight Gain from Control

Male			Female		
100 mg	300 mg	2000 mg	100 mg	300 mg	2000 mg
4.64	6.68	14.02	11.57	4.38	16.78

Therefore, relative to the control, there was a 14.02% in body weight gain in high dose group in male mice and a 16.78% in body weight gain in female mice.

The mortality rates at the end of the experiment were as follows:

Mortality Rates at the End of the Experiment

	Cont.	100 mg	300 mg	2000 mg
Male	61.7%	51.7%	58.3%	55.0%
Female	65.0%	60.0%	55.0%	51.7%

This shows that the mortality rate of in the high dose group in males is 6.7% lower than the control, while in female it is about 13.3% lower in high dose group compared to the control.

Based on the survival criterion Haseman proposed, it could be concluded that there were enough animals exposed to the high dose for a sufficient amount of time for the female and male experiments. It could also be concluded

that the high dose groups of the female and male experiments were not close to MTD based on mortality increase and loss in body weight gain criteria. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

4.2. Mouse Study

The following is the summary of survival data of mice in the high dose groups in males and females:

Percentage of survival in the high dose group (GS-9137 2000mg) at the end of Weeks 52 and 79

	Percentage of survival	
	End of 52 weeks	End of 79 weeks
Male	77.1%	55.7%
Female	91.3%	82.9%

Based on the survival criterion Haseman proposed, it could be concluded that there were enough mice in both males and females that were exposed to the high dose for a sufficient amount of time.

The following table shows the percent difference in mean body weight gain of treated groups when compared with the concurrent combined control, defined as

$$\text{Percent difference} = \frac{(\text{Final BW} - \text{Baseline BW})_{\text{Treated}} - (\text{Final BW} - \text{Baseline BW})_{\text{Control}}}{(\text{Final BW} - \text{Baseline BW})_{\text{Control}}} \times 100$$

Percent Difference in Mean body Weight Gain from Control

Male			Female		
200 mg	600 mg	2000 mg	200 mg	600 mg	2000 mg
-4.58	-8.18	1.96	-9.14	-14.32	-3.83

Therefore, relative to the control, there was a 1.96% in body weight gain in high dose group in male mice and a 3.83% loss in body weight gain in female mice.

The mortality rates at the end of the experiment were as follows:

Mortality Rates at the End of the Experiment

	Cont.	200 mg	600 mg	2000 mg
Male	47.1%	45.7%	55.7%	62.9%
Female	51.4%	51.4%	61.4%	62.3%

This shows that the mortality rate of in the high dose group in males is 14.8% higher than the control, while in

females it is about 10.9% higher in high dose group compared to the control.

Based on the survival criterion Haseman proposed, it could be concluded that there were enough animals exposed to the high dose for a sufficient amount of time for both female and male experiments. It could be concluded that the high doses of the female and male experiments were close to MTD based on mortality increase criterion. However, based on loss in body weight gain criterion, it could be concluded that the high doses of the females were close to MTD and that the high dose of the male experiments was not close to MTD. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

5. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. The purpose of rat study was to investigate the carcinogenic potential of GS-9137 following daily oral administration by gavage to Crl:CD(SD) rats for a minimum of 104 consecutive weeks. However, because the number of surviving animals in the control groups reached 20 earlier than expected, males were dosed for a minimum of 88 weeks and females were dosed for a minimum of 90 weeks. The purpose of mouse study was to investigate the carcinogenic potential of GS-9137 with or without Ritonavir following daily oral administration by gavage to Crl:CD1 (ICR) mice for a minimum of 104 consecutive weeks.

Rat Study: Two separate experiments were conducted, one in males and one in females. Male and female Crl:CD(SD) rats were assigned to 4 groups (60/sex/group) and received either the vehicle (0.5% methyl cellulose), or 100, 300, and 2000 mg/kg/day GS-9137 in vehicle at a dose volume of 10 mL/kg. The test results showed no statistically significant dose-response relationship and statistically significant difference in mortality in either sex when compared with the control group. Tests showed no statistically significant positive dose response relationship and the statistically significant difference in pair-wise comparisons in tumor incidence when compared to the control group in both females and males. Based on the survival criterion Haseman proposed, it could be concluded that there were enough animals exposed to the high dose for a sufficient amount of time for female and male experiments. It could also be concluded that the high dose groups of the female and male experiments were not close to MTD based on mortality increase and loss in body weight gain criteria. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

Mouse Study: Male and female Crl:CD1 (ICR) mice were assigned to 7 groups (70/sex/group). The animals received either the vehicle for GS-9137 (0.5% methylcellulose [MC]), 200, 600 and 2000 mg/kg/day GS-9137 alone, 25 mg/kg/day ritonavir alone, the vehicles for GS-9137 and ritonavir (0.5% MC and 43:15:42 ethanol: water: propylene glycol), or 2000/25 mg/kg/day GS-9137/ritonavir. GS-9137 and ritonavir were formulated separately and were given in sequential gavages to the 2000/25 mg/kg/day GS-9137/ritonavir animals. Satellite animals (6/sex/vehicle groups and 21/sex/toxicity groups) were used for toxicokinetic evaluation on Weeks 1 and 26. The tests showed a statistically significant dose response relationship and a statistically significant pair-wise difference between high dose group and the control group in survivals in males using groups 1, 4, 5 and 6. Also the tests showed a statistically significant pair-wise difference between high dose group and the control group in survivals in males using groups 2 and 7. Tests showed no statistically significant positive dose response relationship and the statistically significant difference in pair-wise comparisons in tumor incidence when compared to the control group in both females and males for all four sets of analysis (groups 1, 4, 5, 6; groups 2, 3; groups 6, 7 and groups 2, 7). Based on the survival criterion Haseman proposed, it could be concluded that there were enough animals exposed to the high dose for a sufficient amount of time for both female and male experiments. It could be concluded that the high doses of the female and male experiments were

close to MTD based on mortality increase criterion. However, based on loss in body weight gain criterion, it could be concluded that the high doses of the females were close to MTD and that high dose of the male experiments was not close to MTD. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

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6. Appendix

**Table 1A: Intercurrent Mortality Rate
Male Rats**

Week	CONTROL		LOW		MEDIUM		HIGH	
	NO.OF DEATH	PERCENT						
0-52	6	10.0%	4	6.7%	6	10.0%	9	15.0%
53-78	23	48.3%	13	28.3%	22	46.7%	15	40.0%
79-87	8	61.7%	14	51.7%	7	58.3%	9	55.0%
Term. Sac.	23	100.0%	29	100.0%	25	100.0%	27	100.0%

**Table 1B: Intercurrent Mortality Rate
Female Rats**

Week	CONTROL		LOW		MEDIUM		HIGH	
	NO.OF DEATH	PERCENT						
0-52	5	8.3%	2	3.3%	2	3.3%	1	1.7%
53-78	27	53.3%	19	35.0%	21	38.3%	19	33.3%
79-89	7	65.0%	15	60.0%	10	55.0%	11	51.7%
Term. Sac.	21	100.0%	24	100.0%	27	100.0%	29	100.0%

**Table 2A: Intercurrent Mortality Comparison
Male Rats**

Test	P-Value (across four groups)	P-Value (control vs low)	P-Value (control vs medium)	P-Value (control vs high)
Dose Response	0.7458	0.2624	0.6299	0.8419
Homogeneity	0.3370	0.0605	0.3136	0.5347

**Table 2B: Intercurrent Mortality Comparison
Female Rats**

Test	P-Value (across four groups)	P-Value (control vs low)	P-Value (control vs medium)	P-Value (control vs high)
Dose Response	0.5345	0.3606	0.1538	0.2530
Homogeneity	0.1904	0.1968	0.0436	0.1325

**Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Rats**

Organ Name	Tumor Name	0 mg	100 mg	300 mg	2000 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=60	Low N=60	Med N=60	High N=60	Dos Resp	C vs. L	C vs. M	C vs. H
ABDOMEN	Pheochromocytoma	0	1	0	0	0.761	0.533	.	.
ADRENAL	Adenoma: cortical	0	2	1	2	0.191	0.282	0.506	0.253
	Benign pheochromocyt	4	4	7	1	0.945	0.703	0.260	0.972
	Carcinoma: cortical	0	0	0	1	0.244	.	.	0.506
	Ganglioneuroma	0	0	1	0	0.489	.	0.506	.
	Malignant pheochromo	0	0	2	0	0.489	.	0.253	.
ALL_SITES	Hemangiosarcoma	0	2	0	1	0.432	0.282	.	0.506
BRAIN	Benign granular cell	0	1	1	0	0.623	0.533	0.506	.
	Malignant astrocytom	1	0	0	1	0.430	1.000	1.000	0.759
CAVITY CRANIAL	Malignant schwannoma	0	1	0	0	0.761	0.533	.	.
CAVITY ORAL	Carcinoma: squamous	0	2	0	0	0.813	0.282	.	.
EPIDIDYMIS	Hemangioma	0	0	1	0	0.489	.	0.506	.
	Mesothelioma(M)	0	1	0	0	0.761	0.533	.	.
EYE	Benign schwannoma	0	0	1	0	0.489	.	0.506	.
FAT	Lipoma	1	0	0	0	1.000	1.000	1.000	1.000
HEAD	Sarcoma (not otherwi	1	0	0	0	1.000	1.000	1.000	1.000
HEART	Benign schwannoma	1	0	0	0	1.000	1.000	1.000	1.000
HEMOLYM. TISSUE	Histiocytic sarcoma	1	1	0	1	0.529	0.785	1.000	0.759
	Leukemia: granulocyt	0	0	0	1	0.244	.	.	0.506
	Leukemia: mononuclea	1	0	0	0	1.000	1.000	1.000	1.000
	Malignant lymphoma	0	1	1	0	0.624	0.533	0.512	.
KIDNEY	Lipoma	0	1	0	0	0.761	0.533	.	.
	Renal mesenchymal tu	0	0	0	1	0.244	.	.	0.506
L.NODE MESENTER	Hemangioma	0	2	0	0	0.813	0.282	.	.
LIVER	Adenoma: hepatocellu	4	0	1	1	0.794	1.000	0.972	0.972
	Carcinoma: hepatocel	2	7	0	1	0.932	0.121	1.000	0.884
LUNG	Hemangiosarcoma	0	0	0	1	0.244	.	.	0.506
MAMMARY GLAND	Adenocarcinoma	0	1	0	1	0.313	0.533	.	0.506

**Table 3A (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Rats**

Organ Name	Tumor Name	0 mg	100 mg	200 mg	2000 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=60	Low N=60	Med N=60	High N=60	Dos Resp	C vs. L	C vs. M	C vs. H
MAMMARY GLAND	Fibroadenoma	2	1	1	4	0.083	0.902	0.884	0.349
	Fibroma	0	1	0	0	0.761	0.533	.	.
PANCREAS	Adenoma: acinar cell	1	0	0	0	1.000	1.000	1.000	1.000
	Adenoma: islet cell	7	3	2	3	0.749	0.970	0.985	0.956
	Carcinoma: islet cel	2	4	2	3	0.424	0.393	0.692	0.500
PITUITARY	Adenoma: pars distal	35	40	35	38	0.243	0.401	0.466	0.273
	Adenoma: pars interm	0	2	0	1	0.432	0.282	.	0.506
	Carcinoma: pars dist	2	1	0	0	0.986	0.898	1.000	1.000
PROSTATE	Adenocarcinoma	1	0	0	0	1.000	1.000	1.000	1.000
SKIN MISCELLANE	Adenoma: basal cell	0	1	0	0	0.761	0.533	.	.
	Adenoma: sebaceous	1	0	0	1	0.430	1.000	1.000	0.759
	Carcinoma: basal cel	0	2	0	0	0.813	0.282	.	.
	Hemangioma	1	0	0	0	1.000	1.000	1.000	1.000
	Hemangiosarcoma	0	1	0	0	0.761	0.533	.	.
	Keratoacanthoma	4	2	4	0	0.970	0.930	0.657	1.000
	Malignant melanoma	0	0	0	1	0.244	.	.	0.506
	Papilloma: squamous	0	2	1	1	0.409	0.282	0.506	0.506
SUBCUTANEOUS TI	Fibroma	0	0	0	1	0.244	.	.	0.506
	Fibrosarcoma	1	2	0	0	0.941	0.551	1.000	1.000
	Hemangiosarcoma	0	1	0	0	0.761	0.533	.	.
	Lipoma	0	1	1	2	0.115	0.533	0.512	0.253
	Malignant schwannoma	0	0	1	2	0.059	.	0.506	0.259
TAIL	Hemangioma	0	1	0	0	0.761	0.533	.	.
TESTIS	Adenoma: interstitia	2	1	1	0	0.926	0.902	0.884	1.000
THYROID	Adenoma: C-cell	1	4	1	6	0.033	0.225	0.759	0.058
	Adenoma: follicular	2	3	2	0	0.945	0.564	0.701	1.000
	CCELL_ADENOMA+CARCIN	1	4	2	6	0.040	0.225	0.509	0.058
	Carcinoma: C-cell	0	0	1	0	0.489	.	0.506	.
	Carcinoma: follicula	1	0	1	1	0.378	1.000	0.759	0.759
	FOLLICULAR_ADENOMA+C	3	3	3	1	0.856	0.723	0.673	0.945
URINARY BLADDER	Papilloma: transitio	0	1	0	0	0.761	0.533	.	.

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Rats

Organ Name	Tumor Name	0 mg	100 mg	300 mg	2000 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=60	Low N=60	Med N=60	High N=60	Dos Resp	C vs. L	C vs. M	C vs. H
ABDOMEN	Lipoma	0	0	1	0	0.523	.	0.547	.
ADRENAL	Adenoma: cortical	0	2	0	0	0.836	0.284	.	.
	Benign pheochromocyt	0	0	0	1	0.257	.	.	0.536
	Malignant pheochromo	0	1	0	1	0.334	0.536	.	0.536
		0	0	0	2	0.065	.	.	0.284
BRAIN	Malignant mixed glio	0	0	1	0	0.520	.	0.541	.
CAVITY CRANIAL	Carcinoma: squamous	0	1	0	0	0.777	0.536	.	.
FAT	Lipoma	0	0	0	1	0.257	.	.	0.536
HEAD	Sarcoma (not otherwi	0	1	0	0	0.777	0.536	.	.
HEART	Malignant schwannoma	0	0	0	1	0.261	.	.	0.541
HEMOLYM. TISSUE	Histiocytic sarcoma	1	0	0	0	1.000	1.000	1.000	1.000
	Malignant lymphoma	0	0	1	0	0.523	.	0.547	.
KIDNEY	Adenoma: tubular cel	0	1	0	1	0.333	0.541	.	0.536
	Carcinoma: squamous	0	0	0	1	0.257	.	.	0.536
	Carcinoma: tubular c	0	1	0	0	0.777	0.536	.	.
L.NODE MESENTER	Hemangiosarcoma	1	0	0	0	1.000	1.000	1.000	1.000
LIVER	Adenoma: hepatocellu	1	2	2	3	0.212	0.554	0.570	0.364
	Carcinoma: hepatocel	0	0	1	0	0.523	.	0.547	.
LUNG	Carcinoma: squamous	0	0	1	0	0.520	.	0.541	.
MAMMARY GLAND	Adenocarcinoma	10	12	11	13	0.354	0.573	0.661	0.483
MAMMARY GLAND	Adenoma	5	7	2	2	0.947	0.482	0.964	0.964
	Fibroadenoma	27	26	23	27	0.511	0.890	0.946	0.824
PANCREAS	Adenoma: islet cell	1	2	1	4	0.092	0.554	0.792	0.236
	Carcinoma: islet cel	3	3	0	4	0.244	0.728	1.000	0.593
PITUITARY	Adenoma: pars distal	51	50	52	54	0.314	0.867	0.715	0.595
	Carcinoma: pars dist	1	3	2	2	0.496	0.373	0.570	0.562
RECTUM	Benign granular cell	0	1	0	0	0.777	0.536	.	.

**Table 3B (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Rats**

Organ Name	Tumor Name	0 mg	100 mg	300 mg	2000 mg	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		Cont N=60	Low N=60	Med N=60	High N=60				
SKIN MISCELLANE	Carcinoma: squamous	0	1	0	0	0.777	0.536	.	.
	Keratoacanthoma	0	0	1	0	0.520	.	0.541	.
STOMACH	Leiomyosarcoma	1	0	0	0	1.000	1.000	1.000	1.000
SUBCUTANEOUS TI	Fibroma	0	0	0	1	0.257	.	.	0.536
	Lipoma	0	0	0	1	0.257	.	.	0.536
TAIL	Fibroma	0	0	1	0	0.520	.	0.541	.
THYROID	Adenoma: C-cell	3	6	4	4	0.598	0.319	0.605	0.593
	Adenoma: follicular	0	0	0	2	0.065	.	.	0.284
	Carcinoma: follicula	1	0	0	0	1.000	1.000	1.000	1.000
	FOLLICULAR_ADENOMA+C	1	0	0	2	0.163	1.000	1.000	0.554
URINARY BLADDER	Papilloma: transitio	0	0	1	0	0.523	.	0.547	.
UTERUS	Benign granular cell	1	1	1	0	0.853	0.787	0.792	1.000
	Leiomyoma	0	0	0	1	0.257	.	.	0.536
	Malignant schwannoma	3	0	0	0	1.000	1.000	1.000	1.000
	Polyp: endometrial s	5	0	3	1	0.887	1.000	0.913	0.991
UTERUS	Sarcoma: endometrial	1	0	0	0	1.000	1.000	1.000	1.000
VAGINA	Benign granular cell	0	0	1	0	0.520	.	0.541	.
	Polyp	1	0	1	1	0.414	1.000	0.792	0.787

**Table 4A: Intercurrent Mortality Rate
Male Mice (Seven Groups)**

Week	CONTROL(GS-9137)		Control(ritonavir)		Ritonavir 25mg		GS-9137 200mg	
	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT
0-52	7	10.0%	8	11.4%	13	18.6%	4	5.7%
53-78	7	20.0%	16	34.3%	18	44.3%	9	18.6%
79-92	8	31.4%	7	44.3%	5	51.4%	11	34.3%
93-104	11	47.1%	7	54.3%	8	62.9%	8	45.7%
Term. Sac.	37	100.0%	32	100.0%	26	100.0%	38	100.0%

Week	GS-9137 600mg		GS-9137 2000mg		GS-9137/Ritonavir 2000/25 mg	
	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT
0-52	10	14.3%	9	12.9%	22	31.4%
53-78	18	40.0%	22	44.3%	9	44.3%
79-92	7	50.0%	6	57.9%	9	57.1%
93-104	4	55.7%	7	62.9%	9	70.0%
Term. Sac.	31	100.0%	26	100.0%	21	100.0%

**Table 4B: Intercurrent Mortality Rate
Female Mice (Seven groups)**

Week	CONTROL(GS-9137)		Control(ritonavir)		Ritonavir 25mg		GS-9137 200mg	
	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT
0-52	4	5.7%	17	24.3%	9	12.3%	3	4.3%
53-78	15	27.1%	17	48.6%	10	27.1%	8	15.7%
79-92	15	48.6%	7	58.6%	9	40.0%	19	42.9%
93-102	2	51.4%	8	70.0%	17	64.3%	6	51.4%
Term. Sac.	34	100.0%	21	100.0%	25	100.0%	34	100.0%

Week	GS-9137 600mg		GS-9137 2000mg		GS-9137/Ritonavir 2000/25 mg	
	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT
0-52	2	2.3%	6	8.7%	18	25.7%
53-78	15	24.3%	6	17.1%	8	37.1%
79-92	16	47.1%	23	50.0%	7	47.1%
93-102	10	61.4%	9	62.3%	14	67.1%
Term. Sac.	27	100.0%	26	100.0%	23	100.0%

**Table 5A1: Intercurrent Mortality Comparison
Male Mice (Groups 1, 4, 5, 6)**

Test	P-Value (across four groups)	P-Value (GS-9137 control vs GS-9137 200mg)	P-Value (GS-9137 control vs GS-9137 600 mg)	P-Value (GS-9137 control vs GS-9137 2000mg)
Dose Response	0.0033	0.9471	0.1429	0.0108
Homogeneity	0.0380	0.9699	0.1258	0.0234

**Table 5A2: Intercurrent Mortality Comparison
Male Mice (Groups 2, 3)**

Test	P-Value (Control 0/0 vs ritonavir 25 mg)
Dose Response	0.3322
Homogeneity	0.2376

**Table 5A3: Intercurrent Mortality Comparison
Male Mice (Groups 6, 7)**

Test	P-Value (GS-9137 2000 mg vs GS-9137 2000mg / ritonavir 25mg)
Dose Response	0.1841
Homogeneity	0.2526

**Table 5A4: Intercurrent Mortality Comparison
Male Mice (Groups 2, 7)**

Test	P-Value (Control 0/0 vs GS-9137 2000mg / ritonavir 25mg)
Dose Response	0.0095
Homogeneity	0.0244

**Table 5B1: Intercurrent Mortality Comparison
Female Mice (Groups 1, 4, 5, 6)**

Test	P-Value (across four groups)	P-Value (GS-9137 control vs GS-9137 200mg)	P-Value (GS-9137 control vs GS-9137 600 mg)	P-Value (GS-9137 control vs GS-9137 2000mg)
Dose Response	0.4439	0.6887	0.6938	0.6180
Homogeneity	0.8228	0.5875	0.8624	0.7930

**Table 5B2: Intercurrent Mortality Comparison
Female Mice (Groups 2, 3)**

Test	P-Value (ritonavir control vs ritonavir 25 mg)
Dose Response	0.2468
Homogeneity	0.2434

**Table 5B3: Intercurrent Mortality Comparison
Female Mice (Groups 6, 7)**

Test	P-Value (GS-9137 2000 mg vs GS-9137 2000mg / ritonavir 25mg)
Dose Response	0.3312
Homogeneity	0.2578

**Table 5B4: Intercurrent Mortality Comparison
Female Mice (Groups 2, 7)**

Test	P-Value (Control 0/0 vs GS-9137 2000mg / ritonavir 25mg)
Dose Response	0.5857
Homogeneity	0.7909

Table 6A1: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Mice (Groups 1, 4, 5, 6)

Organ Name	Tumor Name	0 mg	200 mg	600 mg	2000 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=70	Low N=70	Med N=70	High N=70	Dos Resp	C vs. L	C vs. M	C vs. H
ADRENAL	Adenoma: cortical	2	0	1	0	0.853	1.000	0.841	1.000
	Carcinoma: cortical	0	1	0	0	0.725	0.505	.	.
ALL_SITES	Hemangioma	0	1	2	1	0.255	0.505	0.203	0.442
	Hemangiosarcoma	5	6	4	1	0.946	0.513	0.657	0.972
	Hemangiosarcoma+Hema	5	7	6	2	0.868	0.394	0.372	0.894
EPIDIDYMIS	Fibrosarcoma	0	0	0	1	0.218	.	.	0.442
	Leiomyosarcoma	0	0	1	0	0.446	.	0.454	.
FAT	Hemangioma	0	1	0	0	0.725	0.505	.	.
HARDERIAN GLAND	Adenocarcinoma	1	0	0	0	1.000	1.000	1.000	1.000
	Adenoma	9	9	11	5	0.767	0.635	0.254	0.837
HEAD	Carcinoma (not other	0	0	1	0	0.449	.	0.459	.
HEMOLYM. TISSUE	Histiocytic sarcoma	3	0	0	1	0.644	1.000	1.000	0.908
	Malignant lymphoma	6	2	6	2	0.762	0.968	0.489	0.937
	Mast cell tumor	0	0	1	0	0.446	.	0.454	.
JEJUNUM	Adenocarcinoma	0	1	0	0	0.725	0.505	.	.
KIDNEY	Adenoma: tubular cel	1	0	0	0	1.000	1.000	1.000	1.000
	Carcinoma: tubular c	1	1	0	0	0.926	0.757	1.000	1.000
	Hemangioma	0	0	1	0	0.446	.	0.454	.
LIVER	ADENOMA+CARCINOMA	16	10	16	9	0.739	0.943	0.425	0.899
	Adenoma: hepatocellu	13	7	11	9	0.459	0.959	0.599	0.748
	Carcinoma: hepatocel	4	3	6	0	0.948	0.789	0.271	1.000
LIVER	Hemangioma	0	0	0	1	0.218	.	.	0.442
	Hemangiosarcoma	5	3	2	1	0.909	0.871	0.905	0.972
LUNG	ADENOMA+CARCINOMA	19	24	11	11	0.931	0.290	0.917	0.893
	Adenoma: alveolar/br	9	17	7	9	0.564	0.071	0.659	0.386
	Carcinoma: alveolar/	11	8	4	3	0.970	0.854	0.972	0.987
LYMPH NODE	Hemangioma	0	0	1	0	0.446	.	0.454	.
MUSCLE SKELETAL	Rhabdomyosarcoma	0	0	1	0	0.449	.	0.459	.
PANCREAS	Adenoma: islet cell	0	1	0	0	0.725	0.505	.	.

Table 6A1 (Continue): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Mice (Groups 1, 4, 5, 6)

Organ Name	Tumor Name	0 mg	200 mg	600 mg	2000 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=70	Low N=70	Med N=70	High N=70	Dos Resp	C vs. L	C vs. M	C vs. H
PITUITARY	Adenoma: pars distal	0	1	0	0	0.725	0.505	.	.
	Adenoma: pars interm	0	0	0	1	0.218	.	.	0.442
SALIV.GL. MANDI	Fibrosarcoma	0	0	1	0	0.446	.	0.454	.
SKIN MISCELLANE	Adenoma: basosquamou	1	0	0	0	1.000	1.000	1.000	1.000
	Carcinoma: basosquam	0	1	0	0	0.725	0.505	.	.
	Carcinoma: squamous	1	0	0	0	1.000	1.000	1.000	1.000
SPLEEN	Hemangiosarcoma	0	3	1	0	0.772	0.125	0.454	.
STOMACH	Adenocarcinoma	0	0	1	0	0.446	.	0.454	.
	Carcinoma: squamous	0	1	0	0	0.725	0.505	.	.
	Hemangiosarcoma	0	0	0	1	0.218	.	.	0.442
SUBCUTANEOUS TI	Benign fibrous histi	0	1	0	0	0.725	0.505	.	.
	Fibrosarcoma	1	0	0	1	0.389	1.000	1.000	0.691
SUBCUTANEOUS TI	Hemangiosarcoma	0	0	1	0	0.449	.	0.459	.
	Lipoma	0	0	1	0	0.446	.	0.454	.
TESTIS	Adenoma: interstitia	0	0	1	2	0.042	.	0.454	0.193
	Adenoma: rete testis	1	0	0	0	1.000	1.000	1.000	1.000
	Carcinoma: interstit	0	0	1	1	0.146	.	0.454	0.442
TONGUE	Carcinoma: squamous	0	1	0	0	0.725	0.505	.	.
URINARY BLADDER	Carcinoma: transitio	0	1	0	0	0.725	0.505	.	.

**Table 6A2: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Mice (Groups 2, 3)**

Organ Name	Tumor Name	0/0 mg	25 mg	P_Value Dos Resp
		Cont N=70	Low N=70	
ABDOMEN	Fibrosarcoma	0	1	0.471
ADRENAL	Adenoma: cortical	0	1	0.471
	Benign pheochromocyt	1	1	0.723
ALL_SITES	Hemangioma	8	0	1.000
	Hemangiosarcoma	4	1	0.963
	Hemangiosarcoma+Hema	11	1	1.000
BRAIN	Malignant meningioma	1	0	1.000
FAT	Hemangioma	1	0	1.000
HARDERIAN GLAND	Adenocarcinoma	1	0	1.000
	Adenoma	9	7	0.735
HEMOLYM. TISSUE	Histiocytic sarcoma	3	1	0.924
	Malignant lymphoma	1	0	1.000
JEJUNUM	Adenocarcinoma	1	1	0.723
KIDNEY	Hemangioma	1	0	1.000
L.NODE MESENTER	Hemangioma	1	0	1.000
LIVER	ADENOMA+CARCINOMA	14	15	0.360
	Adenoma: hepatocellu	11	11	0.479
	Carcinoma: hepatocel	3	6	0.188
	Hemangioma	2	0	1.000
	Hemangiosarcoma	2	1	0.857
LUNG	ADENOMA+CARCINOMA	16	13	0.731
	Adenoma: alveolar/br	10	9	0.596
	Carcinoma: alveolar/	6	4	0.804
PITUITARY	Adenoma: pars distal	1	0	1.000
PREPUTIAL GLAND	Hemangioma	1	0	1.000
SKIN MISCELLANE	Hemangioma	1	0	1.000
SPLEEN	Hemangioma	1	0	1.000
	Hemangiosarcoma	1	0	1.000

Table 6A2 (Continue): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Mice (Groups 2, 3)

Organ Name	Tumor Name	0/0 mg	25 mg	P_Value
		Cont N=70	High N=70	
SUBCUTANEOUS TI	Benign fibrous histi	1	0	1.000
	Hemangiosarcoma	1	0	1.000
TESTIS	Adenoma: interstitia	1	1	0.723
THORAX	Sarcoma (not otherwi	1	0	1.000
URINARY BLADDER	Leiomyoma	1	0	1.000

Table 6A3: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Mice (Groups 6, 7)

Organ Name	Tumor Name	2000 mg 2000 /25 mg		P_Value
		High1 N=70	High2 N=70	
ADRENAL	Benign pheochromocyt	0	1	0.468
ALL_SITES	Hemangioma	1	0	1.000
	Hemangiosarcoma	1	3	0.271
	Hemangiosarcoma+Hema	2	3	0.452
EPIDIDYMIS	Fibrosarcoma	1	0	1.000
HARDERIAN GLAND	Adenoma	5	3	0.823
HEMOLYM. TISSUE	Histiocytic sarcoma	1	1	0.721
	Malignant lymphoma	2	1	0.850
KIDNEY	Adenoma: tubular cel	0	1	0.468
LIVER	ADENOMA+CARCINOMA	9	18	0.015
	Adenoma: hepatocellu	9	14	0.093
	Carcinoma: hepatocel	0	4	0.047
	Hemangioma	1	0	1.000
	Hemangiosarcoma	1	2	0.462
LUNG	ADENOMA+CARCINOMA	11	19	0.056
	Adenoma: alveolar/br	9	9	0.559
	Carcinoma: alveolar/	3	10	0.024
MUSCLE SKELETAL	Rhabdomyosarcoma	0	1	0.475
PITUITARY	Adenoma: pars interm	1	0	1.000
	Carcinoma: pars dist	0	1	0.468
SPLEEN	Hemangiosarcoma	0	1	0.468
STOMACH	Hemangiosarcoma	1	0	1.000
SUBCUTANEOUS TI	Fibrosarcoma	1	0	1.000
TESTIS	Adenoma: interstitia	2	0	1.000
	Adenoma: rete testis	0	1	0.468
	Carcinoma: interstit	1	0	1.000
THORAX	Sarcoma (not otherwi	0	1	0.468

**Table 6A4: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Mice (Groups 2, 7)**

Organ Name	Tumor Name	0/0 mg	2000 /25 mg	P_Value
		Cont N=70	High2 N=70 Dos Resp	
ADRENAL	Benign pheochromocyt	1	1	0.696
ALL_SITES	Hemangioma	8	0	1.000
	Hemangiosarcoma	4	3	0.686
	Hemangiosarcoma+Hema	11	3	0.988
BRAIN	Malignant meningioma	1	0	1.000
FAT	Hemangioma	1	0	1.000
HARDERIAN GLAND	Adenocarcinoma	1	0	1.000
	Adenoma	9	3	0.963
HEMOLYM. TISSUE	Histiocytic sarcoma	3	1	0.908
	Malignant lymphoma	1	1	0.696
JEJUNUM	Adenocarcinoma	1	0	1.000
KIDNEY	Adenoma: tubular cel	0	1	0.446
	Hemangioma	1	0	1.000
L.NODE MESENTER	Hemangioma	1	0	1.000
LIVER	ADENOMA+CARCINOMA	14	18	0.094
	Adenoma: hepatocellu	11	14	0.137
	Carcinoma: hepatocel	3	4	0.393
	Hemangioma	2	0	1.000
	Hemangiosarcoma	2	2	0.608
LUNG	ADENOMA+CARCINOMA	16	19	0.178
	Adenoma: alveolar/br	10	9	0.526
	Carcinoma: alveolar/	6	10	0.117
MUSCLE SKELETAL	Rhabdomyosarcoma	0	1	0.452
PITUITARY	Adenoma: pars distal	1	0	1.000
	Carcinoma: pars dist	0	1	0.446
PREPUTIAL GLAND	Hemangioma	1	0	1.000
SKIN MISCELLANE	Hemangioma	1	0	1.000
SPLEEN	Hemangioma	1	0	1.000
	Hemangiosarcoma	1	1	0.696

**Table 6A4 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Mice (Groups 2, 7)**

Organ Name	Tumor Name	0/0 mg	2000 /25 mg	P_Value
		Cont N=70	High2 N=70	
SUBCUTANEOUS TI	Benign fibrous histi	1	0	1.000
	Hemangiosarcoma	1	0	1.000
TESTIS	Adenoma: interstitia	1	0	1.000
	Adenoma: rete testis	0	1	0.446
THORAX	Sarcoma (not otherwi	1	1	0.696
URINARY BLADDER	Leiomyoma	1	0	1.000

**Table 6B1: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Mice (Groups 1, 4, 5, 6)**

Organ Name	Tumor Name	0 mg	200 mg	600 mg	2000 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=70	Low N=70	Med N=70	High N=70	Dos Resp	C vs. L	C vs. M	C vs. H
ABDOMEN	Liposarcoma	0	1	0	0	0.760	0.525	.	.
ADRENAL	Adenoma: cortical	0	0	0	2	0.059	.	.	0.253
ALL_SITES	Hemangioma	1	0	0	2	0.153	1.000	1.000	0.516
	Hemangiosarcoma	2	3	3	4	0.230	0.547	0.520	0.359
	Hemangiosarcoma+Hema	3	3	3	6	0.107	0.707	0.681	0.275
FAT	Hemangioma	0	0	0	1	0.245	.	.	0.505
HARDERIAN GLAND	Adenoma	4	5	2	2	0.862	0.575	0.907	0.907
HEMOLYM. TISSUE	Histiocytic sarcoma	9	6	4	1	0.997	0.884	0.964	0.999
	Leukemia (not otherw	1	0	0	0	1.000	1.000	1.000	1.000
	Malignant lymphoma	13	17	14	12	0.679	0.384	0.523	0.656
KIDNEY	Hemangiosarcoma	0	0	1	0	0.495	.	0.510	.
L.NODE MESENTER	Hemangioma	0	0	0	1	0.249	.	.	0.510
LIVER	ADENOMA+CARCINOMA	2	1	0	1	0.675	0.896	1.000	0.886
	Adenoma: hepatocellu	2	1	0	1	0.675	0.896	1.000	0.886
	Carcinoma: hepatocel	0	0	0	1	0.249	.	.	0.510
	Cholangiocarcinoma	1	0	0	0	1.000	1.000	1.000	1.000
	Hemangioma	1	0	0	0	1.000	1.000	1.000	1.000
	Hemangiosarcoma	0	2	3	3	0.125	0.273	0.129	0.129
LUNG	ADENOMA+CARCINOMA	8	7	10	9	0.354	0.776	0.416	0.536
	Adenoma: alveolar/br	4	5	7	8	0.115	0.549	0.262	0.188
	Carcinoma: alveolar/	4	2	3	1	0.883	0.915	0.798	0.973
MAMMARY GLAND	Adenocarcinoma	1	2	1	1	0.606	0.538	0.763	0.758
OVARY	Adenoma: tubulostrom	1	0	1	1	0.383	1.000	0.763	0.758
	Benign granulosa-the	0	1	0	0	0.760	0.525	.	.
	Benign luteoma	1	1	0	0	0.943	0.777	1.000	1.000
	Carcinoma: tubulostr	0	1	0	0	0.760	0.525	.	.
	Cystadenocarcinoma	1	0	0	0	1.000	1.000	1.000	1.000
	Cystadenoma	0	1	0	1	0.313	0.525	.	0.505
	Hemangiosarcoma	2	1	1	3	0.194	0.889	0.882	0.500
	Malignant granulosa-	0	0	1	1	0.185	.	0.510	0.510
	Malignant luteoma	0	0	1	0	0.495	.	0.510	.

**Table 6B1: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Mice (Groups 1, 4, 5, 6)**

Organ Name	Tumor Name	0 mg	200 mg	600 mg	2000 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=70	Low N=70	Med N=70	High N=70	Dos Resp	C vs. L	C vs. M	C vs. H
ABDOMEN	Liposarcoma	0	1	0	0	0.760	0.525	.	.
ADRENAL	Adenoma: cortical	0	0	0	2	0.059	.	.	0.253
ALL_SITES	Hemangioma	1	0	0	2	0.153	1.000	1.000	0.516
	Hemangiosarcoma	2	3	3	4	0.230	0.547	0.520	0.359
	Hemangiosarcoma+Hema	3	3	3	6	0.107	0.707	0.681	0.275
FAT	Hemangioma	0	0	0	1	0.245	.	.	0.505
HARDERIAN GLAND	Adenoma	4	5	2	2	0.862	0.575	0.907	0.907
HEMOLYM. TISSUE	Histiocytic sarcoma	9	6	4	1	0.997	0.884	0.964	0.999
	Leukemia (not otherw	1	0	0	0	1.000	1.000	1.000	1.000
	Malignant lymphoma	13	17	14	12	0.679	0.384	0.523	0.656
KIDNEY	Hemangiosarcoma	0	0	1	0	0.495	.	0.510	.
L.NODE MESENTER	Hemangioma	0	0	0	1	0.249	.	.	0.510
LIVER	ADENOMA+CARCINOMA	2	1	0	1	0.675	0.896	1.000	0.886
	Adenoma: hepatocellu	2	1	0	1	0.675	0.896	1.000	0.886
	Carcinoma: hepatocel	0	0	0	1	0.249	.	.	0.510
	Cholangiocarcinoma	1	0	0	0	1.000	1.000	1.000	1.000
	Hemangioma	1	0	0	0	1.000	1.000	1.000	1.000
	Hemangiosarcoma	0	2	3	3	0.125	0.273	0.129	0.129
LUNG	ADENOMA+CARCINOMA	8	7	10	9	0.354	0.776	0.416	0.536
	Adenoma: alveolar/br	4	5	7	8	0.115	0.549	0.262	0.188
	Carcinoma: alveolar/	4	2	3	1	0.883	0.915	0.798	0.973
MAMMARY GLAND	Adenocarcinoma	1	2	1	1	0.606	0.538	0.763	0.758
OVARY	Adenoma: tubulostrom	1	0	1	1	0.383	1.000	0.763	0.758
	Benign granulosa-the	0	1	0	0	0.760	0.525	.	.
	Benign luteoma	1	1	0	0	0.943	0.777	1.000	1.000
	Carcinoma: tubulostr	0	1	0	0	0.760	0.525	.	.
	Cystadenocarcinoma	1	0	0	0	1.000	1.000	1.000	1.000
	Cystadenoma	0	1	0	1	0.313	0.525	.	0.505
	Hemangiosarcoma	2	1	1	3	0.194	0.889	0.882	0.500
	Malignant granulosa-	0	0	1	1	0.185	.	0.510	0.510
	Malignant luteoma	0	0	1	0	0.495	.	0.510	.

**Table 6B1 (Continue): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Mice (Groups 1, 4, 5, 6)**

Organ Name	Tumor Name	0 mg	200 mg	600 mg	2000 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=70	Low N=70	Med N=70	High N=70	Dos Resp	C vs. L	C vs. M	C vs. H
PITUITARY	Adenoma: pars distal	4	0	2	1	0.804	1.000	0.907	0.973
SKIN MISCELLANE	Carcinoma: squamous	1	0	1	0	0.744	1.000	0.758	1.000
	Keratoacanthoma	0	0	0	1	0.245	.	.	0.505
	Papilloma: squamous	0	1	0	0	0.760	0.525	.	.
SPLEEN	Hemangiosarcoma	2	1	0	1	0.675	0.896	1.000	0.886
SUBCUTANEOUS TI	Benign fibrous histi	0	0	2	0	0.493	.	0.258	.
	Fibrosarcoma	0	0	0	1	0.245	.	.	0.505
	Hemangioma	0	1	0	0	0.760	0.525	.	.
	Rhabdomyosarcoma	0	0	1	0	0.495	.	0.510	.
THORAX	Benin granular cell	0	1	0	0	0.760	0.525	.	.
THYMUS	Malignant thymoma	0	0	1	0	0.495	.	0.510	.
THYROID	Adenoma: follicular	0	0	0	1	0.245	.	.	0.505
UTERUS	Adenocarcinoma: endo	3	2	0	0	0.995	0.848	1.000	1.000
	Carcinoma (not other	1	0	0	0	1.000	1.000	1.000	1.000
	Carcinoma: squamous	0	0	0	1	0.245	.	.	0.505
	Choriocarcinoma	1	1	0	0	0.943	0.777	1.000	1.000
	Deciduoma	0	0	0	1	0.245	.	.	0.505
	Fibroma	0	0	0	1	0.245	.	.	0.505
	Hemangiosarcoma	3	2	4	0	0.947	0.842	0.523	1.000
	LEIOMYOMA+LEIOMA	7	4	5	6	0.436	0.917	0.831	0.723
	Leiomyoma	2	4	2	1	0.838	0.377	0.699	0.879
	Leiomyosarcoma	5	0	3	5	0.167	1.000	0.878	0.643
VAGINA	Polyp: endometrial s	10	10	11	5	0.936	0.670	0.521	0.955
	Sarcoma (not otherwi	0	1	0	1	0.313	0.525	.	0.505
	Sarcoma: endometrial	6	3	1	1	0.973	0.933	0.994	0.994
	Benign granular cell	0	0	0	1	0.249	.	.	0.510
	Leiomyosarcoma	0	0	2	0	0.493	.	0.258	.
	Polyp	0	1	2	0	0.636	0.525	0.258	.
	Sarcoma: stromal	0	0	1	0	0.495	.	0.510	.

Table 6B2: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Mice (Groups 2, 3)

Organ Name	Tumor Name	0/0 mg	25 mg	P_Value Dos Resp
		Cont N=70	High N=70	
ADRENAL	Adenoma: cortical	1	0	1.000
ALL_SITES	Hemangioma	0	1	0.558
	Hemangiosarcoma	2	4	0.466
	Hemangiosarcoma+Hema	2	5	0.335
HARDERIAN GLAND	Adenocarcinoma	1	1	0.808
	Adenoma	5	7	0.564
HEMOLYM. TISSUE	Histiocytic sarcoma	1	6	0.099
	Malignant lymphoma	10	11	0.699
	Mast cell tumor	1	0	1.000
LIVER	ADENOMA+CARCINOMA	0	2	0.309
	Adenoma: hepatocellu	0	2	0.309
	Hemangiosarcoma	1	4	0.270
LUNG	ADENOMA+CARCINOMA	7	6	0.853
	Adenoma: alveolar/br	6	4	0.914
	Carcinoma: alveolar/	1	2	0.588
LYMPH NODE	Hemangioma	0	1	0.558
MAMMARY GLAND	Adenocarcinoma	0	1	0.558
OVARY	Adenoma: tubulostrom	0	1	0.558
	Benign luteoma	1	0	1.000
	Cystadenoma	3	2	0.884
	Hemangiosarcoma	2	0	1.000
	Malignant luteoma	1	0	1.000
SPLEEN	Hemangiosarcoma	1	0	1.000
SUBCUTANEOUS TI	Liposarcoma	1	0	1.000
	Myxosarcoma	0	1	0.558
URINARY BLADDER	Carcinoma: transitio	1	0	1.000
UTERUS	Adenocarcinoma: endo	2	3	0.611
	Benign granular cell	1	0	1.000
	Deciduoma	0	1	0.563
	Hemangioma	1	0	1.000
	Hemangiosarcoma	1	1	0.812

**Table 6B2 (Continue): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Mice (Groups 2, 3)**

Organ Name	Tumor Name	0/0 mg 25 mg		P_Value Dos Resp
		Cont N=70	High N=70	
UTERUS	LEIOMYOMA+LEIOMA	1	4	0.262
	Leiomyosarcoma	1	4	0.262
	Malignant granular c	0	1	0.558
	Polyp: endometrial s	6	10	0.430
	Sarcoma (not otherwi	0	1	0.558
	Sarcoma: endometrial	2	3	0.611
VAGINA	Polyp	1	0	1.000

**Table 6B3: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Mice (Groups 6, 7)**

Organ Name	Tumor Name	2000 mg 2000 /25 mg		P_Value
		High1 N=70	High2 N=70	
ADRENAL	Adenoma: cortical	2	0	1.000
	Benign pheochromocyt	0	1	0.462
ALL_SITES	Hemangioma	2	2	0.623
	Hemangiosarcoma	4	1	0.957
	Hemangiosarcoma+Hema	6	3	0.865
BONE MISCELLANE	Osteosarcoma	0	2	0.210
FAT	Hemangioma	1	0	1.000
HARDERIAN GLAND	Adenoma	2	6	0.085
HEMOLYM. TISSUE	Histiocytic sarcoma	1	0	1.000
	Malignant lymphoma	12	9	0.729
L.NODE MESENTER	Hemangioma	1	0	1.000
LIVER	ADENOMA+CARCINOMA	1	2	0.434
	Adenoma: hepatocellu	1	1	0.707
	Carcinoma: hepatocel	1	1	0.707
	Hemangioma	0	2	0.210
	Hemangiosarcoma	3	1	0.918
LUNG	ADENOMA+CARCINOMA	9	7	0.656
	Adenoma: alveolar/br	8	4	0.885
	Carcinoma: alveolar/	1	3	0.254
MAMMARY GLAND	Adenocarcinoma	1	0	1.000
MUSCLE SKELETAL	Rhabdomyosarcoma	0	1	0.462
OVARY	Adenoma: tubulostrom	1	0	1.000
	Carcinoma: tubulostr	0	1	0.462
	Cystadenoma	1	2	0.442
	Hemangiosarcoma	3	0	1.000
	Malignant granulosa-	1	0	1.000
PITUITARY	Adenoma: pars distal	1	0	1.000
SKIN MISCELLANE	Keratoacanthoma	1	0	1.000

**Table 6B3 (Continue): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Mice (Groups 6, 7)**

Organ Name	Tumor Name	2000 mg 2000 /25 mg		P_Value
		High1 N=70	High2 N=70	
SPLEEN	Hemangiosarcoma	1	0	1.000
SUBCUTANEOUS TI	Fibrosarcoma	1	1	0.713
THYROID	Adenoma: follicular	1	0	1.000
UTERUS	Carcinoma: squamous	1	0	1.000
	Deciduoma	1	0	1.000
	Fibroma	1	0	1.000
	Hemangioma	0	1	0.462
	Hemangiosarcoma	0	1	0.462
	LEIOMYOMA+LEIOMA	6	2	0.953
	Leiomyoma	1	1	0.713
	Leiomyosarcoma	5	1	0.979
	Polyp: endometrial s	5	3	0.812
SARCOMA	Sarcoma (not otherwi	1	0	1.000
	Sarcoma: endometrial	1	5	0.075
VAGINA	Benign granular cell	1	0	1.000

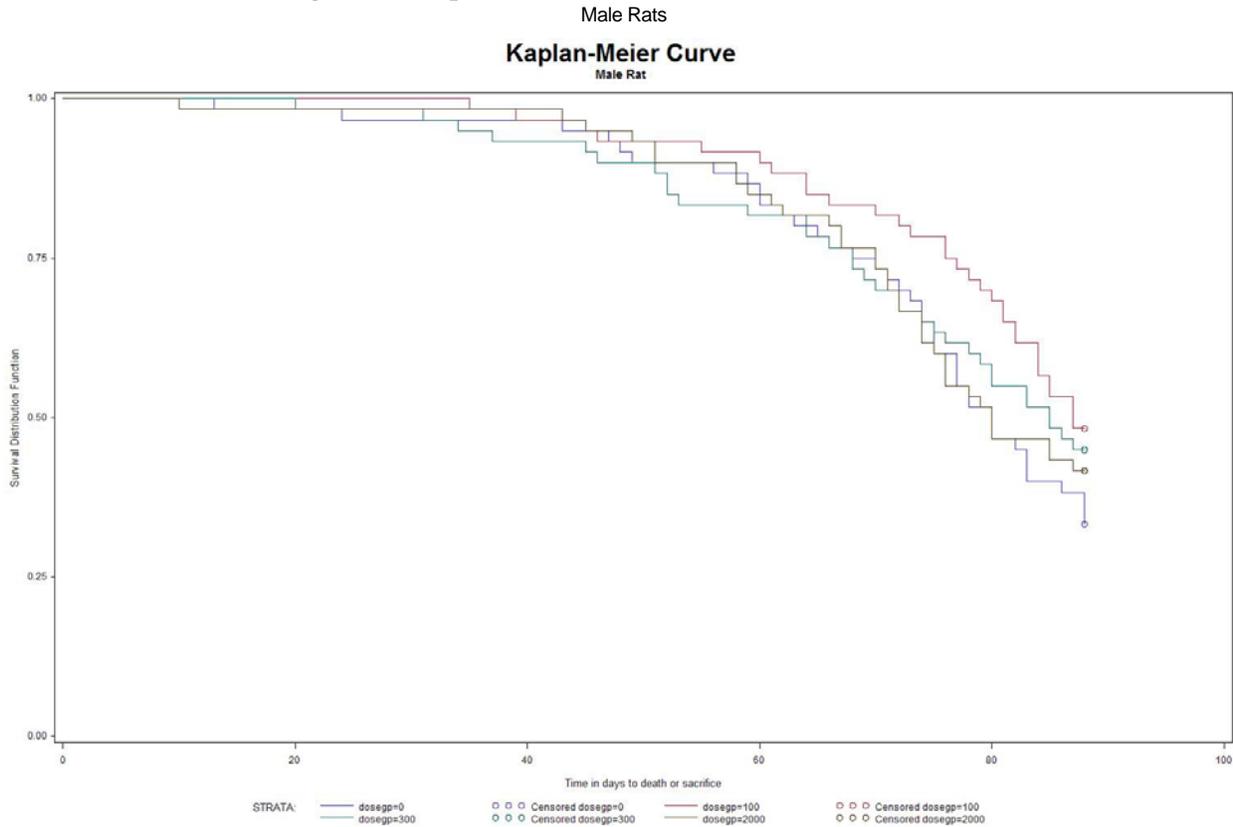
**Table 6B4: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Mice (Groups 2, 7)**

Organ Name	Tumor Name	0/0 mg	2000 /25 mg	P_Value
		Cont N=70	High N=70 Dos Resp	
ADRENAL	Adenoma: cortical	1	0	1.000
	Benign pheochromocyt	0	1	0.525
ALL_SITES	Hemangioma	0	2	0.273
	Hemangiosarcoma	2	1	0.897
	Hemangiosarcoma+Hema	2	3	0.548
BONE MISCELLANE	Osteosarcoma	0	2	0.273
HARDERIAN GLAND	Adenocarcinoma	1	0	1.000
	Adenoma	5	6	0.553
HEMOLYM. TISSUE	Histiocytic sarcoma	1	0	1.000
	Malignant lymphoma	10	9	0.774
	Mast cell tumor	1	0	1.000
LIVER	ADENOMA+CARCINOMA	0	2	0.273
	Adenoma: hepatocellu	0	1	0.525
	Carcinoma: hepatocel	0	1	0.525
	Hemangioma	0	2	0.273
	Hemangiosarcoma	1	1	0.778
LUNG	ADENOMA+CARCINOMA	7	7	0.690
	Adenoma: alveolar/br	6	4	0.873
	Carcinoma: alveolar/	1	3	0.356
MUSCLE SKELETAL	Rhabdomyosarcoma	0	1	0.525
OVARY	Benign luteoma	1	0	1.000
	Carcinoma: tubulostr	0	1	0.525
	Cystadenoma	3	2	0.850
	Hemangiosarcoma	2	0	1.000
	Malignant luteoma	1	0	1.000
SPLEEN	Hemangiosarcoma	1	0	1.000
SUBCUTANEOUS TI	Fibrosarcoma	0	1	0.525
	Liposarcoma	1	0	1.000
URINARY BLADDER	Carcinoma: transitio	1	0	1.000
UTERUS	Adenocarcinoma: endo	2	0	1.000
	Benign granular cell	1	0	1.000
	Hemangioma	1	1	0.778

Table 6B4 (Continue): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Mice (Groups 2, 7)

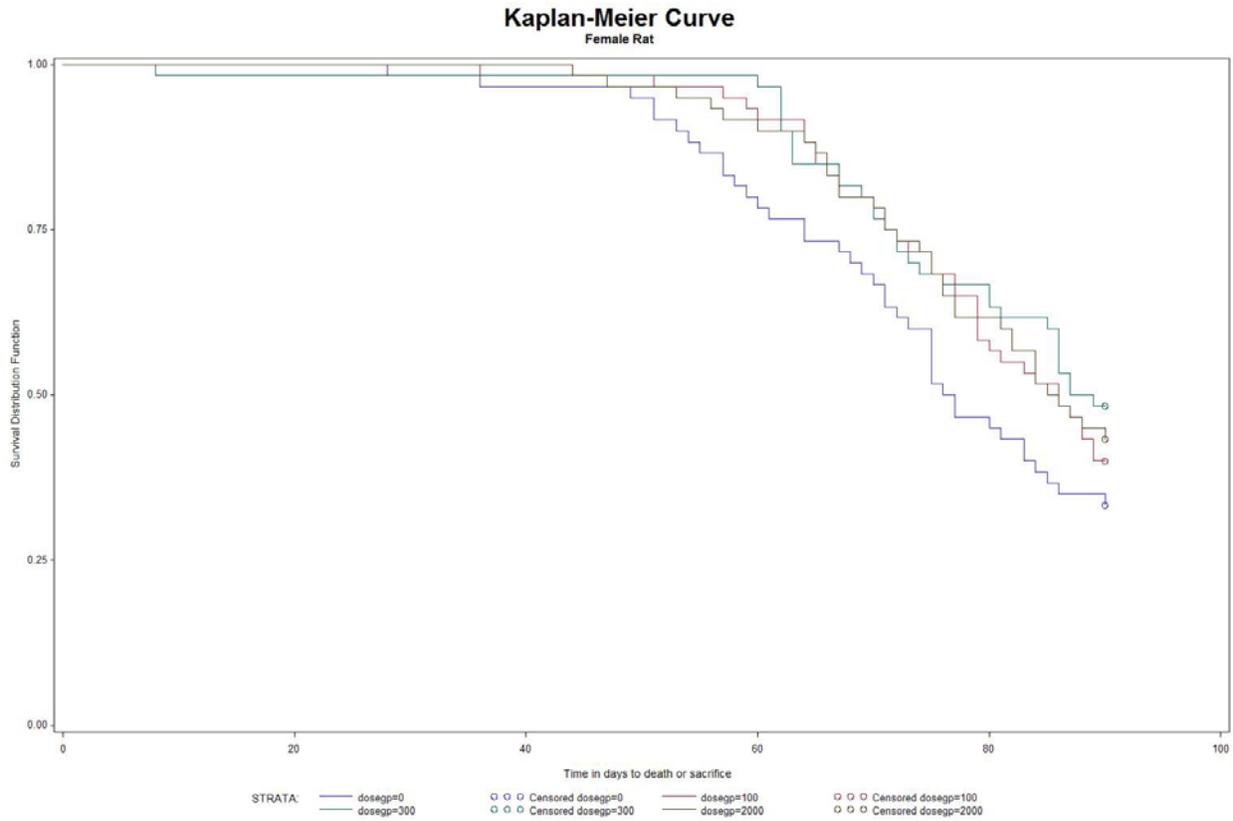
Organ Name	Tumor Name	0/0 mg	2000 /25 mg	P_Value
		Cont N=70	High N=70 Dos Resp	
UTERUS	Hemangiosarcoma	1	1	0.778
	LEIOMYOMA+LEIOMA	1	2	0.547
	Leiomyoma	0	1	0.525
	Leiomyosarcoma	1	1	0.783
	Polyp: endometrial s	6	3	0.948
	Sarcoma: endometrial	2	5	0.282
VAGINA	Polyp	1	0	1.000

Figure 1A: Kaplan-Meier Survival Functions for Male Rats



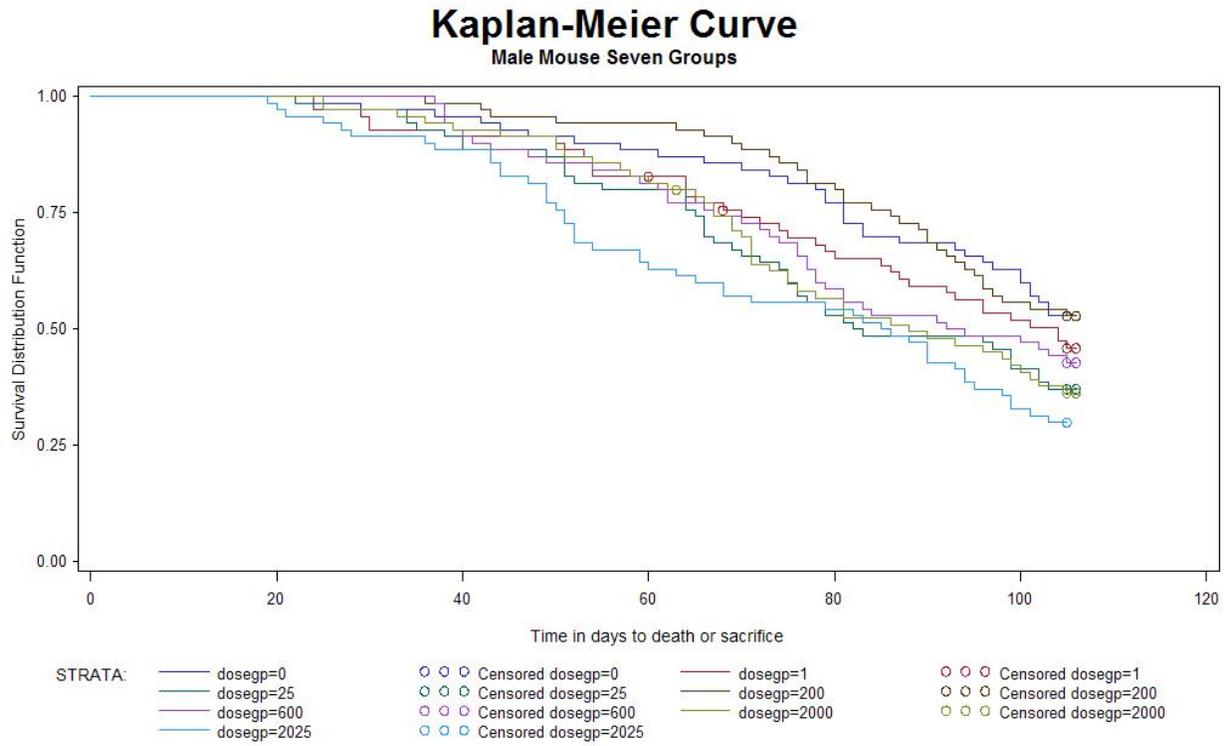
X-Axis: Weeks, Y-Axis: Survival rates

Figure 1B: Kaplan-Meier Survival Functions for Female Rats
Female Rats



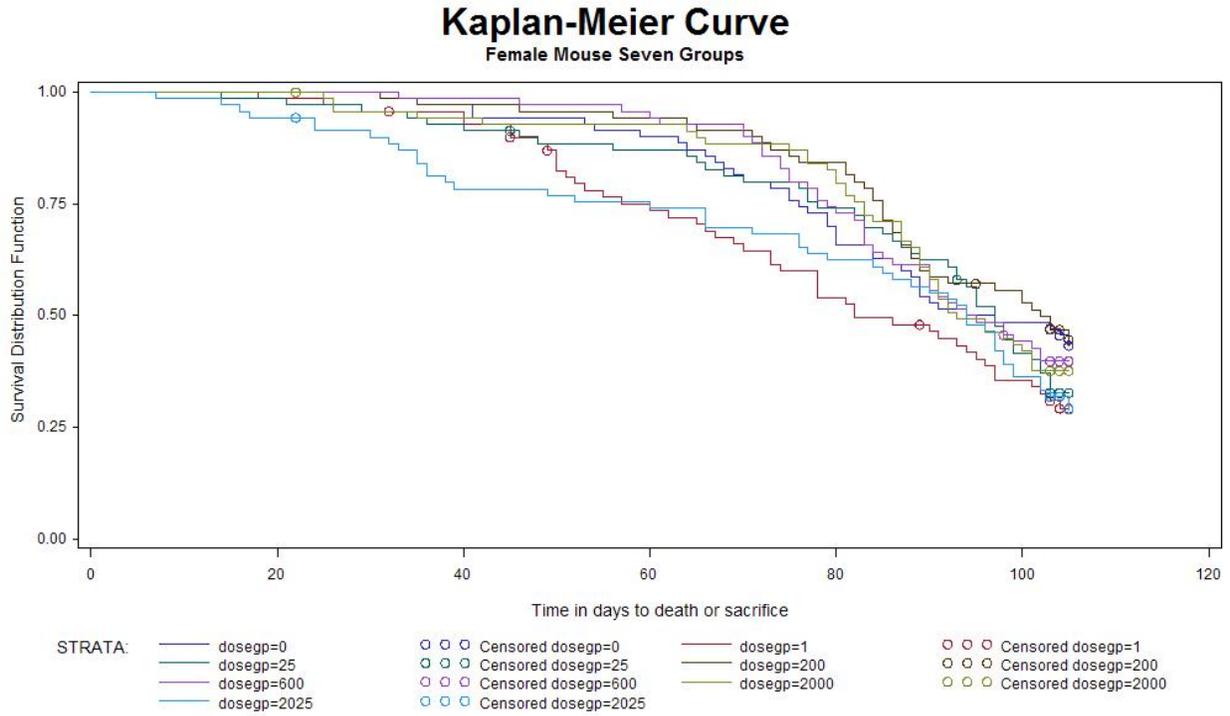
X-Axis: Weeks, Y-Axis: Survival rates

Figure 2A: Kaplan-Meier Survival Functions for Male Mice
Male Mice (seven groups)



X-Axis: Weeks, Y-Axis: Survival rates

Figure 2B: Kaplan-Meier Survival Functions for Female Mice
Female Mice (seven groups)



X-Axis: Weeks, Y-Axis: Survival rates

7. References:

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2. Bieler, G. S. and Williams, R. L. (1993). "Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity". *Biometrics* 49, 793-801.
3. Cox D. R. (1972) "Regression models and life tables", *Journal of the Royal Statistical Society*, B, 34, 187-220.
4. Gehan (1965) "A generalized Wilcoxon test for comparing arbitrarily singly censored samples", *Biometrika*, 52, 203-223.
5. Haseman, J (1983), "A re-examination of false-positive rates for carcinogenesis studies", *Fundamental and Applied Toxicology*, 3: 334-339.
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10. U.S. Department of Health and Human Services, "Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals", Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, 2001.

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/s/

MIN MIN
02/29/2012

KARL K LIN
02/29/2012
Concur with review

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 203,100

Applicant: Gilead

Stamp Date: Oct. 27, 2011

Drug Name:
ELVITEGRAVIR/COBICISTAT/E
MTRICITABINE/
TENOFVIR DISOPROXIL
FUMARATE
(EVG/COBI/FTC/TDF, QUAD
STR)

NDA/BLA Type: NDA

Standard

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	Y			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	Y			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	Y			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	Y			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	Y			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	Y			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	Y			Only meeting minutes are available, not the data
Appropriate references for novel statistical methodology (if present) are included.			NA	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	Y			ISS datasets can be opened.
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	Y			

File name: 5_Statistics Filing Checklist for a New NDA 203,100

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

One potential issue with the final randomization listed submitted in S0001 for study GS-US-236-103.

In this submission, there are 4 files for studies GS-US-236-102 (phase 3), GS-US-236-103 (phase 3), and GS-US-236-104 (phase 2) each. They are:

1. List-based-randomization-req-v1-1-signed;
2. Dummy-randomization-list-approval-v1-signed; (it is the same as the first one?)
3. Final-randlist-ver-1-1; (This final list should be generated before first patient in according to the Memo: All FINAL randomization lists must be created and finalized before development may begin, and thus before the launch of the system).
4. Unblinded-randomization-19Oct2011;

Study	Event	Event Occurred Date	Source
102	First Subject Screened	Mar. 16, 2010	CSR in S0000
	First Subject Randomized	Apr. 09, 2010	CSR in S0000
	Item 3 generated (RandDate)	Jan. 11, 2010	File in S0001
103	First Subject Screened	Apr. 06, 2010	CSR in S0000
	First Subject Randomized	May. 20, 2010	CSR in S0000
	Item 3 generated (RandDate)	Dec. 08, 2010	File in S0001
	Last Subject Randomized	Sep. 30, 2010	CSR in S0000
	Treatment Unblinded	Sep. 16, 2011	CSR in S0000
104	First Subject Screened	Mar. 30, 2009	CSR in S0000
	First Subject Randomized	Apr. 16, 2009	CSR in S0000
	Item 3 generated (RandDate)	Mar. 05, 2009	File in S0001

If RandDate is the generation date of final randomization list, it indicates that the full randomization list for study GS-US-236-103 was generated after the last subject was randomized, which contradicts the (b) (4) SOP-OP-002. Please ask the sponsor to clarify this.

Wen Zeng Dec. 16, 2011

 Reviewing Statistician (Wen Zeng) Date

Fraser Smith Dec. 16, 2011

 Supervisor/Team Leader (Fraser Smith, acting team leader) Date

1 Page(s) has been Withheld in Full as b5 immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WEN ZENG
12/19/2011

FRASER B SMITH
12/21/2011