

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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**STATISTICAL REVIEW(S)**

## STATISTICAL REVIEW AND EVALUATION

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## STATISTICAL REVIEW AND EVALUATION

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# 1. Executive Summary

The applicant has conducted seven trials to test the efficacy of dolutegravir (DTG) at 50mg QD or BID in HAART regimens among HIV-1 infected patients ranging from treatment naïve to integrase inhibitor resistant. Three of these trials (ING113086 or Spring 2, ING114467 or Single, and ING111762 or Sailing) are randomized, controlled, phase 3 trials, one (ING112574 or Viking 3) was a single arm trial large and long enough to be considered a pivotal phase 3 trial, and the other three (ING111521, ING112276 or Spring 1, and ING112961 or Viking) are phase 2 single arm or dose ranging studies. For the sake of brevity, all seven trials will be identified by their last four digits.

Four of the trials (ING111521, ING112276 or Spring 1, ING113086 or Spring 2, and ING114467 or Single) were conducted in treatment naïve subjects; one (ING111762 or Sailing) was conducted in treatment experienced, two class resistant, integrase inhibitor naïve subjects, and two (ING112574 or Viking 3 and ING112961 or Viking) were conducted in integrase inhibitor resistant subjects.

In treatment naïve patients, the applicant conducted four trials: one short term dose ranging study, one long term dose ranging study, and two long term pivotal trials.

In the short term dose ranging study, trial 1521, DTG at 50mg QD achieved statistically significant superiority over placebo with respect to change in log HIV at day 11. In the long term dose ranging study, trial Spring 1, DTG at 50mg QD was slightly (but not statistically significantly) superior to efavirenz (EFV) with respect to both change in log HIV and percent BLQ to at least 96 weeks.

In one of the two pivotal trials, trial Single, DTG at 50mg QD was statistically significantly superior to the EFV arm at 48 weeks with respect to both endpoints change in log HIV and percent BLQ.

In the second pivotal trial, trial Spring 2, DTG at 50mg QD was statistically non-inferior to raltegravir (RAL) at week 48.

The applicant conducted one pivotal trial in treatment experienced, two class resistant, integrase inhibitor (INI) naïve patients. In this trial DTG at 50mg QD was slightly, but not

statistically significantly, superior to RAL arm with respect to both change in log HIV and percent BLQ. It was statistically non-inferior to RAL with respect to percent BLQ, the endpoint where there is an agreed margin of clinical non-inferiority and which was the protocol specified primary endpoint.

The applicant conducted two trials among INI resistant patients. The small dose ranging trial, the Viking trial, DTG at 50mg BID showed a clinically important and almost statistically significant superiority to DTG at 50mg QD. This comparison involved sequentially enrolled cohorts, not randomized cohorts. Nonetheless, the difference between the BID and QD doses did not diminish when the comparison was adjusted for baseline covariates.

The large trial in this population was a single arm trial because ethical constraints precluded any control arm. In this trial, DTG at 50mg BID both change in log HIV and percent BLQ were statistically significantly greater than zero. The 95% lower confidence bounds on both endpoints were comparable to what one expects from an effective three drug HAART regimen in any population.

The applicant has convincingly demonstrated the efficacy of dolutegravir at 50mg qd in treatment naïve and treatment experienced, INI naïve HIV-1 infected patients and the efficacy of dolutegravir at 50mg bid in INI resistant HIV-1 infected patients.

## **2. Introduction**

### **2.1 Overview**

The applicant submitted seven trials in support of the efficacy of dolutegravir (DTG) as part of a multi-drug regimen for the treatment of HIV-1. Three of these trials (ING113086 or Spring 2, ING114467 or Single, and ING111762 or Sailing) are randomized, controlled, phase 3 trials, one (ING112574 or Viking 3) was a single arm trial large and long enough to be considered a pivotal phase 3 trial, and the other three (ING111521, ING112276 or Spring 1, and ING112961 or Viking) are phase 2 single arm or dose ranging studies. For the sake of brevity, all seven trials will be identified by their last four digits.

Four of the trials (ING111521, ING112276 or Spring 1, ING113086 or Spring 2, and ING114467 or Single) were conducted in treatment naïve subjects; one (ING111762 or Sailing) was conducted in treatment experienced, two class resistant, integrase inhibitor naïve subjects, and two (ING112574 or Viking 3 and ING112961 or Viking) were conducted in integrase inhibitor resistant subjects.

## **2.2 Data Sources**

### **2.2.1 Objectives in Trials**

The primary objective of the seven trials was to establish the efficacy of dolutegravir at either 50 mg either once or twice daily in a wide variety of HIV-1 infected patients. The objectives included showing that the once daily dose was effective in both treatment naïve patients and in treatment experienced patients with resistance to at least two classes of anti-retroviral drugs, accompanied by either susceptibility or resistance to integrase inhibitors.

Trial 3086 (also called Spring 2) and trial 4467 (also called Single) are pivotal phase 3 trials to support efficacy of 50 mg qd DTG as part of an ART regimen for treatment naïve subjects. There were also two supportive phase 2 studies in the treatment naïve population: trial 1521 and trial 2276 (also called Spring 1).

Trial 1762 (also called Sailing) is a pivotal phase 3 trial to support efficacy of 50 mg qd DTG as part of an ART regimen for treatment experienced, two class resistant, integrase inhibitor naïve subjects.

Trial 2961 (also called Viking) and trial 2574 (also called Viking 3) are, respectively, phase 2 and phase 3 studies to support the efficacy of 50 mg bid DTG as part of an ART regimen for treatment experienced, two class resistant, integrase inhibitor resistant subjects.

### **2.2.2 Summary of Study Design**

Trial 1521 was a 10 day placebo controlled, dose ranging study. 35 subjects were randomized 1:1:1:1 to placebo or DTG at 2, 10, or 50 mg qd. Dosing was fasted. Subjects could be either treatment naïve or treatment experienced but had to have had no ART for at least 12 weeks.

Trial 2276 (also called Spring 1) was a randomized, active controlled, dose ranging study. 208 subjects were randomized 1:1:1:1 to DTG at 10, 25, or 50 mg qd or EFV. Subjects were also given a background regimen of either ABC/3TC or TDF/FTC. Randomization was stratified by screening HIV-1 RNA (< or >100 K) and by the choice of background regimen. Subjects were treatment naïve.

Trial 3086 (also called Spring 2) and trial 4467 (also called Single) are both randomized, multi-center, double blind, double dummy, active controlled trials. Subjects in both trials were anti-retroviral therapy (ART) naïve. In trial 3086 (Spring 2), 827 subjects were randomized 1:1 to either DTG 50 mg qd or raltegravir (RAL) 400 mg qd plus a background regimen of either abacavir (ABC) 600 mg qd and lamivudine (3TC) 300 mg qd or tenofovir (TDF) 300 mg qd and FTC 200 mg qd. Randomization was stratified by screening HIV-1 RNA (< or >100 K) and by choice of background regimen.

In trial 4467 (Single), 844 subjects were randomized 1:1 to either DTG 50 mg qd plus ABC 600 mg qd and 3TC 300 mg qd or to efavirenz (EFV) 600 mg qd plus TDF 200 mg qd and FTC 300 mg qd. Randomization was stratified by screening HIV-1 RNA (< or >100 K) and screening CD4 count (< or > 200).

Trial 1762 (also called Sailing) is a randomized, multi-center, double blind, double dummy, active controlled trial. In this trial, subjects were ART experienced but integrase inhibitor (INI) naïve. ART experienced meant their virus was resistant to at least two classes of ART drugs. 715 subjects were randomized 1:1 to either DTG 50 mg qd or RAL 400 mg qd plus a physician chosen optimal background regimen (OBR). The randomization was stratified by three factors: baseline HIV-1 RNA (< or > 50K), use of ritonavir boosted darunavir (DRV/r) with no resistance mutations or not, and number of active drugs in selected background regimen (2 or <2).



Trial 2961 (also called Viking) and trial 2574 (also called Viking 3) are both single arm, open label, multi-center trials. In both trials, subjects had virus resistant to at least two classes (not counting INIs) as well as documented viral resistance to at least one INI. In trial 2961 (Viking) subjects had to have documented RAL resistance at screening. This trial had two sequential cohorts. 27 subjects in cohort 1 were given DTG at 50 mg qd; 24 subjects in cohort 2 were given DTG at 50mg bid. Subjects added DTG to their current failing background regimen for the first 11 days. After that period of functional monotherapy, they added a new optimized background regimen (OBR) to their DTG.

In trial 2574 (Viking 3) subjects had to have virologic failure on RAL or elvitegravir (EVG) plus documented resistance at screening to the same INI. 183 subjects were treated with DTG 50 mg bid plus 8 days of their original failing background regimen and then a new OBR. Subjects were required to have at least one fully active agent in the OBR. A randomized control arm was excluded from this study for ethical reasons, there not being any effective control.

## **2.2.3 Patient Accounting and Baseline Characteristics**

### **2.2.3.1 Trials with Treatment Naïve Patients**

The two large phase 3 trials in treatment naïve subjects were Spring 2 (3086) and Single (4467). Spring 2 randomized 827 subjects out of 1035 screened; Single randomized 844 subjects out of 1090 screened. The progress of the subjects is documented in table 2.2.3.1 A.

TABLE 2.2.3.1 A  
SUBJECTS' DISPOSITION IN NAÏVE SUBJECTS  
(TRIALS SPRING 2 AND SINGLE)

	SPRING 2		SINGLE	
	DTG QD	RAL	DTG QD	ATRIPLA
Randomized	413	414	422	422
Treated	411	411	414	419
Ongoing	364	355	363	335
Withdrew	47	56	51	84
Viral_Failure	16	24	14	13
AE	10	7	10	42
LTFU	4	7	14	9
Other	17	18	13	20

(Protocol defined liver endpoint included as AE, LTFU=loss to follow-up)

In trial 3086 (Spring 2), 100 investigational sites enrolled subjects: 59 centers in Europe (France, Germany, Italy, Spain, United Kingdom), 19 in the USA, 11 in Russia, 7 in Canada, and 4 in Australia. Number and percent of total enrollment in each country is given in table 2.2.3.1 B.

TABLE 2.2.3.1 B  
NUMBER AND PERCENT OF SUBJECTS IN EACH COUNTRY  
SPRING 2 TRIAL 3086

COUNTRY	NUMBER	PERCENT
US	136	17%
Canada	61	7%
France	93	11%
Germany	95	12%
Italy	48	6%
Spain	243	30%
UK	17	2%
Russia	90	11%
Australia	39	5%

In trial 4467 (Single), 136 investigational sites enrolled subject: 4 in Australia, 10 in Canada, 71 in Europe (Belgium, Denmark, France, Germany, Italy, the Netherlands, Romania, Spain, and the UK), and 51 in the US. Number and percent of total enrollment in each country is given in table 2.2.3.1 C.

TABLE 2.2.3.1 C  
NUMBER AND PERCENT OF SUBJECTS IN EACH COUNTRY  
SINGLE TRIAL 4467

COUNTRY	NUMBER	PERCENT
US	322	39%
Canada	57	7%
Spain	233	28%
Germany	71	9%
Italy	31	4%
France	27	3%
UK	23	3%
Belgium	19	2%
Netherlands	10	1%
Denmark	5	<1%
Romania	18	2%
Australia	17	2%

The two trials were similar in their baseline demographic and illness characteristics. Subjects in trial 3086 (Spring 2) had a median age of 36 years, were 86% male, were 12% Hispanic, were 85% White and 11% Black, and were 86% CDC class A. 65% identified homosexual activity as their risk factor, 29% heterosexual contact and 5% injectable drug use. Median baseline HIV-1 RNA was 4.55 log copies/ml, median baseline CD4 count was 360. 15 subjects had hepatitis B, 76 had hepatitis C and one had both.

Subjects in trial 4467(Single) had a median age of 35 years, were 84% male, were 13% Hispanic, were 68% White and 24% Black, and were 83% CDC class A. 69% identified homosexual activity as their risk factor, 30% heterosexual contact and 4% injectable drug use. Median baseline HIV-1 RNA was 4.68 log copies/ml, median baseline CD4 count was 338. 56 subjects had hepatitis C.

Trial 1521 was a 10 day study, conducted at sites in the US, with 7 subjects randomized to placebo, 9 each of 2 mg qd DTG and 10 mg qd DTG and 10 randomized to 50 mg qd DTG. All subjects completed the 10 day trial. All 35 subjects were male and 80% were White with a median age of 41 years. 89% were CDC class A with median baseline log HIV-1 RNA = 4.4 and median baseline CD4 count = 440.

Trial 2276 (Spring 1) randomized 208 subjects out of 278 screened. The progress of the subjects is documented in table 2.2.3.1 D.

TABLE 2.2.3.1 D  
SUBJECTS' DISPOSITION IN NAÏVE SUBJECTS  
(TRIAL SPRING 1)

	DTG QD			EFV
	10 MG	25 MG	50 MG	600 MG
Randomized	53	52	51	52
Treated	53	51	51	50
Ongoing	47	45	46	42
Withdrew	6	6	5	8
Viral_Failure	1	1	0	0
AE	1	1	2	5
LTFU	0	2	1	1
Other	4	2	2	2

(LTFU=loss to follow-up)

In trial 2276 (Spring 1), 34 investigational sites enrolled subjects: 19 centers in Europe Spain, France, Germany and Italy), 12 in the US and 3 in Russia. Spring 1 was conducted by Shinogi for ViiV and did not include documentation of the number enrolled in each country.

Subjects were 80% White and 86% male with a mean age of 37 years. 87% had CDC class A illness. 68% identified homosexual activity as their risk factor, 29% heterosexual contact and 3% injectable drug use. Median baseline HIV-1 RNA was 4.5 log copies/ml, median baseline CD4 count was 308. 1 subject had hepatitis B, 18 had hepatitis C and none had both. The demographic and baseline illness patterns in the smaller treatment naïve studies are similar to those in the larger studies Spring 2 and Single.

### **2.2.3.2 Trials with Treatment Experienced, Integrase Inhibitor Naïve Patients**

The pivotal trial in treatment experienced, INI naïve subjects (1762 or Sailing) randomized 724 subjects out of 1441 screened. The progress of the subjects is documented in table 2.2.3.2 A.

TABLE 2.2.3.2 A  
SUBJECTS' DISPOSITION IN EXPERIENCED, INI NAÏVE SUBJECTS  
(TRIAL SAILING)

	DTG QD	RAL
Randomized	360	364
Treated	357	362
Excluded*	3	1
Completed	1	111
Ongoing	305	189
Withdrew	48	61
Viral_Failure	15	26
AE	8	13
LTFU	5	10
Other	20	12

(Protocol defined liver endpoint included as AE, LTFU=loss to follow-up)

\*One Site (083523, in Russia) was excluded for violation of GCP standards

Subjects randomized to DTG were continued beyond week 48 on the open label extension portion of the study; subjects randomized to RAL were considered to have completed the study after week 48. Thus, in table 2.2.3.2 A, one should compare the 306 ongoing or completed subjects on DTG to the 300 ongoing or completed subjects on RAL. The design of the study artificially inflates the number of completers on RAL relative to the number ongoing.

In trial 1762 (Sailing), 156 investigational sites enrolled subjects: 68 centers in North America (US, Canada, and Mexico); 46 in Europe (Belgium, France, Greece, Hungary, Italy, the Netherlands, Spain, Romania, and the United Kingdom), 42 in Rest of World (Argentina, Australia, Brazil, Chile, Russia, South Africa, and Taiwan). Number and percent of total enrollment in each country is given in table 2.2.3.2 B.

TABLE 2.2.3.2 B  
NUMBER AND PERCENT OF SUBJECTS IN EACH COUNTRY  
SAILING TRIAL 1762

COUNTRY	NUMBER	PERCENT
North America	272	38%
Europe	99	14%
Rest of the World	344	48%
US	227	32%
Canada	4	<1%
Mexico	41	6%
Italy	11	2%
Netherlands	1	<1%
Spain	34	5%
UK	6	<1%
Belgium	8	1%
France	18	3%
Greece	3	<1%
Hungary	1	<1%
Australia	4	<1%
Argentina	47	7%
Brazil	125	17%
Chile	25	3%
Russia	32	4%
South Africa	100	14%
Taiwan	11	2%

Subjects in trial 1762 (Sailing) had a median age of 43 years, were 68% male, were 36% Hispanic, were 49% White and 42% Black, and were 31% CDC class A. Median baseline HIV-1 RNA was 4.18 log copies/ml, median baseline CD4 count was 200. 33 subjects had hepatitis B only, 79 had hepatitis C only and two had both.

As one would expect, subjects had more advanced disease (as measured by CDC class) and lower baseline CD4 counts than in the four trials with treatment naïve subjects.

Prior experience with ART was extensive. The median prior exposure to ART was 6 years. 54% of subjects had taken at least 5 prior ART drugs; >99% had taken one or more NRTIs (nucleoside reverse transcriptase inhibitor); 84% had taken one or more NNRTIs (non-nucleoside reverse transcriptase inhibitor); 60% had taken one or more PIs (protease inhibitor); 47% had taken drugs in three or more ART classes. In contrast, only 4% had taken a fusion inhibitor, only 2% had taken a CCR5 antagonist, and only 1 subject had taken an integrase inhibitor.

### 2.2.3.3 Trials with Integrase Inhibitor Resistant Patients

Integrase inhibitor resistant subjects were analyzed in one small trial (2961 or Viking) and one large trial (2574 or Viking 3). Both trials were single arm because INI resistant subjects had no ethically acceptable control, i.e. no effective control. The progress of the subjects is documented in table 2.2.3.3 A.

TABLE 2.2.3.3 A  
SUBJECTS' DISPOSITION IN INI RESISTANT SUBJECTS  
(TRIALS VIKING AND VIKING 3)

	VIKING		VIKING 3
	50 mg qd	50 mg bid	50 mg bid
Treated	27	24	183
Ongoing,<24 weeks	.	.	65
Ongoing,>24 weeks	16	.	90
Ongoing,>48 weeks	.	19	.
Withdrew,<24 weeks	11	.	24
Withdrew,<48 weeks	.	5	.
LOE	9	2	15
AE	2	2	5
LTFU	0	0	2
Other	0	1	2
Withdrew,>24 weeks	.	.	4
Viral_Failure	.	.	4
AE	.	.	0
LTFU	.	.	0
Other	.	.	0

(Protocol defined liver endpoint included as AE, LTFU=loss to follow-up, LOE=lack of efficacy)

In trial 2961 (Viking), 16 sites in France, Italy, Canada, Spain and the US enrolled subjects.



In trial 2574 (Viking 3), 65 sites enrolled subjects: 1 in Belgium, 3 in Canada, 13 in France, 6 in Italy, 4 in Portugal, 3 in Spain, and 35 in the US. Number and percent of total enrollment in each country is given in table 2.2.3.3 B.

TABLE 2.2.3.3 B  
NUMBER AND PERCENT OF SUBJECTS IN EACH COUNTRY  
VIKING 3 TRIAL 2574

COUNTRY	NUMBER	PERCENT
US	99	54%
Canada	3	2%
Belgium	1	<1%
France	38	21%
Italy	30	16%
Portugal	6	3%
Spain	6	3%

Subjects in trial 2961 (Viking) had a median age of 48 years in cohort 1 and 47 years in cohort 2, were 93% male in cohort 1 and 75% male in cohort 2, were 11% Hispanic in cohort 1 and 21% Hispanic in cohort 2, were 89% White and 3% Black in cohort 1 and 79% White and 3% Black in cohort 2. Among subjects in cohort 1 52% identified homosexual activity as their risk factor, 41% heterosexual contact and 7% injectable drug use; in cohort 2 67% identified homosexual activity as their risk factor, 28% heterosexual contact and 6% injectable drug use. Subjects in cohort 1 were 59% CDC class C, those in cohort 2 were 83% CDC class C. In cohort 1 median baseline HIV-1 RNA was 4.48 log copies/ml and median baseline CD4 count was 114, in cohort 2 median baseline HIV-1 RNA was 4.26 log copies/ml, median baseline CD4 count was 202. In cohort 1, no one had hepatitis B, 2 out of 27 had hepatitis C; in cohort 2, 2 out of 24 had hepatitis B, 6 out of 24 had hepatitis C. One should keep in mind that the uncertainty simply due to random variability in samples of size 24-27 is around 10% for percentages. One must be careful about assuming any substantive difference between the cohorts at baseline.

In the two cohorts of Viking, 41 out of 51 were currently failing RAL; the other 10 had failed it previously.

Subjects in trial 2574 (Viking 3) had a median age of 48 years, were 77% male, were 11% Hispanic, were 71% White and 27% Black, and were 56% CDC class C. 52% identified homosexual activity as their risk factor, 29% heterosexual contact and 15% injectable drug use. Median baseline HIV-1 RNA was 4.38 log copies/ml, median baseline CD4 count was 140. 10 out of 183 had hepatitis B, 26 out of 183 had hepatitis C, and 2 had both.

101 out of 183 had either RAL or EVG in the regimen at enrollment; 124 had genotypic or phenotypic resistance at screening. The others had prior use and detection of resistance.

### 2.2.3.4 Summary

One will notice that increasing severity of illness in the three categories mainly manifests itself in lower CD4 counts and a shift from CDC class A to class C. This is documented in table 2.2.3.4 A.

TABLE 2.2.3.4 A  
INCREASING BASELINE SEVERITY

GROUP, TRIAL	N	% IN CDC CLASS A	CLASS C	MEDIAN BASELINE HIV-1 RNA	CD4 COUNT
Naïve					
Spring 2	822	86%	2%	4.55	360
Single	833	83%	4%	4.68	338
1521	35	89%	3%	4.4	440
Spring 1	208	87%	1%	4.5	308
2-Class Resistant, INI Naïve					
Sailing	715	31%	46%	4.18	200
INI Resistant					
Viking					
Cohort 1	27	4%	59%	4.48	114
Cohort 2	24	10%	83%	4.26	202
Viking 3	183	24%	56%	4.38	140

## **2.2.4 Summary of Methods of Assessment**

### **2.2.4.1 Schedule of Measurements**

Two of the trials, 1521 in treatment naïve and Viking in INI resistant subjects, were small. Trial 1521 was also intended to be fairly short. Trial 1521 measured HIV-1 RNA by Amplicor Standard assay at baseline on days 1-4, by the Ultrasensitive assay on days 7, 8, 9, 10, 11, and 14. The Viking trial measured HIV-1 RNA on days 1, 7, 11, 21, and on weeks 4, 8, 12, 16, 20, 24, 32, 40, 48, and every 12 weeks thereafter.

The five larger trials all had similar schedules for the measurement of HIV-1 RNA (by Ultrasensitive assay) and of CD4 count. The key efficacy parameters were measured at baseline and at weeks 1, 2, 4, every 4 weeks to week 16 (or 24), then every 8 weeks to week 48, and then every 12 weeks.

### **2.2.4.2 Assessment of Treatment Effects**

The primary endpoint in trial 1521 was log change in HIV-1 RNA between baseline and day 11. The primary endpoint in the dose ranging trial, Spring 1, was confirmed and sustained viral suppression at week 16, with secondary endpoints being percent with confirmed and sustained suppression at weeks 24, 48, and 96. Both suppression and rebound were required to be confirmed by a second measurement at a subsequent visit.

The primary endpoint in both phase 3 trials with treatment naïve subjects, Spring 2 and Single, was HIV-1 RNA observed BLQ at week 48 (regardless of subsequent confirmation or prior rebound, i.e. snapshot).

The primary endpoint in the phase 3 trial with treatment experienced, INI naïve subjects, Sailing, was HIV-1 RNA observed BLQ by snapshot at week 24.

The primary endpoint in the Viking trial (the small, unrandomized trial in INI-resistant subjects) was percent of subjects with HIV-1 RNA on day 11 either <400 c/ml or <baseline - .7 log copies/ml. Mean change from baseline to day 11 was a secondary endpoint, as were percent of subjects with HIV-1 RNA <400 c/ml at weeks 16, 48 and 96. For the later time points, confirmed and sustained suppression was required, as in trial Spring 1.

The primary endpoint in the Viking 3 trial (the large, unrandomized trial in INI resistant subjects) was the mean change from baseline in log HIV-1 RNA after 8 days of functional monotherapy. A secondary endpoint was the percent of subjects with HIV-1 RNA BLQ (<50 c/ml) after 24 weeks of DTG plus new OBR.

### ***2.2.5 Summary of Statistical Analysis***

The primary analysis in trial 1521 of day 11 log change from baseline was an ANCOVA with treatment and log baseline value as predictors.

The primary analysis in the dose-ranging Spring 1 trial used percent with sustained viral suppression to BLQ (below limit of quantitation = <50 copies/ml) at week 16. Dose selection for continuation was based on interim analyses at week 16, week 24, and week 48. Only descriptive statistics are reported: the sponsor gives no confidence intervals for percents suppressed and no statistical comparisons between the DTG arms and the EFV control arm.

The primary analysis in both phase 3 trials in naïve subjects, Spring 2 and Single, used percent observed suppressed to BLQ at week 48. In both trials, the DTG and control arms (RAL in Spring 2, EFV in Single) were compared by the Cochran-Mantel-Haenszel (CMH) method, stratifying by the randomization factors (baseline HIV-1 RNA and NRTI background regimen in Spring 2, baseline HIV-1 RNA and baseline CD4 count in Single). Non-inferiority to RAL or EFV was declared if the lower confidence bound for the week 48 differences was >-10%. In both trials, a secondary CMH comparison was done at week 96. Since the week 48 analysis was primary, no multiple comparison adjustment was done at week 96.

One Russian site in the Spring 2 trial, site 083505, was found in violation of GCP (good clinical practice) and sensitivity analyses excluding this site were also conducted. There were 8 DTG subjects and 6 RAL subjects at this site.

The primary analysis in the phase 3 trial in experienced, INI naïve subjects, Sailing, used percent observed suppressed to BLQ at week 24 with a CMH confidence interval. In this trial, the CMH strata were generated by baseline HIV-1 RNA, DRV/r use without primary PI mutations or not, and number of active drugs in the background regimen. Non-inferiority to RAL was declared if the lower confidence bound for the week 24 differences was  $>-12\%$ .

The same Russian site that was found in violation of GCP in the Spring 2 trial was also included in the Sailing trial (here as site 083523). Again, sensitivity analyses excluding the four subjects at this site were performed.

The Viking and Viking 3 trials in INI resistant subjects are uncontrolled so statistical determinations of efficacy were based on the 95% confidence intervals for percent successful at day 11 in Viking or mean change from baseline at day 8 in Viking 3 entirely excluding zero. Percent successful meant  $<400$  or baseline-.7 logs in Viking. The Viking 3 trial conducted an interim analysis on the secondary endpoint of percent  $<50$  at week 24 when the first 100 subjects reached the 24 week time point. Since neither trial was randomized, there are no stratification factors and simple normal approximations are used for confidence intervals.

## ***2.2.6 Summary of Applicant's Results***

### ***2.2.6.1 Trials with Treatment Naïve Patients***

The results for trial 1521 are given in table 2.2.6 A. This table gives the mean log change from baseline at day 11 and the mean difference between DTG and placebo, adjusted for baseline log HIV-1 RNA value, together with 95% confidence intervals on the difference and the p-value for the difference. Even with this small sample size, all three doses of DTG were statistically significantly superior to placebo at day 11.

TABLE 2.2.6 A				
TRIAL 1521 HIV RNA RESULTS				
LOG CHANGE FROM BASELINE AT DAY 11				
	Placebo	2 mg qd	10 mg qd	50 mg qd
N	7	9	9	10
Log Change from				
Baseline	.05	-1.51	-2.03	-2.46
Adj. Mean Diff. from				
Placebo	NA	-1.54	-2.04	-2.46
95% Confidence				
Limits	NA	-2.0, -1.07	-2.52, -1.55	-2.94, -2.02
p-value	NA	<.001	<.001	<.001

The results for trial Spring 1 (2276) are given in tables 2.2.6 B and C. The first table gives the percent with sustained viral suppression without confirmed rebound in each of the four arms at weeks 16, 24, 48 and 96. Subjects discontinued or switched to other therapy are classified as failures. The second table gives a breakdown of the reasons for failure at week 96. In general, the results are suggestive of better performance by the DTG regimens than by the EFV regimen. The starred DTG results in table 2.2.6 B are all statistically significantly superior to the EFV result at the same week. These are all at the nominal .025 level, with no multiple comparison adjustment. At the protocol specified primary endpoint, week 16, all three doses of DTF were statistically significantly superior to EFV.

TABLE 2.2.6 B  
 SPRING 1 TRIAL (2276) HIV RNA RESULTS  
 SUSTAINED HIV-1 RNA<50 C/ML

	EFV	DTG 10mg qd	25mg qd	50mg qd
N	50	53	51	51
Week_16	29/50=58%	51/53=96%*	46/51=90%*	47/51=92%*
Week_24	41/50=82%	51/53=96%*	46/51=90%	47/51=92%
Week_48	40/50=80%	48/53=91%	45/51=88%	46/51=90%
Week_96	36/50=72%	42/53=79%	40/51=78%	45/51=88%*

TABLE 2.2.6 C  
 SPRING 1 TRIAL (2276) HIV RNA RESULTS  
 SUPPRESSIONS AND FAILURES AT WEEK 96

	DTG 10mg qd	25mg qd	50mg qd	EFV
N	53	51	51	50
Success	42 79%	40 78%	45 88%	36 72%
Never<50	1 2%	0	0	0
Rebound	6 11%	4 8%	2 4%	4 8%
Non-Responder				
AE	0	1 2%	0	4 8%
Other	0	1 2%	2 4%	1 2%
Changed Therapy while Suppressed				
Death	1 2%	0	0	0
Other AE	0	0	1 2%	1 2%
Other	3 6%	5 10%	1 2%	4 8%

The results for trial Spring 2 (3086) are given in tables 2.2.6 D and E. The first table gives the percent with snapshot viral suppression in the two arms at week 48, together with the DTG-RAL difference and 95% confidence limits, computed adjusting for the weights in the different strata. Subjects discontinued or switched to other therapy are classified as failures. The second row in the table give the results of the sensitivity analysis excluding the 14 subjects from the one Russian site that violated GCP. The second table gives a breakdown of the reasons for failure at week 48. Week 96 data are not yet available for this trial. At week 48, the primary conclusion of non-inferiority of DTG to RAL is established, whether or not the data from the suspect Russian site are included.

TABLE 2.2.6 D  
 SPRING 2 TRIAL (3086) HIV RNA RESULTS  
 OBSERVED HIV-1 RNA<50 C/ML

	DTG 50mg qd	RAL	Adjusted Difference	95% Confidence Limits
Week_48	361/411=88%	351/411=85%	2.5%	-2.2%,7.1%
	356/403=88%	347/405=86%	2.6%	-1.9%,7.2%

TABLE 2.2.6 E  
 SPRING 2 TRIAL (3086) HIV RNA RESULTS  
 SUPPRESSIONS AND FAILURES AT WEEK 48

	DTG 50mg qd	RAL
N	411	411
Success	361 88%	351 85%
<50 at Week 48		
or new ART	8 2%	5 1%
Discontinued		
LOE	12 3%	26 7%
AE	9 2%	6 1%
Other	21 5%	23 6%

The results for trial Single (4467) are given in tables 2.2.6 F and G. The first table gives the percent with snapshot viral suppression in the two arms at week 48, together with the DTG-EFV difference and 95% confidence limits, computed adjusting for the weights in the different strata. Subjects discontinued or switched to other therapy are classified as failures. The second table gives a breakdown of the reasons for failure at week 48. Week 96 data are not yet available for this trial. The protocol specified primary comparison of non-inferiority of the DTG regimen to the EFV regimen was established. In fact, the DTG regimen was statistically significantly superior.



TABLE 2.2.6 F  
SINGLE TRIAL (4467) HIV RNA RESULTS  
OBSERVED HIV-1 RNA<50 C/ML

	DTG 50mg qd	EFV	Adjusted Difference	95% Confidence Limits
Week_48	364/414=88%	338/419=81%	7.4%	2.5%,12.3%

TABLE 2.2.6 G  
SINGLE TRIAL (4467) HIV RNA RESULTS  
SUPPRESSIONS AND FAILURES AT WEEK 48

	DTG 50mg qd	EFV
N	414	419
Success	364 88%	338 81%
Missed Wk 48 Visit	0	1 <1%
<50 at Week 48		
or new ART	6 1%	5 1%
Discontinued		
LOE	15 4%	21 5%
AE	9 2%	40 10%
Other	20 5%	14 3%

### ***2.2.6.2 Trials with Treatment Experienced, Integrase Inhibitor Naïve Patients***

The results for trial Sailing (1762) are given in tables 2.2.6 H and I. These analyses give the results of the sensitivity analysis excluding the 4 subjects from the one Russian site that violated GCP. The first table gives the percent with snapshot viral suppression in the two arms at week 24, together with the DTG-RAL difference and 95% confidence limits, computed adjusting for the weights in the different strata. Subjects discontinued or switched to other therapy are classified as failures. The second table gives a breakdown of the reasons for failure at week 24. An intermediate analysis of the week 48 data is the last row of the table. The primary protocol specified endpoint of non-inferiority of DTG to RAL at week 24 was achieved; in fact the data support superiority of DTG to RAL. The partial analysis at week 48, using data available at time of the NDA submission, also support non-inferiority and suggest superiority of DTG.

TABLE 2.2.6 H  
SAILING TRIAL (1762) HIV RNA RESULTS  
OBSERVED HIV-1 RNA<50 C/ML

	DTG 50mg qd	RAL	Adjusted Difference	95% Confidence Limits
Week_24	281/354=79%	252/361=70%	9.7%	3.4%,15.9%
Week_48	116/164=71%	100/165=61%	9.7%	-.2%,19.6%

TABLE 2.2.6 I  
SAILING TRIAL (1762) HIV RNA RESULTS  
SUPPRESSIONS AND FAILURES AT WEEK 48

	DTG 50mg qd	RAL
N	354	361
Success	281 79%	252 70%
Missed Wk 24 Visit	2 <1%	3 <1%
<50 at Week 24 or new ART	40 11%	66 18%
Discontinued		
LOE	13 4%	20 6%
AE	6 2%	9 2%
Other	12 3%	11 3%

### **2.2.6.3 Trials with Integrase Inhibitor Resistant Patients**

The results for the two uncontrolled trials in INI resistant patients, the small Viking (2961) and the large Viking 3 (2574), are given in tables 2.2.6 J, K and L. Table J gives the primary results at the end of functional monotherapy (defined as day 11 in Viking and day 8 in Viking 3). In the Viking trial, the primary endpoint was percent successful, with success defined as HIV-1 RNA < the greater of 400 or <baseline-.7 logs. This endpoint was not evaluated in Viking 3. Mean change from baseline was the secondary endpoint in Viking and the primary endpoint in Viking 3. These endpoints are compared to zero, under the implicit assumption that there would be no change from baseline in the absence of a new, effective drug. The comparison to zero is contained in the 95% confidence intervals for percent successful, which have lower bounds of 58% and 79% for 50mg qd and 50mg bid doses. The other comparison to zero effect is given in the confidence intervals for mean change in log from baseline. The three upper bounds here are -.06, -.70, and -1.34; thus all three groups showed a

statistically significant decrease from baseline after 8-11 days of functional monotherapy.

TABLE 2.2.6 J  
VIKING(2961), VIKING 3(2574) TRIALS HIV RNA RESULTS  
AT END OF FUNCTIONAL MONOTHERAPY

	VIKING	VIKING 3
DTG dose	50mg qd	50mg bid
Day Analyzed	11	8
% Success	21/27=78%	23/24=96%
95% Limits	58%-91%	79%-99%
Mean Change	-1.45	-1.43
95% Limits	-2.96,-.06	-1.52,-1.34

Comparing the 50mg qd to 50mg bid in Viking, the sponsor reported the difference in change from baseline was -.32 with a 95% interval of (-.57,-.06) in favor of the bid dose. The FDA reviewer recalculated the difference, using the data in table J and got a difference of -.31 in favor of the bid dose with 95% interval of (-.67,+.05); the difference in percent successful was 18% in favor of the bid dose with a 95% interval of 0.5% to 36%.

Table K gives the percent with snapshot viral suppression in the two Viking cohorts and the Viking 3 trial at the latest week available at time of submission. Subjects discontinued or switched to other therapy are classified as failures. Table L gives a breakdown of the reasons for failure at week 24, 48 or 96. The results for the 50mg qd cohort are given at both week 96 and week 48 to permit clearer comparison with the week 48 results from the 50mg bid cohort. The pattern observed at the end of functional monotherapy, that 50mg bid dosing is clearly and statistically significantly superior to 50mg qd dosing is confirmed here.

TABLE 2.2.6 H  
VIKING(2961), VIKING 3(2574) TRIALS HIV RNA RESULTS  
OBSERVED HIV-1 RNA<50 C/ML

	VIKING	VIKING 3
	DTG 50mg qd	50mg bid
Week_24	11/27=41%	72/114=63%
Week_48	9/27=33%	17/24=71%
Week_96	7/27=26%	NA

TABLE 2.2.6 I  
VIKING(2961), VIKING 3(2574) TRIALS HIV RNA RESULTS  
SUPPRESSIONS AND FAILURES AT WEEK 24-96

	Viking			Viking 3
	DTG 50mg qd	50mg qd	50mg bid	50mg bid
	At Wk 96	Wk 48	Wk 48	Wk 24
N	27	27	24	114
Success	7 26%	9 33%	17 71%	72 63%
Missing Visit	.	.	.	5 4%
<50	17 62%	15 55%	5 20%	23 20%
Discontinued				
LOE	1 4%	1 4%	1 4%	14 12%
Death	1 4%	1 4%	0	
Other AE	1 4%	1 4%	0	5 4%

## 2.2.7 Summary of Applicant's Conclusions

The applicant concluded that DTG at the appropriate dose and with the appropriate background regimen was demonstrated effective against HIV-1 in three distinct populations: 1)treatment naïve, 2)treatment experienced and 2 class resistant but still integrase inhibitor naïve, and 3)integrase inhibitor resistant.

In treatment naïve class, DTG was effective at 50mg qd with two other ART drugs. This conclusion was supported by two phase 2 trials. Trial 1521 showed that DTG 50mg qd was superior to placebo with respect to early viral load decrease, measured at day 11. The Spring 1 trial (2276) showed that DTG 50mg qd was superior to EFV in percent with viral suppression at week 16 when either drug had a background of either ABC/3TC or TDF/FTC.

The effectiveness of DTG 50mg qd was confirmed in two pivotal trials. Trial Spring 2 (3086) showed that DTG 50mg qd was non-inferior to RAL in percent with viral suppression at week 48 when either drug had a background of either ABC/3TC or TDF/FTC. Trial Single (4467) showed that DTG 50mg qd + ABC/3TC was superior to Atripla (EFV+TDF/FTC) in percent with viral suppression at week 48.

Among subjects who were treatment experienced and two class resistant but INI naïve, trial Sailing (1762) showed that DTG 50mg qd was superior to RAL with respect to viral suppression at week 24 when either drug was combined with a physician chosen OBR.

Incomplete data showed DTG 50mg qd non-inferior to RAL with respect to viral suppression at week 48.

Among subjects who were treatment experienced and INI resistant, two non-randomized trials showed that DTG 50mg bid was superior to no change both in mean decrease of viral load during a short initial period of monotherapy (8 or 11 days) and in percent with viral suppression after 24 weeks with an OBR. One of these trials, the phase 2 Viking trial (2961), also showed a statistically significant superiority of 50mg bid DTG to 50mg qd DTG. (This was a comparison of non-randomized groups.)

### **3. Statistical Evaluation**

#### **3.1 Primary Efficacy Results**

##### **3.1.1 Replication of Applicant's Primary Results**

The applicant provided two data sources for examining their report on efficacy. One dataset for each trial contained their final estimates of log change and/or percent BLQ at the designated primary time points: day 8 or 11, weeks 16, 24, or 48 (depending on the trial and the endpoint, as described above). A second collection of datasets contains the HIV measurements at each visit and additional information as to dates at which subject's discontinued their assigned regimens or started protocol prohibited rescue therapies. This latter information is in a different dataset from the one containing viral load measurements.

There are four other minor issues that affect the reproducibility of the applicant's summary data from the visit by visit data. First, two of the trials (Sailing in two class resistant, INI naïve subjects and Viking 3 in INI resistant subjects) are still ongoing. This reviewer found it somewhat difficult to be certain which subjects had actually been on trial long enough to be included in later endpoints (weeks 40 and later in Sailing, weeks 24 and later in Viking 3).

Second, there are a few subjects who were not included in the viral load dataset but were included in the demographic dataset and flagged as being in the ITT population. There were five such subjects in Spring 2, four in Single, and ten in Sailing. The FDA reviewer assumed that such subjects were treated at least once but never had an HIV measurement. In this review these subjects were all treated as failures (no decrease in viral load from baseline) at all time points. Third, the applicant discovered that one physician in Russia (Cozier) was guilty of GCP (good clinical practice) violations. The subjects from this site were included in the applicant provided datasets for two trials, Spring 2 and Sailing. In all the analyses in this review, the subjects from this site were excluded.

Fourth, two of the trials, Spring 1 and Viking, used the time until confirmed loss of sustained suppression as the determinant of BLQ status rather than the simple snapshot analysis at the designated time window. There were in these trials a few subjects who either had an isolated, unconfirmed rebound in the designated time window or who had two consecutive HIV measurements somewhat higher than 50 c/ml (but <1000) prior to the designated window but

who were re-suppressed in the designated window. These are both classified differently by the two different algorithms.

Table 3.1 A gives the comparison of the results for the major endpoints from applicant's efficacy review, the applicant's Summary dataset, and the FDA reconstruction of the results using the datasets with individual visits. (Control in the Viking trial is DTG 50mg QD.)

TABLE 3.1 A				
COMPARISON OF MAJOR RESULTS FROM 3 SOURCES				
TRIAL	ENDPOINT SOURCE	DTG_50mq	CONTROL	
1521	LOGCHG, Day 8			
	Appl. Report	-2.46		.05
	FDA	-2.418		.129
Spring_1	%BLQ, Week 16			
	Appl. Report	47/51=92%		29/50=58%
	FDA	45/50=90%		32/50=64%
	%BLQ, Week 24			
	Appl. Report	47/51=92%		41/50=82%
	Summary Data	47/51=92%		41/50=82%
	FDA	43/50=86%		41/50=82%
Spring_2	(including Kozyrev data)			
	%BLQ, Week 48			
	Appl. Report	361/411=88%		351/411=85%
	Summary Data	361/411=87.8%		351/411=85.4%
	FDA	361/411=87.8%		350/411=85.2%
	(excluding Kozyrev)			
	%BLQ, Week 48			
	Appl. Report	356/403=88%		347/405=86%
	FDA	355/403=88.1%		346/405=85.4%
Single	%BLQ, Week 48			
	Appl. Report	364/414=88%		338/419=81%
	Summary Data	364/414=87.9%		338/419=80.7%
	FDA	364/414=87.9%		339/419=80.9%

TABLE 3.1 A (continued)				
COMPARISON OF MAJOR RESULTS FROM 3 SOURCES				
TRIAL	ENDPOINT	SOURCE	DTG_50mq	CONTROL
Sailing	%BLQ, Week 24			
		Appl. Report	281/354=79%	252/361=70%
		Summary Data	281/357=78.7%	252/362=69.6%
		FDA	283/357=79.3%	255/362=70.4%
	%BLQ, Week 48			
		Appl. Report	116/164=71%	100/165=61%
Viking		FDA	124/196=63.3%	109/201=54.2%
	LOGCHG, Day 11			
		Appl. Report	-1.76	-1.45
		FDA	-1.73798	-1.41790
	%BLQ, Week 24			
		Appl. Report	19/23=79%	11/27=41%
		Summary DATA	19/24=79.2%	11/27=40.7%
		FDA	17/24=70.8%	12/27=44.4%
	%BLQ, Week 48			
		Appl. Report	17/24=71%	9/27=33%
Viking 3		Summary Data	17/24=70.8%	9/27=33.3%
		FDA	16/24=66.7%	9/27=33.3%
	LOGCHG, Day 8			
		Appl. Report	-1.43	
		FDA	-1.439	
	%BLQ, Week 24			
		Appl. Report	72/114=63%	
		FDA	76/114=66.7%	

One can see that for all the results except %BLQ in week 48 in the Sailing trial, the results are inconsequentially different. As mentioned above, for the later visits in Sailing (week 40 and later), it is difficult to tell from the datasets which subjects are missing viral load data because they have not yet reached that time point in the trial. Even for this endpoint, the difference between DTG and the RAL control is small between the two computations.



### **3.1.2 Comparison of Simple Pooling and Mantel-Haenszel Analyses**

There are two issues that affect the computation of the confidence intervals for percent BLQ. First, for the three randomized pivotal trials, Spring 2, Single, and Sailing, the randomization was stratified by baseline covariates. One may analyze the data by simply pooling all the subjects together, ignoring the strata or by the Mantel-Haenszel method, which consists of computing weighted averages of the arm means and differences between arms computed within each stratum. The statistically preferable method is the weighted average of within-stratum results.

Second, when the endpoint is a percentage, there is a choice of how to select the weights. The conventional method is to use the reciprocal of the square of the standard error, giving greater weight to strata with more accurate estimates. The problem with this is that when the endpoint gets close to 100% (or 0%), the weight gets very large. It is possible for a small stratum to have standard error very close to zero and thus very large weight. The FDA statistical reviewer considers this to be undesirable. A conservative approach is to use  $.5/\sqrt{N}$  as the standard error in these computations. This is chosen because the largest possible value for the standard error of a percent endpoint is  $.5/\sqrt{N}$ .

Table 3.1 B gives a comparison of the confidence on the primary endpoints of percent BLQ conducted by the applicant, who used the Mantel-Haenszel weighting with the observed standard errors, and three FDA sensitivity analyses: pooled analysis using the observed standard errors, pooled analyses using the conservative standard errors, and Mantel-Haenszel weighting, using the conservative standard errors. The abbreviations M-H-Obs, M-H-Cons, Pool-Obs, Pool-Cons are used in the table to designate whether Mantel-Haenszel weighting or simple pooling and whether observed or the conservative standard errors were used.

TABLE 3.1 B						
COMPARISON OF MANTEL-HAENSZEL AND SIMPLE POOLED ESTIMATES						
WITH OBSERVED AND CONSERVATIVE STANDARD ERRORS						
PRIMARY ENDPOINTS IN THE STRATIFIED TRIALS						
	MEAN	95% LIMITS		DTG_50mg	CONTROL	
	DIFF	LOWER	UPPER			
SPRING_2_3086_%BLQ_WEEK_48						
Applicant						
M-H-Obs	2.6%	-1.9%	7.2%	356/403=88%	347/405=86%	
FDA						
Pool-Obs	2.7%	-2.0%	7.3%	355/403=88.1%	346/405=85.4%	
Pool-Cons	2.7%	-4.2%	9.6%			
M-H-Cons	2.9%	-4.0%	9.8%			
SINGLE_4467_%BLQ_WEEK_48						
Applicant						
M-H-Obs	7.4%	2.5%	12.3%	364/414=88%	338/419=81%	
FDA						
Pool-Obs	7.0%	2.1%	11.9%	364/414=87.9%	339/419=80.9%	
Pool-Cons	7.0%	0.2%	13.8%			
M-H-Cons	7.0%	0.2%	13.8%			
SAILING_1762_%BLQ_WEEK_24						
Applicant						
M-H-Obs	9.7%	3.4%	15.9%	281/354=79%	252/361=70%	
FDA						
Pool-Obs	9.0%	2.7%	15.3%	281/354=79.4%	254/361=70.4%	
Pool-Cons	9.0%	1.7%	16.3%			
M-H-Cons	9.0%	1.6%	16.3%			

As must occur, the conservative standard error methods give wider confidence intervals but the overall conclusions are never altered. DTG is, with 95% confidence, statistically above the -10% clinical non-inferiority compared to RAL in Spring 2; DTG is statistically significantly superior to EFV in Single and to RAL in Sailing.

### 3.1.3 Reasons for Failure

Tables 3.1 C-E give the breakdown of successes and failures by reason in the five trials (Spring 2, Single, Sailing, Viking, and Viking 3).

TABLE 3.1 C  
OUTCOMES IN TREATMENT NAÏVE TRIALS

SPRING\_2\_WEEK\_48\_RAL\_VS\_DTG\_50mg  
(including Kozyrev)

OUTCOME	DTG_50mg_QD		RAL	
Success	361	87.8%	350	85.2%
Viral_Failure	20	4.9%	32	7.8%
AE/Death	9	2.2%	6	1.5%
Other_OUTCOME	21	5.1%	23	5.6%

SPRING\_2\_WEEK\_48\_RAL\_VS\_DTG\_50mg  
(excluding Kozyrev)

OUTCOME	DTG_50mg_QD		RAL	
Success	355	88.1%	346	85.4%
Viral_Failure	20	5.0%	30	7.4%
AE/Death	8	2.0%	6	1.5%
Other_OUTCOME	20	5.0%	23	5.7%

SINGLE\_WEEK\_48\_EFV\_VS\_DTG\_50mg

OUTCOME	DTG_50mg_QD		EFV	
Success	364	87.9%	339	80.9%
Viral_Failure	21	5.1%	27	6.4%
AE/Death	9	2.2%	40	9.5%
Other_OUTCOME	20	4.8%	13	3.1%

TABLE 3.1 D

## OUTCOMES IN TWO CLASS RESISTANT, INI NAÏVE TRIAL

SAILING\_WEEK\_24\_RAL\_VS\_DTG\_50mg  
(including Kōzyrev)

OUTCOME	DTG_50mg_QD		RAL	
Success	283	79.3%	255	70.4%
Viral_Failure	55	15.4%	84	23.2%
AE/Death	7	2.0%	9	2.5%
Other_OUTCOME	11	3.1%	11	3.0%
Missing_in_window_but_on_study	1	0.3%	3	0.8%

SAILING\_WEEK\_24\_RAL\_VS\_DTG\_50mg  
(excluding Kōzyrev)

OUTCOME	DTG_50mg_QD		RAL	
Success	281	79.4%	254	70.4%
Viral_Failure	55	15.5%	84	23.3%
AE/Death	6	1.7%	9	2.5%
Other_OUTCOME	11	3.1%	11	3.0%
Missing_in_window_but_on_study	1	0.3%	3	0.8%

## SAILING\_WEEK\_48\_RAL\_VS\_DTG\_50mg

OUTCOME	DTG_50mg_QD		RAL	
Success	128	35.9%	113	31.2%
Viral_Failure	49	13.7%	64	17.7%
AE/Death	9	2.5%	12	3.3%
Other_OUTCOME	15	4.2%	13	3.6%
Missing_in_window_but_on_study	156	43.7%	160	44.2%

TABLE 3.1 E

## OUTCOMES IN INI RESISTANT TRIALS

## VIKING\_WEEK\_24\_DTG\_BID\_VS\_DTG\_QD

OUTCOME	DTG_50mg_BID		DTG_50mg_QD	
Success	17	70.8%	12	44.4%
Viral_Failure	7	29.2%	13	48.1%
AE/Death			2	7.4%

## VIKING\_WEEK\_48\_DTG\_BID\_VS\_DTG\_QD

OUTCOME	DTG_50mg_BID		DTG_50mg_QD	
Success	16	66.7%	9	33.3%
Viral_Failure	7	29.2%	16	59.3%
AE/Death	1	4.2%	2	7.4%

## VIKING\_3\_WEEK\_24

OUTCOME	DTG_50mg_BID	
Success	76	66.7%
Viral_Failure	33	28.9%
AE/Death	5	4.4%

### **3.2 Time Course of Viral Load**

The following graphs provide a brief summary of the comparative effects of DTG and the control over time in the trials considered.

In these graphs, one will notice the following important points supporting the efficacy of DTG 50mg QD or BID in all three populations studied. In trial 1521, the 50mg QD DTG achieved statistically significant superiority over placebo with respect to change in log HIV for the short duration of the trial.

In trial Spring 1, when DTG 50mg QD was compared to EFV, DTG superiority with respect to both change in log HIV and percent BLQ was not quite statistically significant but was maintained in the long term.

In trial Spring 2, DTG 50mg QD was slightly, but not statistically significantly, superior to RAL throughout the trial. The lower 95% confidence bound for the difference exceeded -10%, establishing non-inferiority to RAL throughout the first 48 weeks.

In trial Single, it is important to notice that the DTG 50mg QD arm was statistically significantly superior to the EFV arm throughout the first 48 weeks with respect to both endpoints examined, change in log HIV and percent BLQ.

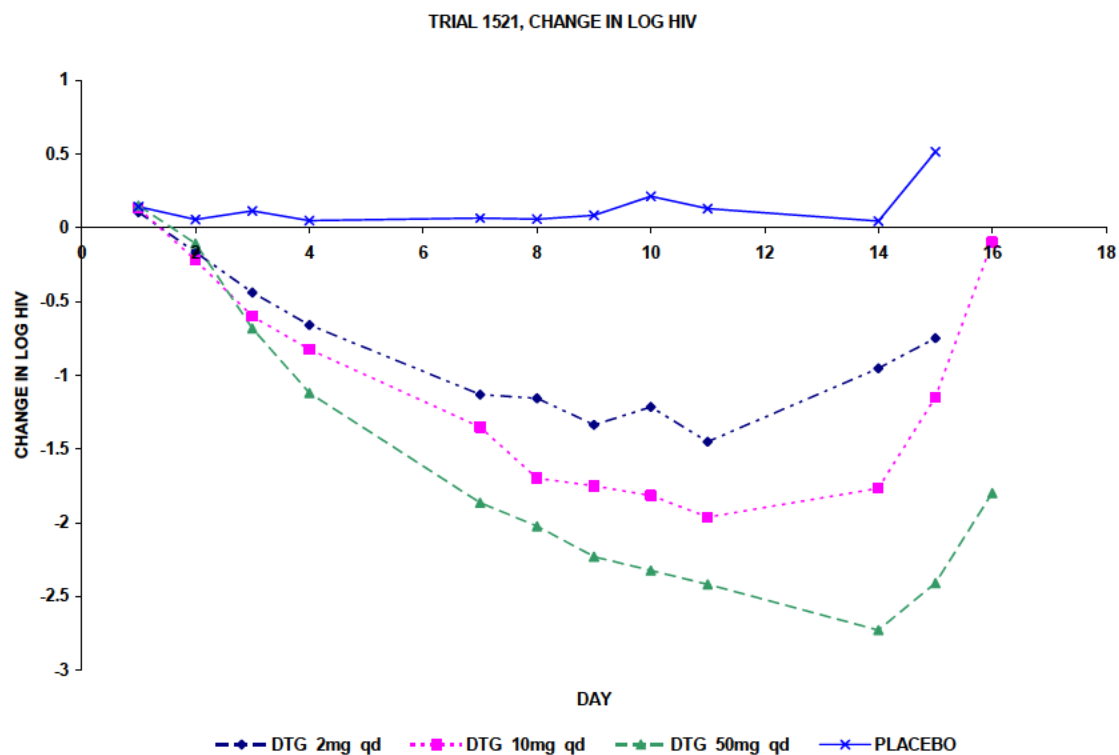
In trial Sailing in two class resistant subjects, the DTG 50mg QD arm was intermittently statistically significantly superior to the RAL arm with respect to both change in log HIV and percent BLQ. With respect to percent BLQ where there is an agreed margin of clinical non-inferiority, DTG 50mg QD was statistically significantly above that margin.

In the INI resistant population, the Viking trial, the DTG 50mg BID cohort showed a clinically important and almost statistically significant superiority to the QD cohort. (Remember that these are enrolled sequentially and are not randomized.)

In the Viking 3 trial, where there a one sample comparison to a constant response of zero, statistically significant superiority was achieved with respect to both log change and percent BLQ throughout the period of observation. In fact, the magnitude of the improvement is comparable to what one expects from an effective three drug HAART regimen in any population.

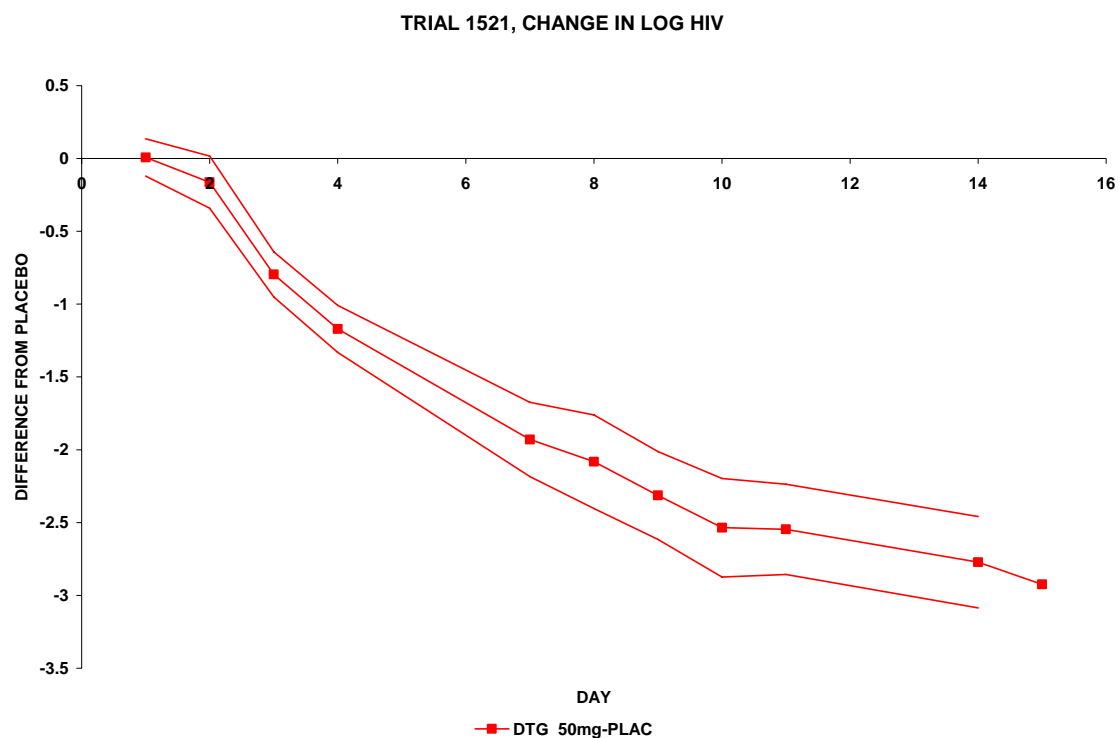
### 3.2.1 Treatment Naïve Trials

The first graph shows the change in log HIV for the four arms of trial 1521 with the superiority of all four doses over placebo readily apparent.



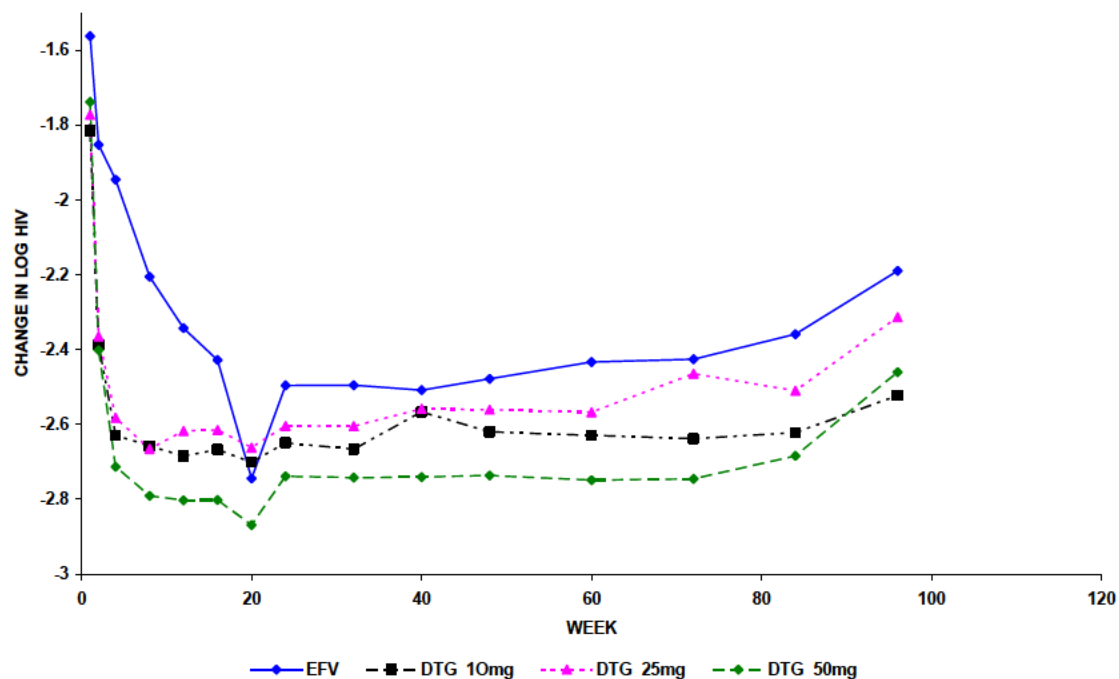


The second graph shows the point estimates and 95% confidence limits for the difference between DTG\_50mg and placebo. Negative values correspond to larger decreases so the statistical superiority of DTG to placebo is again readily apparent.

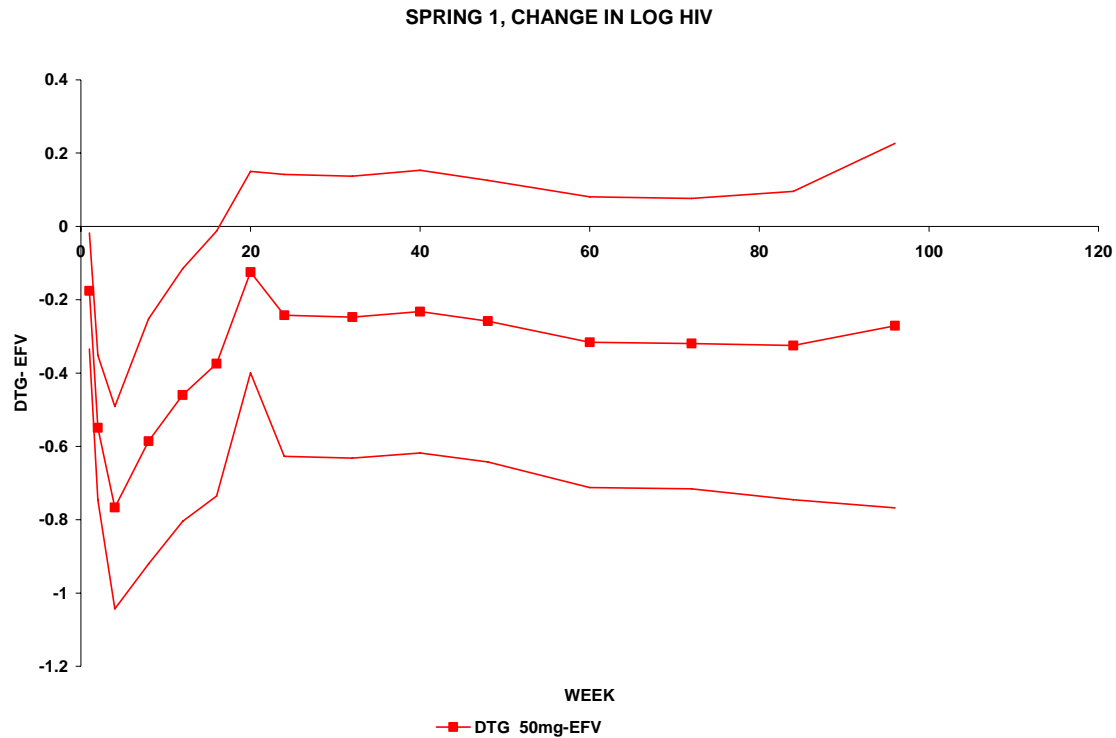


The next graph shows the time course of change in log HIV for the Spring 1 trial. The EFV control does most poorly of the four arms although it does clearly reduce viral load. The 50 mg dose of DTG is the best of the four arms.

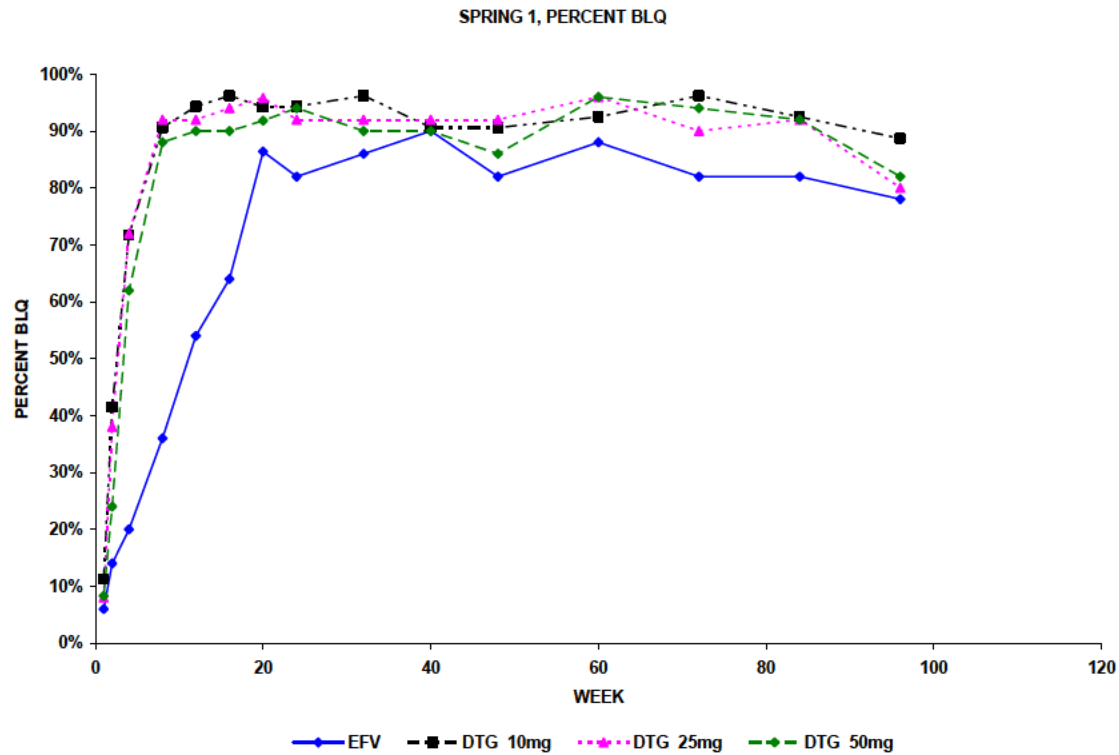
TRIAL SPRING 1



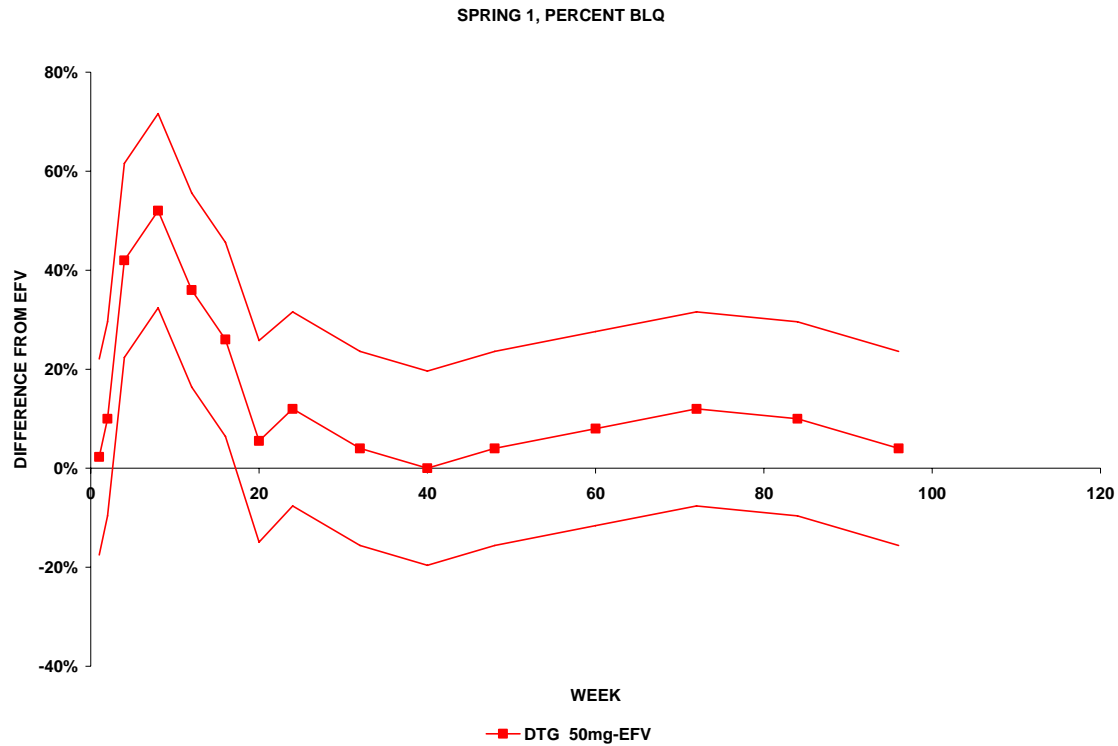
The next graph shows the point estimates and 95% confidence limits for the difference in log change between 50mg DTG and EFV. One can see that the DTG superiority is not quite statistically significant but is maintained in the long term.



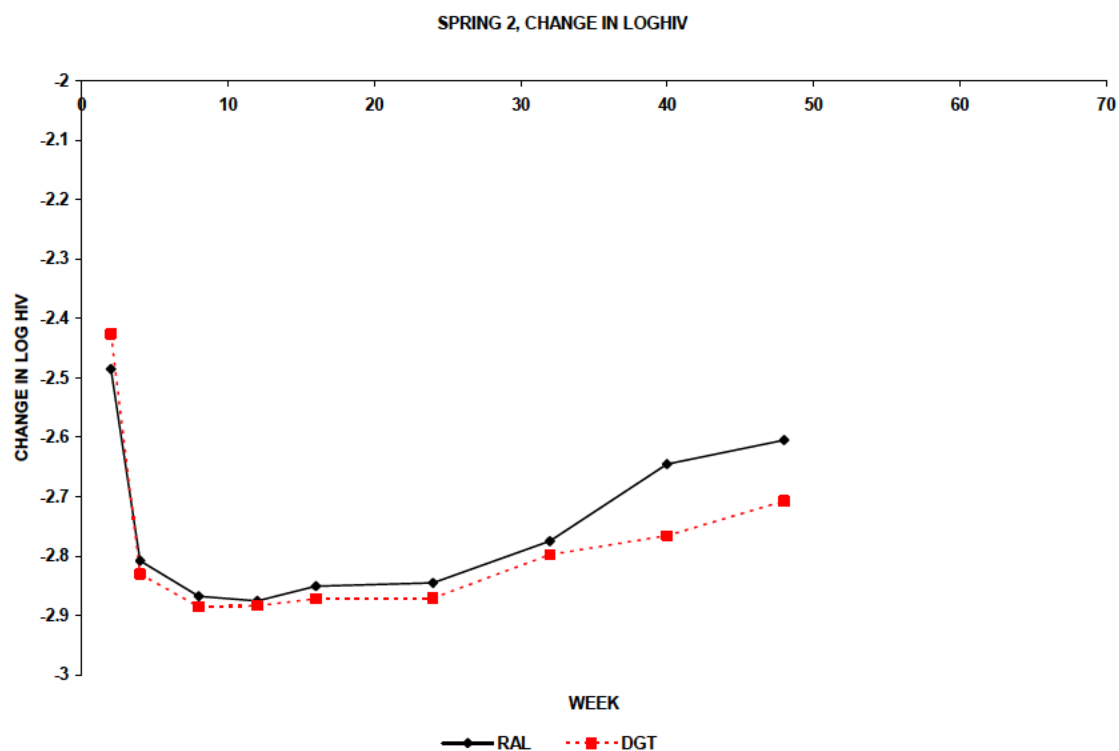
The next graph shows the percent BLQ over time in Spring 1. Interestingly, all three DTG doses seem to do equally well and do slightly, but not statistically significantly, better than EFV.



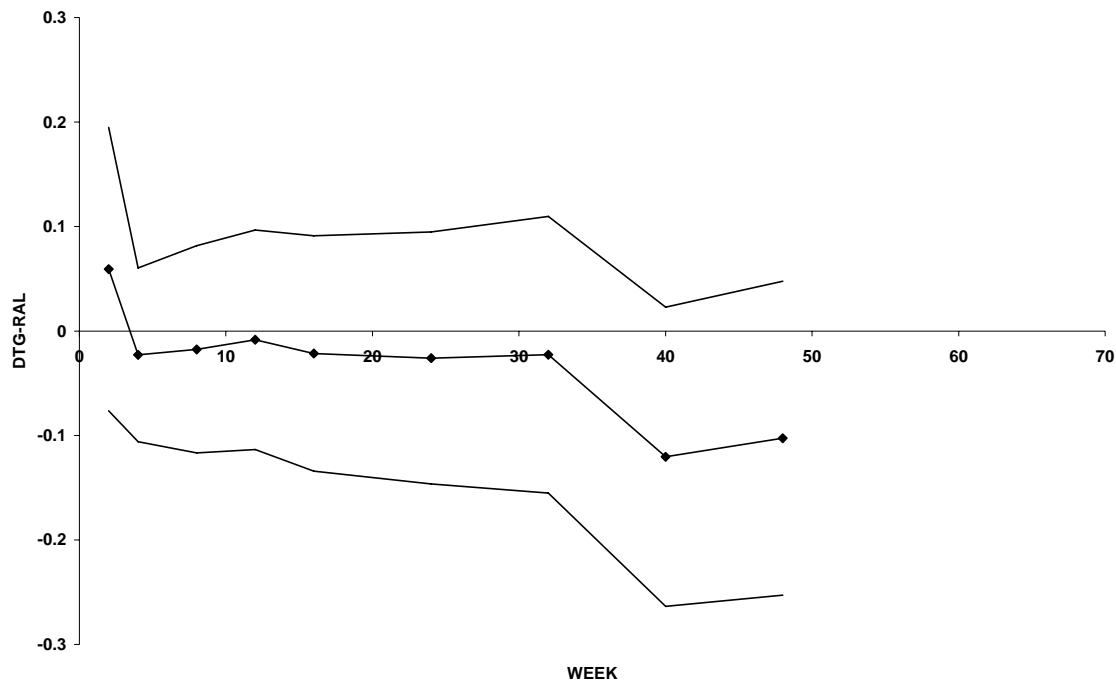
This graph gives the point estimates and 95% confidence limits for the difference between 50mg DTG and EFV in %BLQ. The lower bound is not quite  $>-10\%$  and thus not quite high enough for statistical non-inferiority.



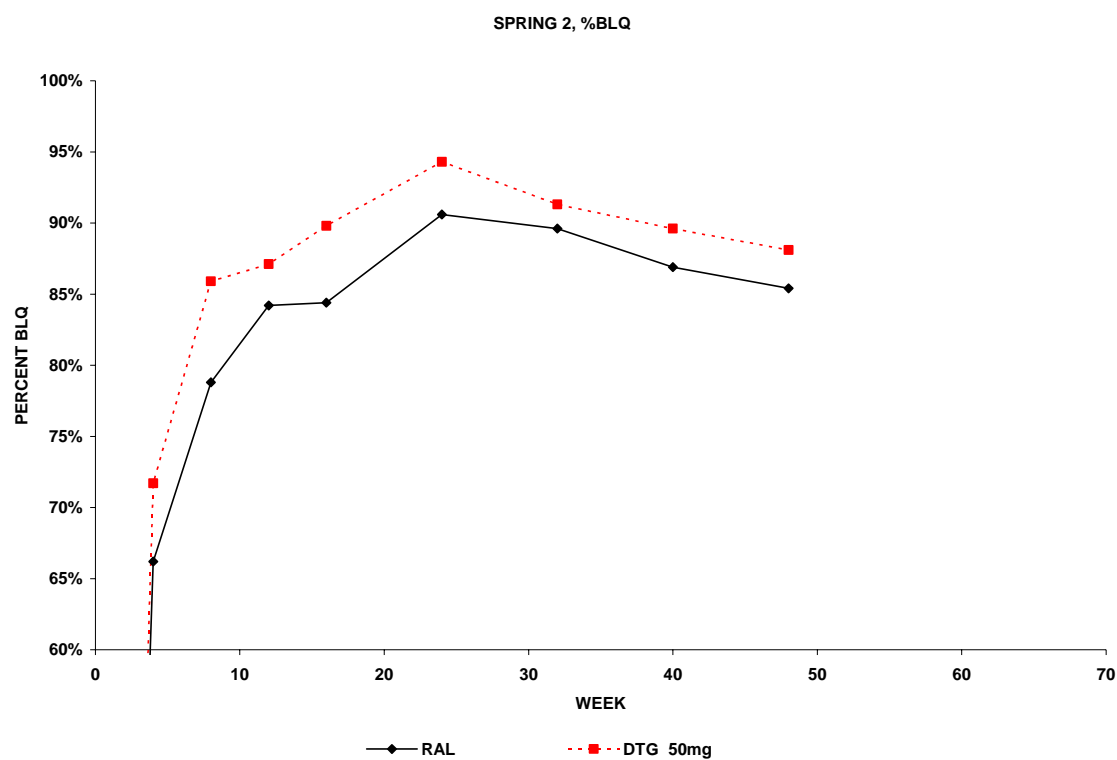
The next two graphs show the change in log HIV in the DTG and RAL arms of Spring 2 and the point estimates and 95% confidence intervals for the DTG-RAL difference in change in log HIV.



SPRING 2, CHANGE IN LOGHIV

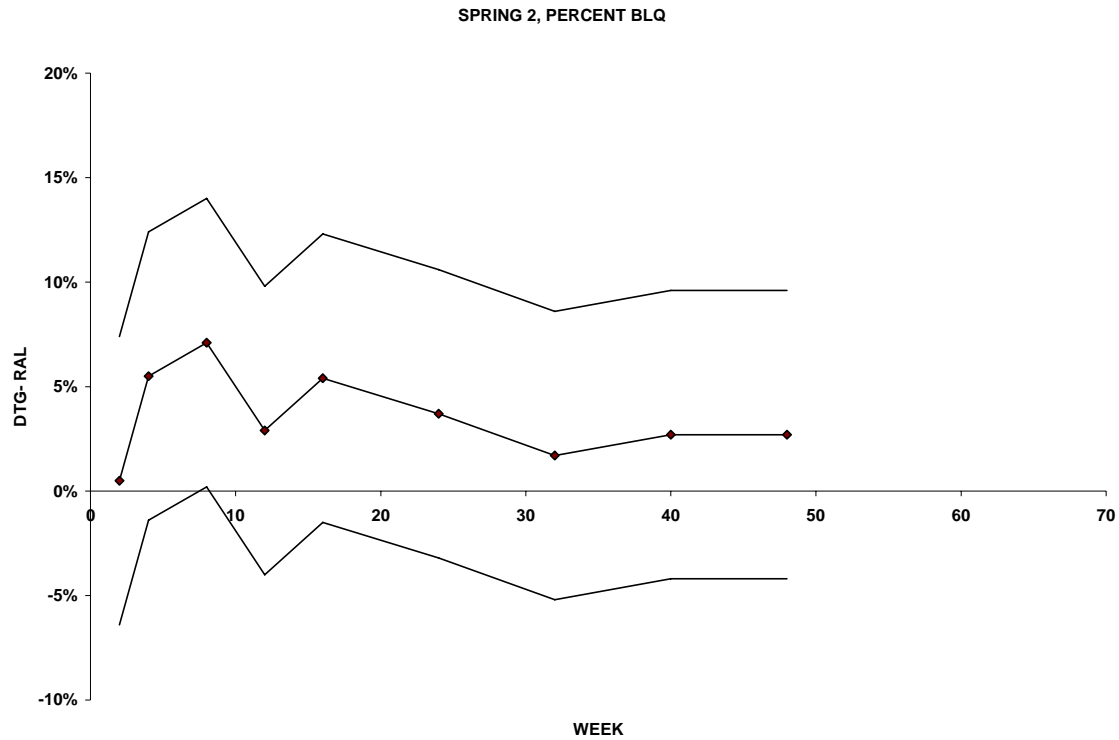


The next two graphs will show the %BLQ for the DTG and RAL arms in trial Spring 2 and the point estimates and 95% confidence limits for their difference.

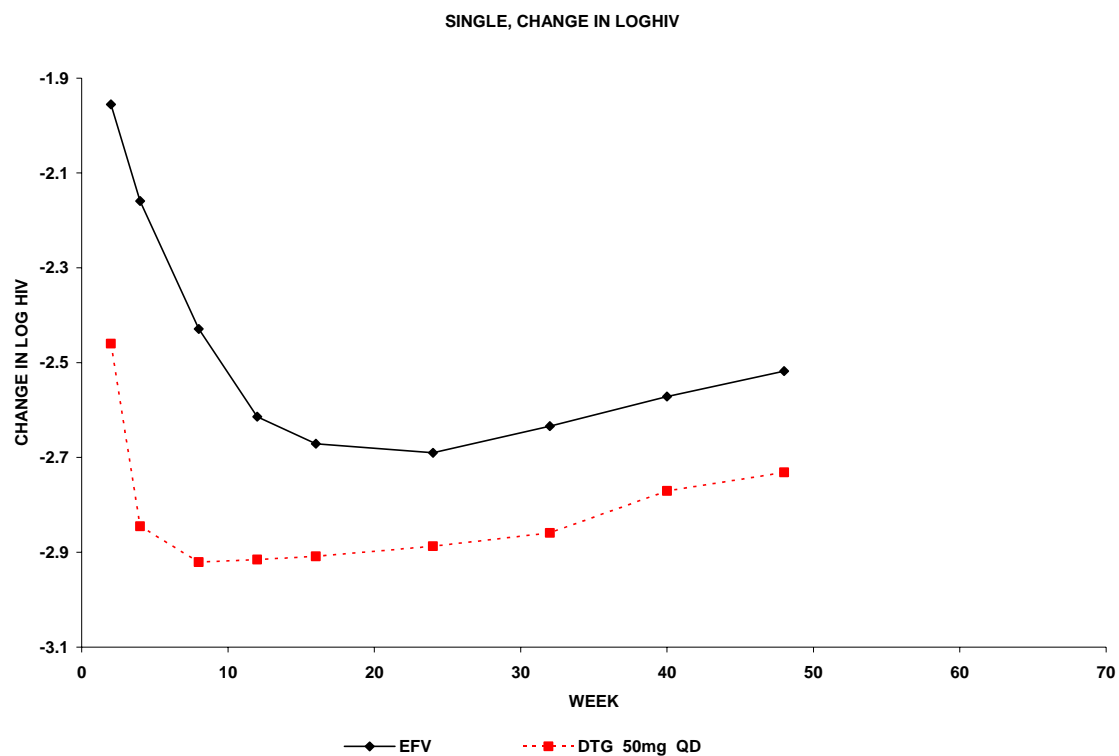




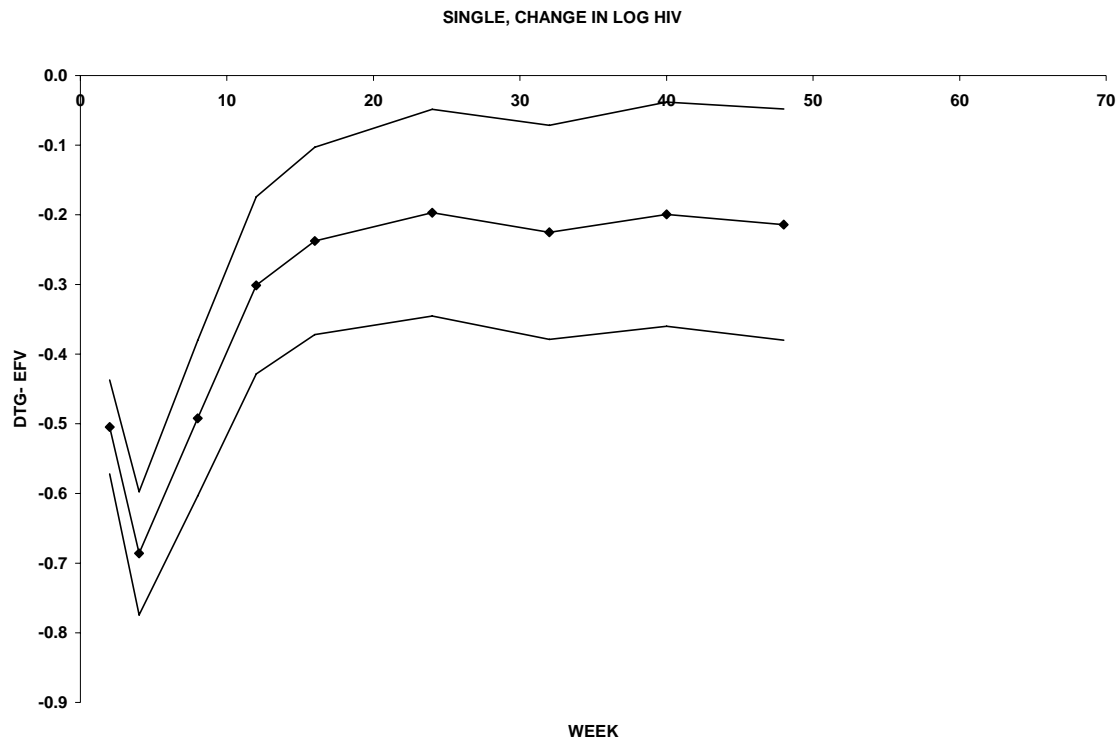
In this graph of the 95% confidence limits around the DTG-RAL difference, one does see that the lower bound exceeds -10%, providing statistically convincing evidence of non-inferiority throughout the first 48 weeks.

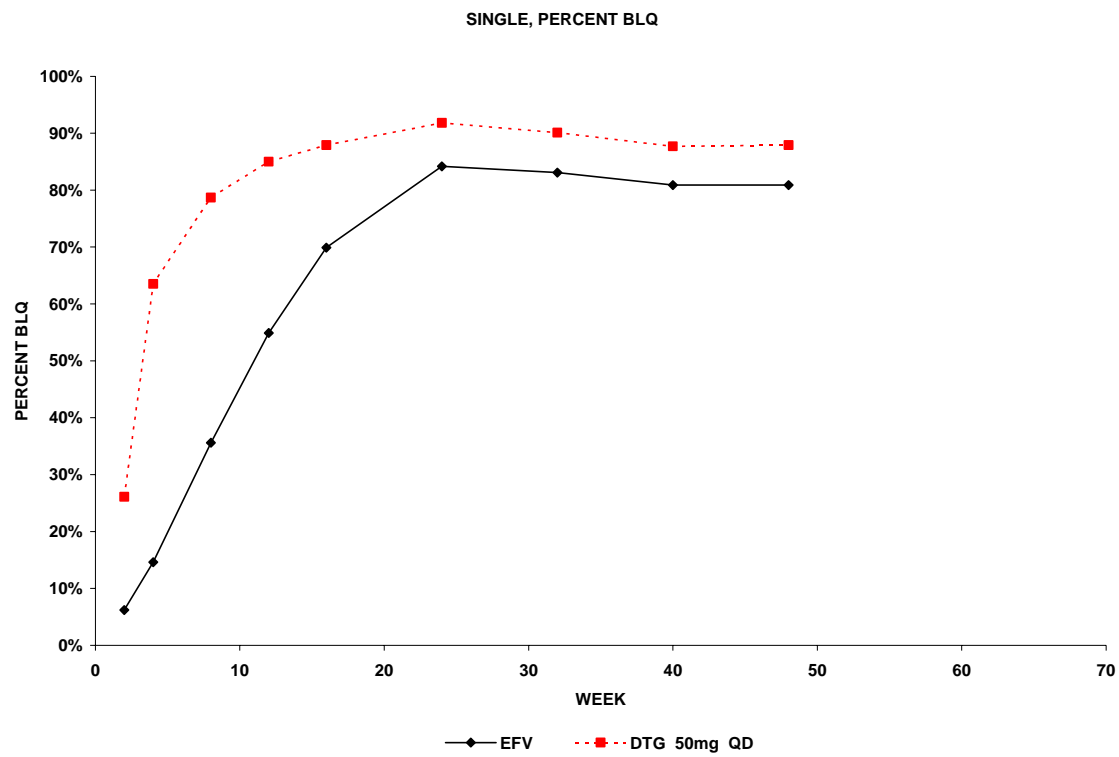


The next four graphs will repeat the previous four graphs for the other pivotal trial in treatment naïve subjects, Single. Change in log HIV and the 95% limits for change in log HIV are given first.

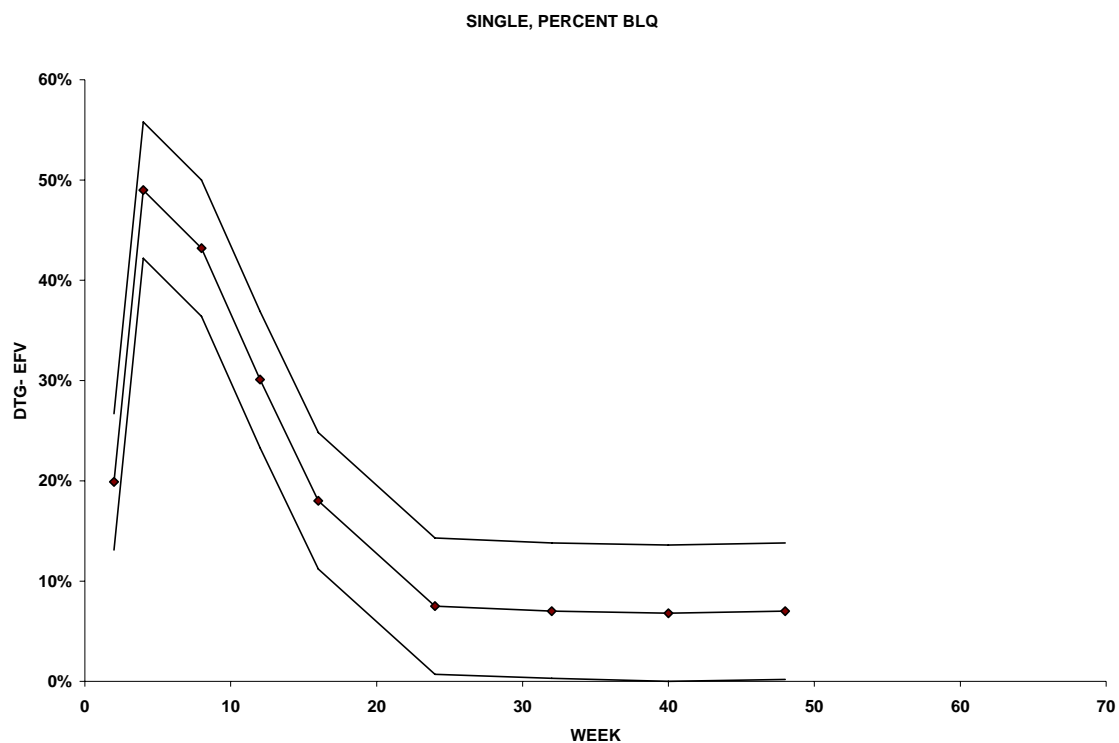


It is important to notice that the DTG 50mg QD arm was statistically significantly superior to the EFV arm throughout the first 48 weeks. Recall negative values in the difference correspond to larger decrease in viral load with DTG.



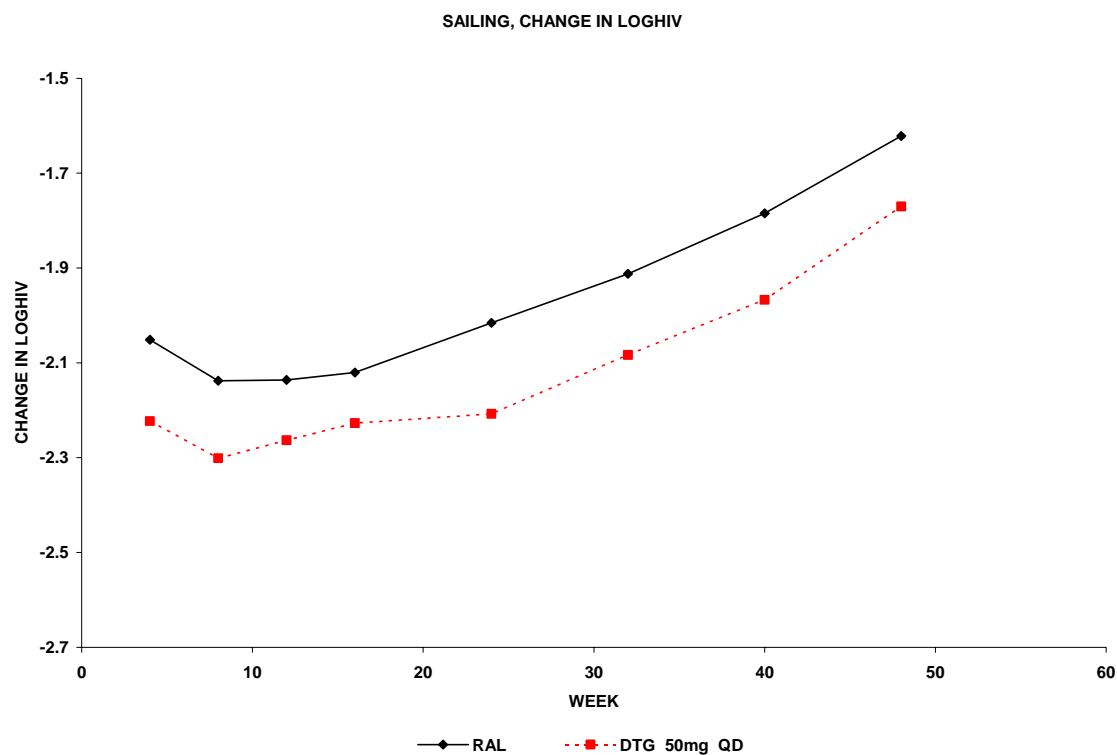


Again, the plot of 95% confidence limits for the difference in %BLQ shows a statistically significant superiority of DTG to EFV.

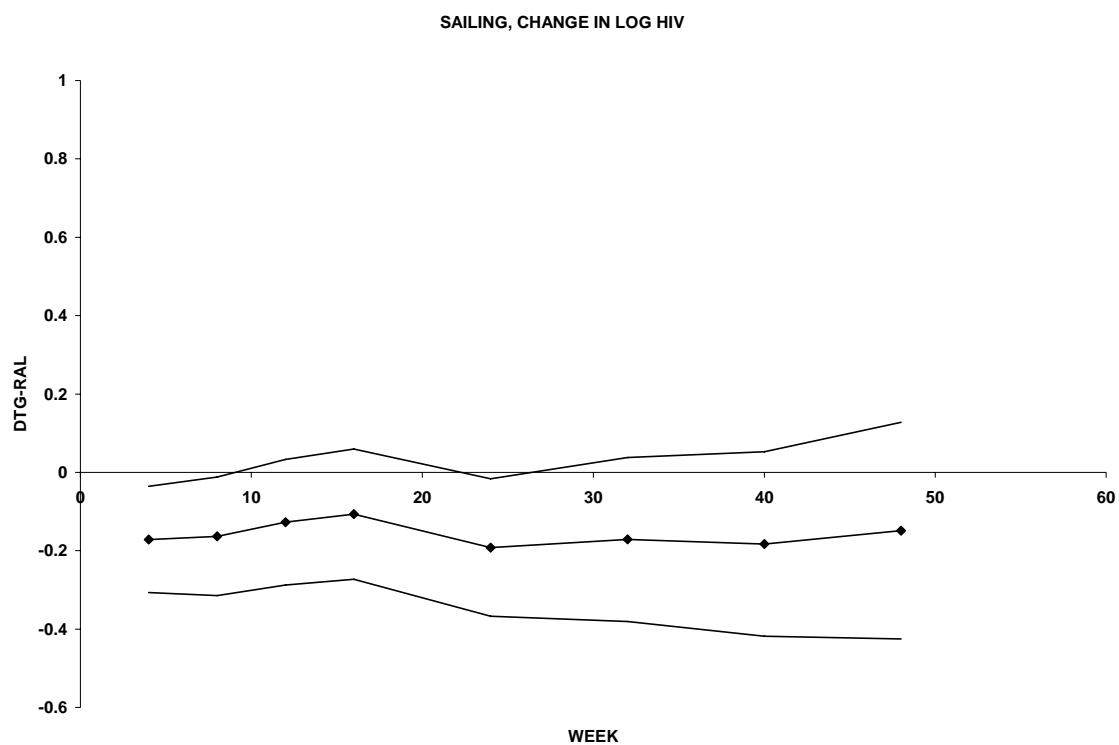


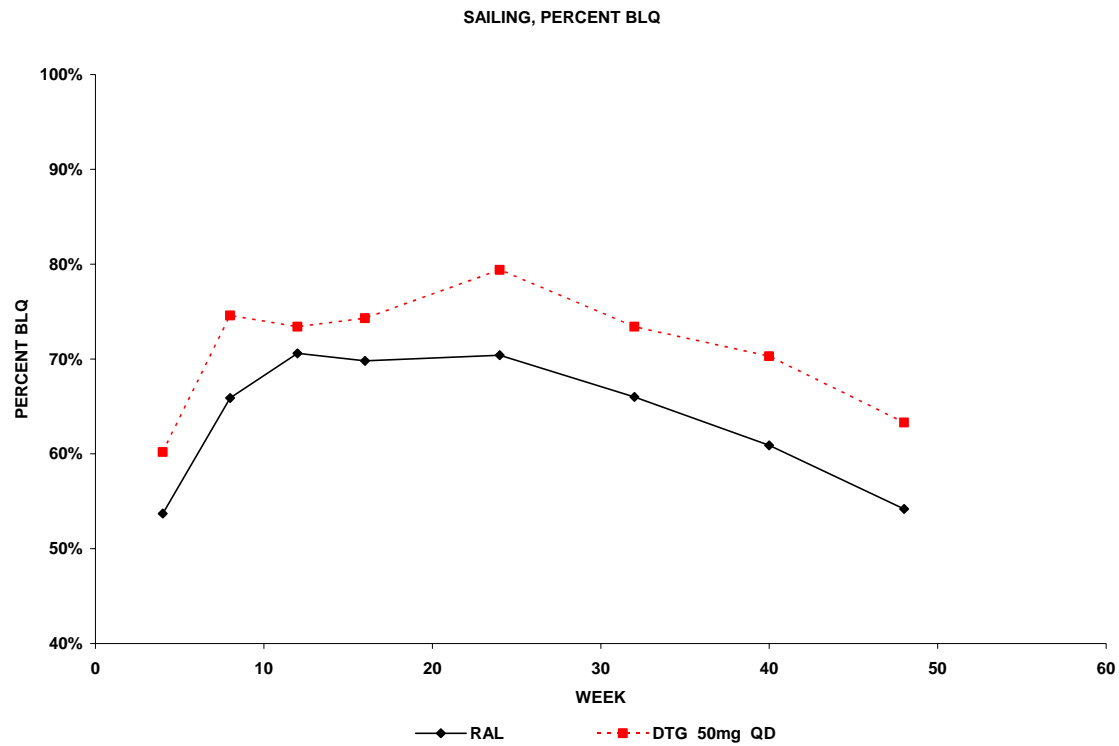
### 3.2.2 Two Class Resistant INI Naïve Trials

The next four graphs will give the time course of change in log HIV for DTG and RAL in the Sailing trial, the 95% confidence limits for the difference in change in log HIV, the %BLQ over time in both arms, and the 95% confidence limits for the difference in %BLQ.



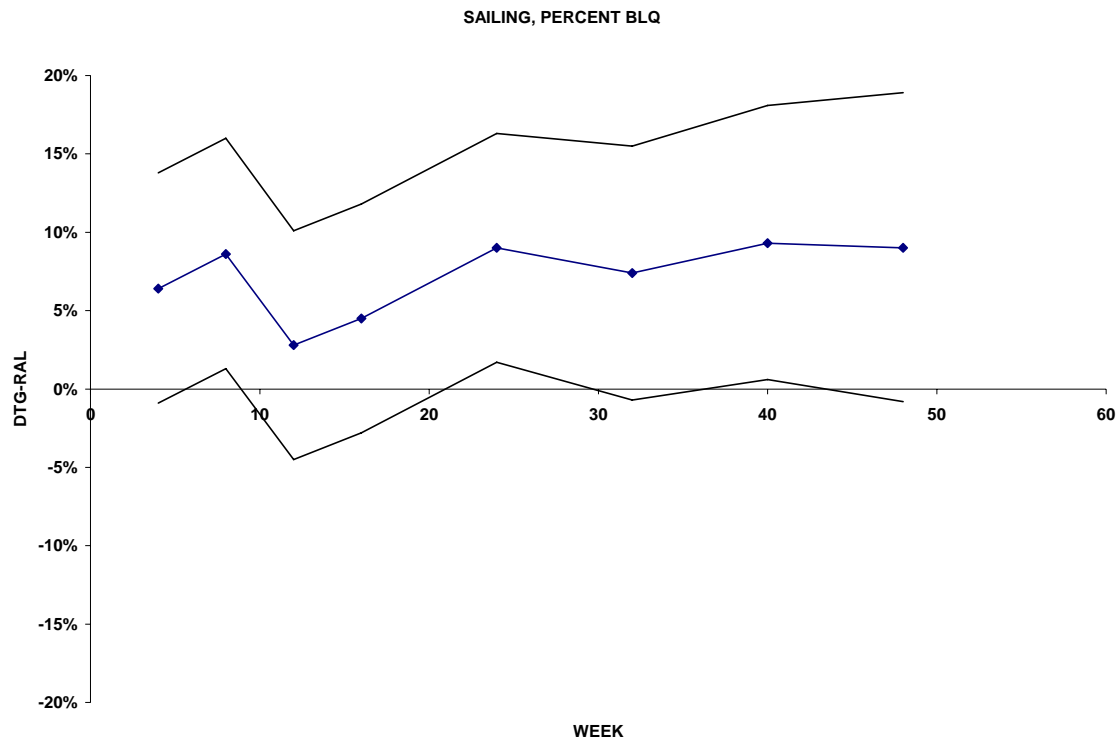
It is worth noting in this graph of the 95% confidence limits on the difference in the change in log HIV that the DTG 50mg QD arm is intermittently statistically significantly superior to the RAL arm.





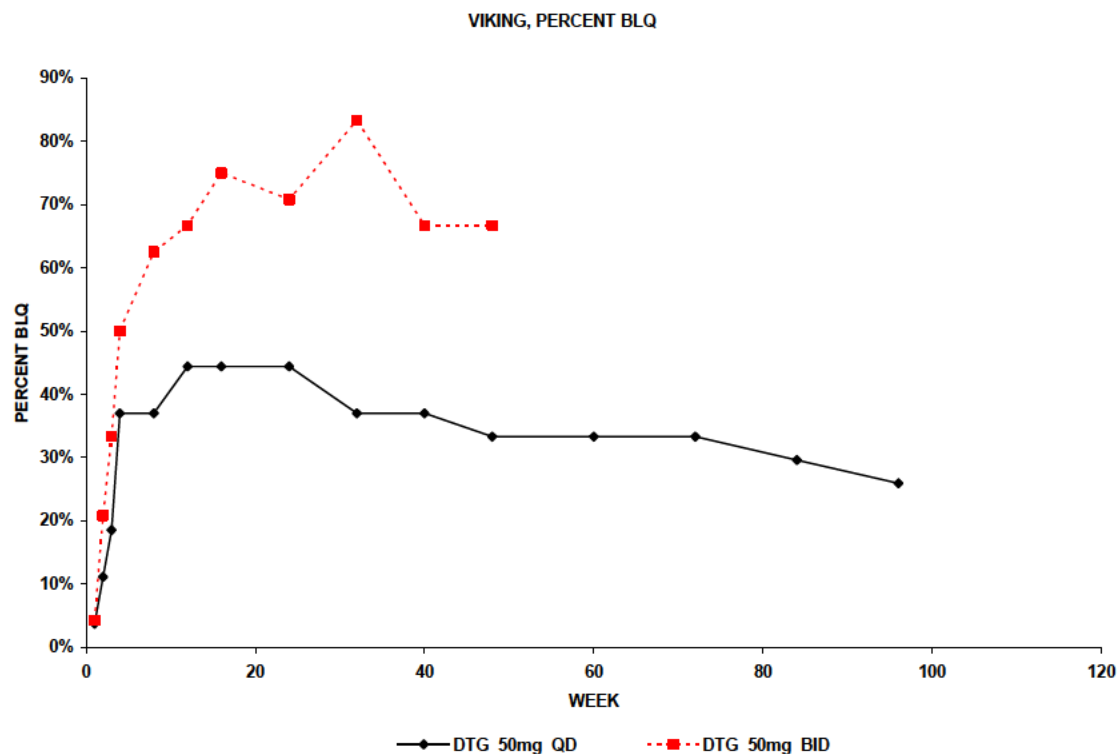


Again, it is important to notice that the DTG arm is almost statistically superior to the RAL arm throughout the first 48 weeks. The 95% lower bound for DTG-RAL is always comfortably above the non-inferiority margin of -10% and intermittently above the superiority margin of 0%.

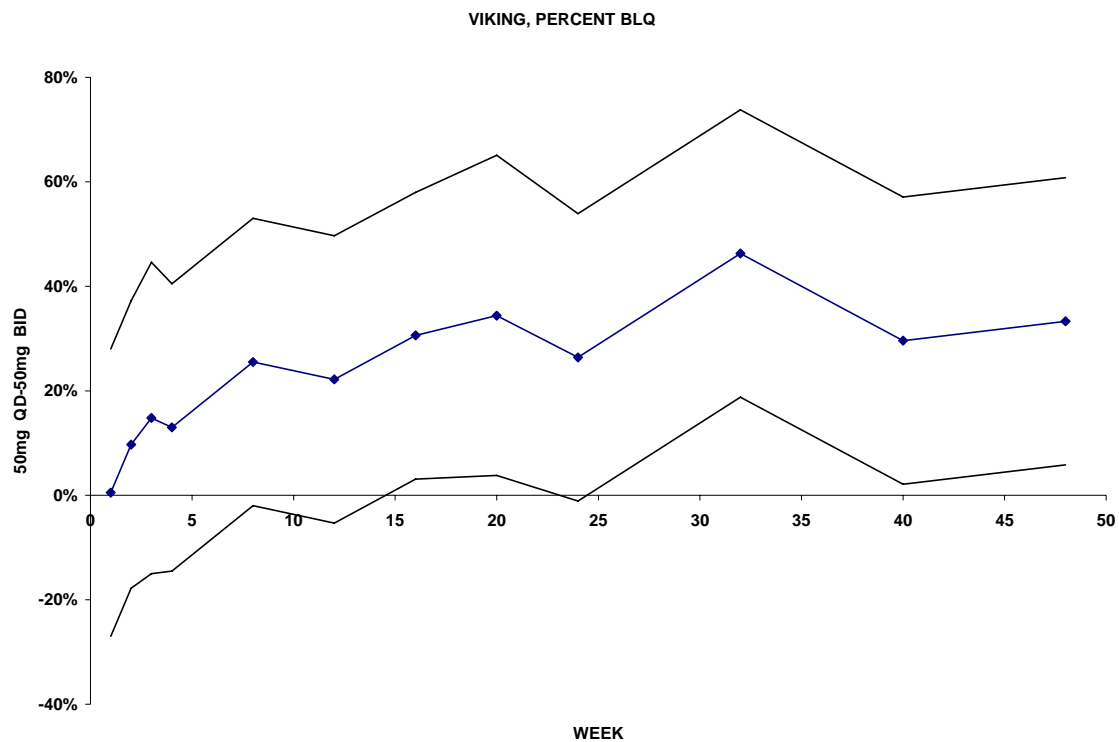


### 3.2.3 Two Class Resistant, INI Resistant Trials

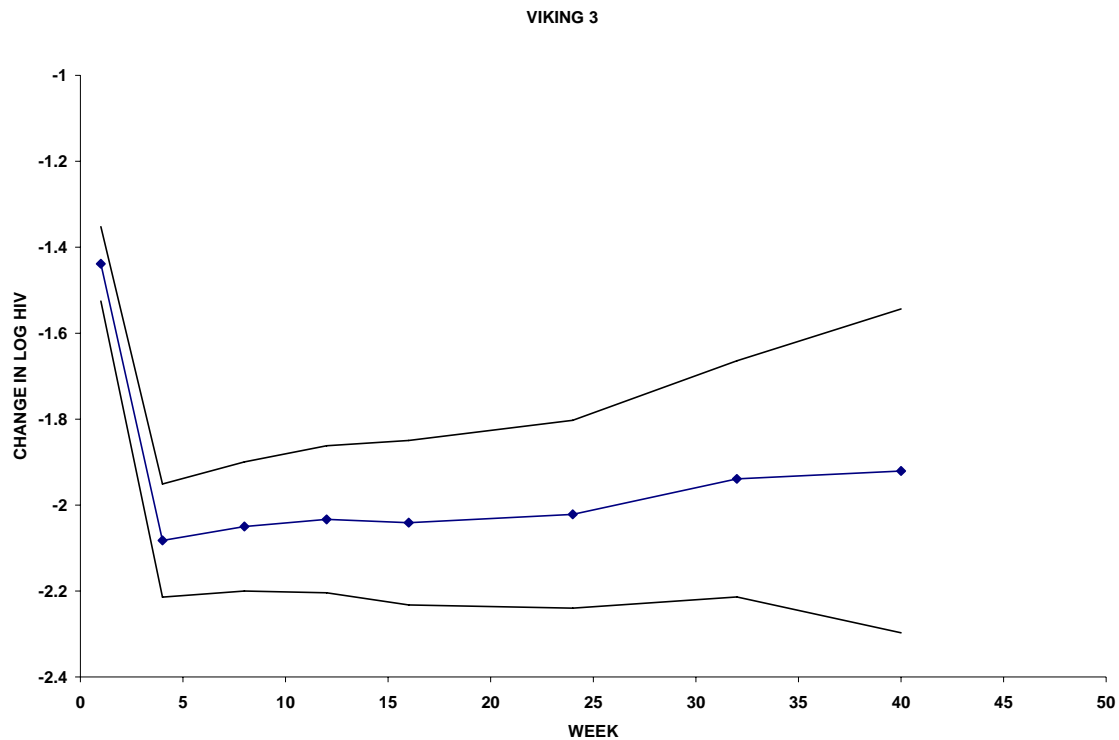
The first two graphs give the %BLQ in the two cohorts of the Viking trial, DTG 50mg QD and BID. Remember that these are enrolled sequentially and are not randomized. This accounts for the shorter duration of the observation of the BID cohort. Nonetheless, one will notice a much higher response rate in the BID cohort.



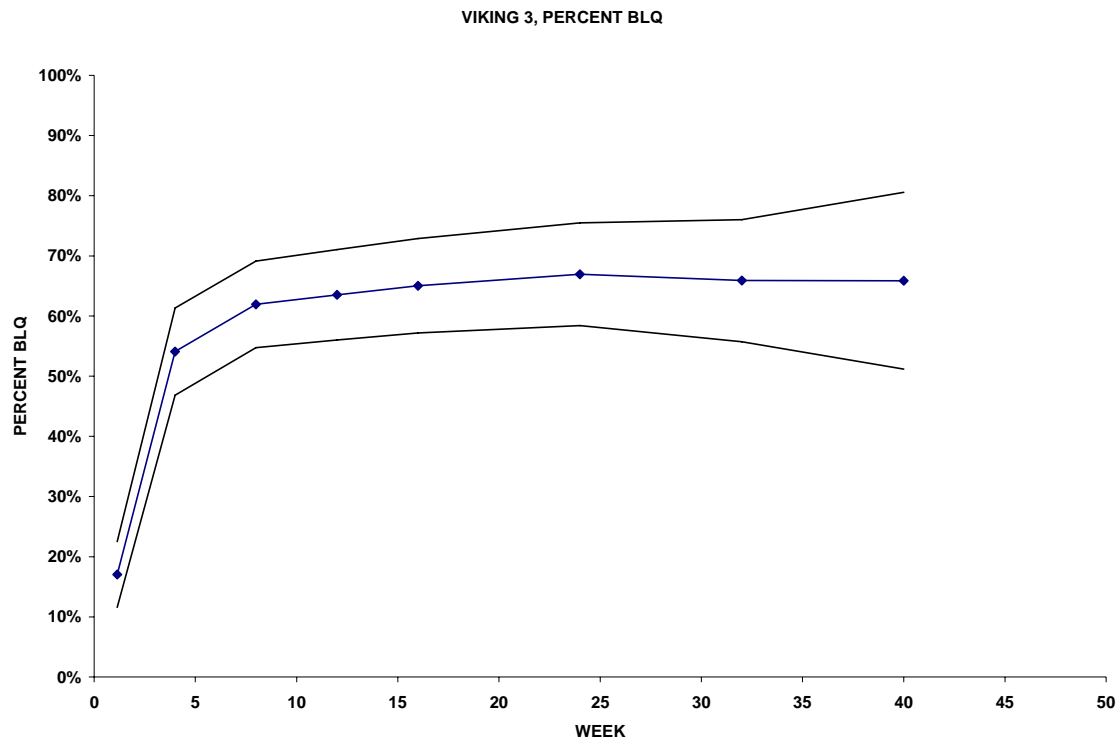
One will notice that the BID cohort (in a non-randomized but still statistically reasonable comparison) is very close to statistically significant superiority over the QD cohort. Given the non-randomized nature of the comparison, some checking for any differences in baseline covariates between the cohorts (see below) is desirable.



The last two graphs give the point estimates and 95% confidence limits for the change in log HIV and for the percent BLQ for the Viking 3 trial. The only comparator in this trial is constant zero so statistically significant superiority is achieved by confidence limits  $<0$  for log change and  $>0$  for percent BLQ. Both are clearly achieved comfortably throughout the period of observation.



In fact, one can see with both change in log HIV and percent BLQ, the magnitude of the improvement is comparable to what one expects from an effective three drug HAART regimen. This would suggest that even in this advanced population, one does not lose much in the way of efficacy even compared to first regimen on treatment naïve subjects.



### ***3.3 Effect of Covariates on Cohort Comparison in Viking***

One concern about the comparison of the BID and QD cohorts in the Viking trial is that these are sequential, non-randomized assignments. One is therefore still in doubt about the superiority of the BID regimen to the QD regimen. The FDA reviewer has examined those baseline covariate which are available and likely to be associated with response. The covariates examined included age, sex, baseline viral load, baseline CD4 count, and baseline fold change in IC50.

The FDA reviewer ran a logistic regression of percent BLQ on treatment (BID or QD), the selected covariate, and the interaction term or terms (for categorical covariates with more than two levels). The conclusion were as follows. The observed odds ratio for BLQ, comparing BID to QD, was 3.036. That is, the odds of a subject's being BLQ at week 24 when the subject was on the BID regimen were 3.036 times the odds of being BLQ on the QD regimen. When baseline covariates were included among the predictors of the logistic model, the fitted odds of being BLQ on the BID regimen varied between 2.098 and 3.486 times the odds of being BLQ on the QD regimen. In other words, the benefit was nearly the same, regardless of adjustment for covariates. None of the interaction terms in the fitted models were statistically significant (the smallest p-value was .17.)

### ***3.4 Change in CD4 Count***

The following graphs are intended to show that the pattern of change in CD4 count reflects the above demonstrated change in log HIV. Missing data in CD4 are treated differently from missing HIV data. Because CD4 count changes more slowly than HIV levels, missing CD4 data have been replaced by previous observation carried forward. In the Sailing and Viking trials, because all subjects have not reached the later time points, late missing data have been left missing.

One should observe these salient features in the following graphs. In the Spring 1 trial, all four doses of DTG are similar and slightly superior to EFV. However, there is not an apparent dose response relationship among the DTG doses as there was for HIV response. The observed superiority of DTG to EFV is close to, but not at, statistical significance.

The CD4 count for the DTG and RAL regimens in the Spring 2 trial are nearly identical. One can be reasonably confident that the DTG regimen is no more than 30-35 cells/ml worse than the RAL regimen.

In the Single trial, the DTG regimen is statistically significantly superior to the EFV regimen throughout the trial. This confirms the findings with the HIV endpoints in this trial.

In the Sailing trial in two class resistant subjects, the DTG and RAL CD4 responses are nearly identical, as was the case with the same drugs in naïve subjects (Spring 2 trial). One can be confident that the DTG regimen is no more than 20 cells/ml worse than the RAL regimen among the resistant subjects.

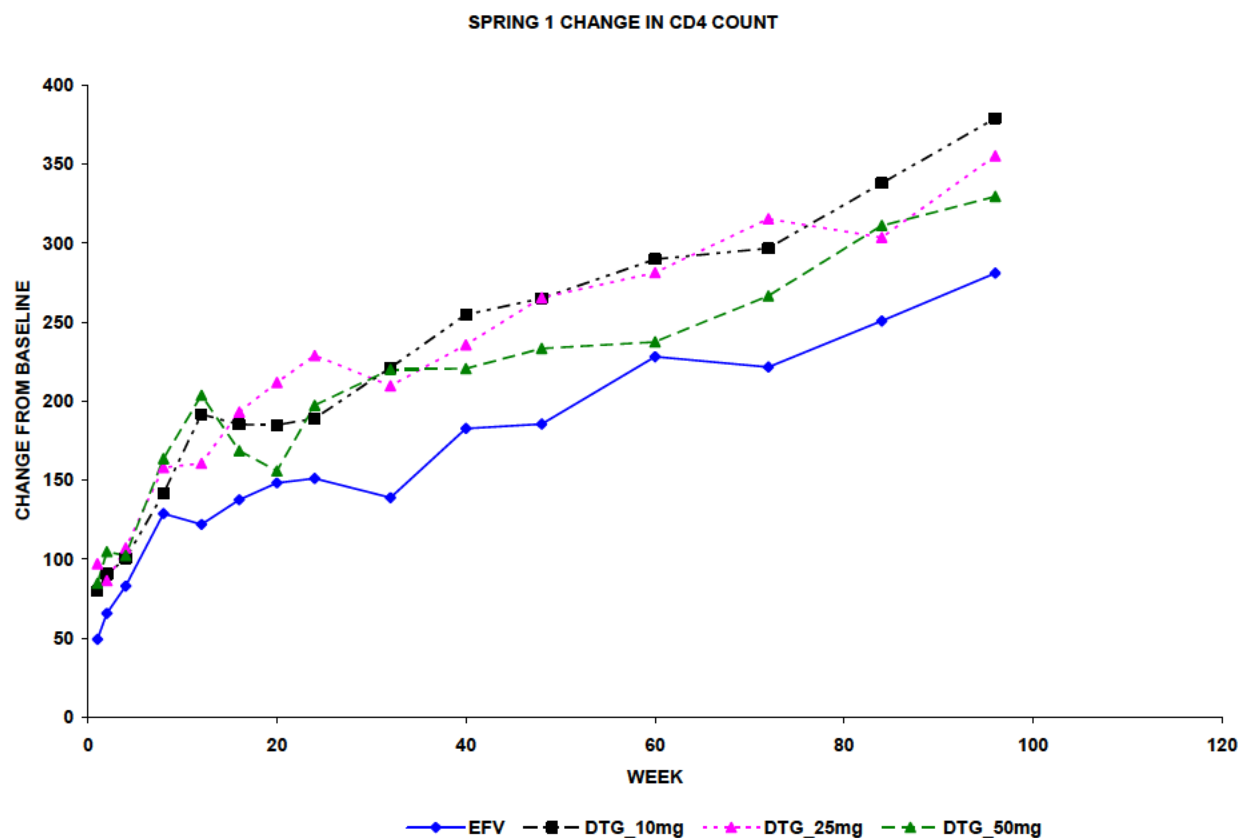
In the Viking trial, the separation between the two cohorts, BID and QD, was not as noticeable with respect CD4 count clear as was the case with the HIV endpoint. The statistical superiority of the BID regimen takes longer to emerge and is less clear with the CD4 endpoint than it was with the HIV endpoint. This may be due to the fact that CD4 count responds more slowly to effective treatment than does HIV.

In the one arm Viking 3 trial, one can be confident that this highly resistant population will experience a gain of at least 50-60 cells/ml in CD4 count with DTG at 50mg BID.

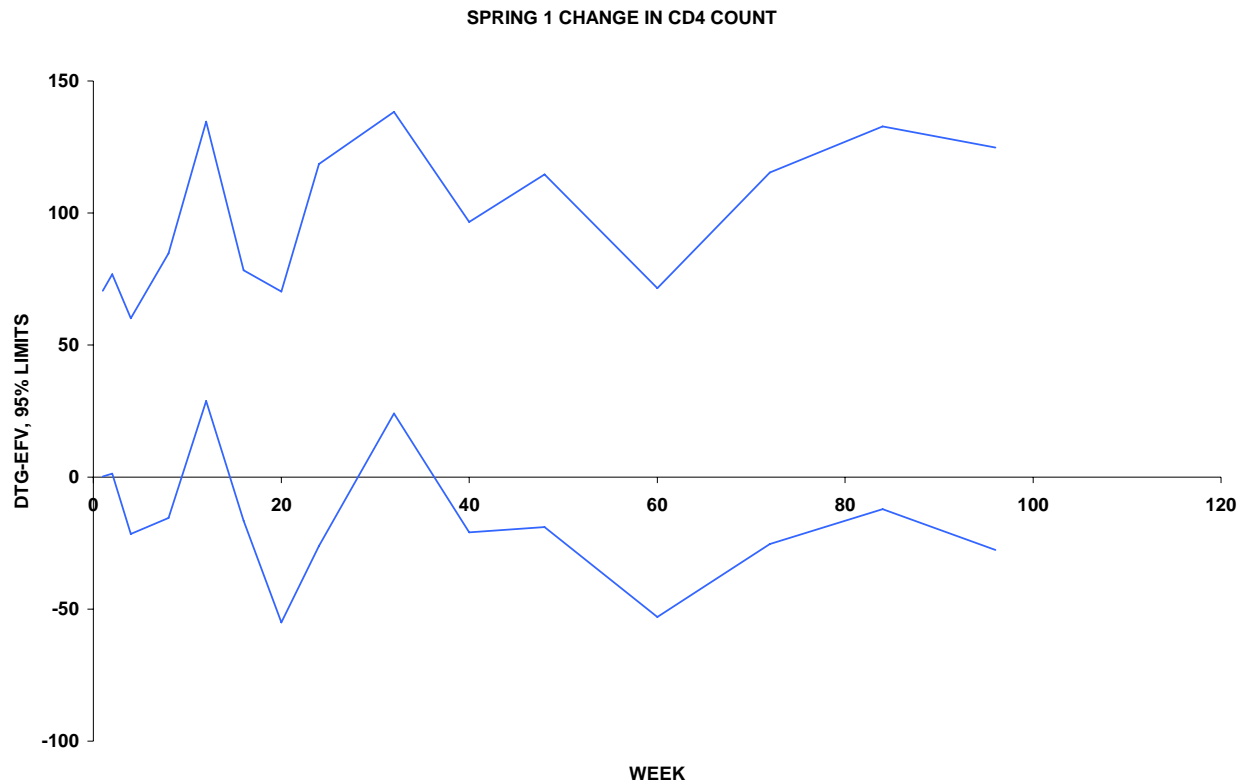


### 3.4.1 Treatment Naïve Trials

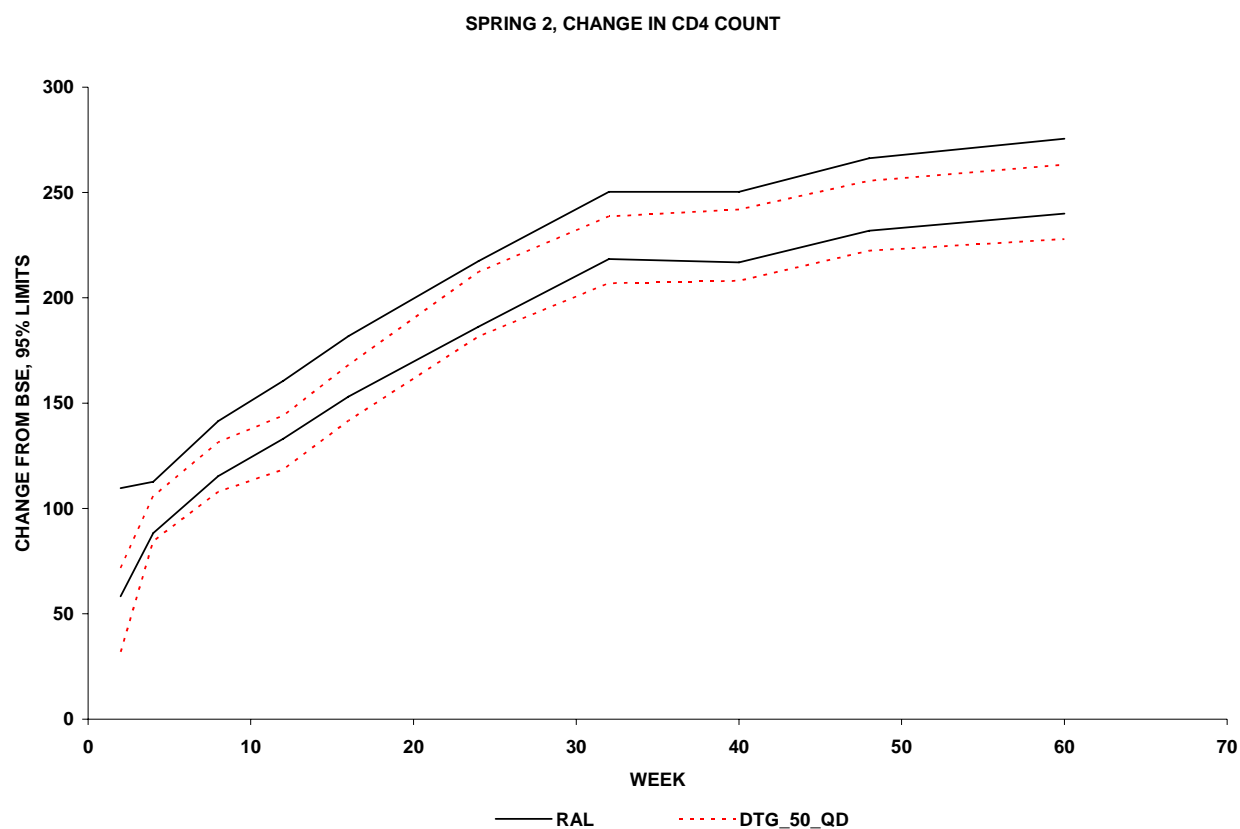
The first graph gives the change from baseline in all four arms of the Spring 1 trial. One will notice that all four doses of DTG are similar and slightly superior to EFV. There is not an apparent dose response relationship among the DTG doses as there was for HIV response.



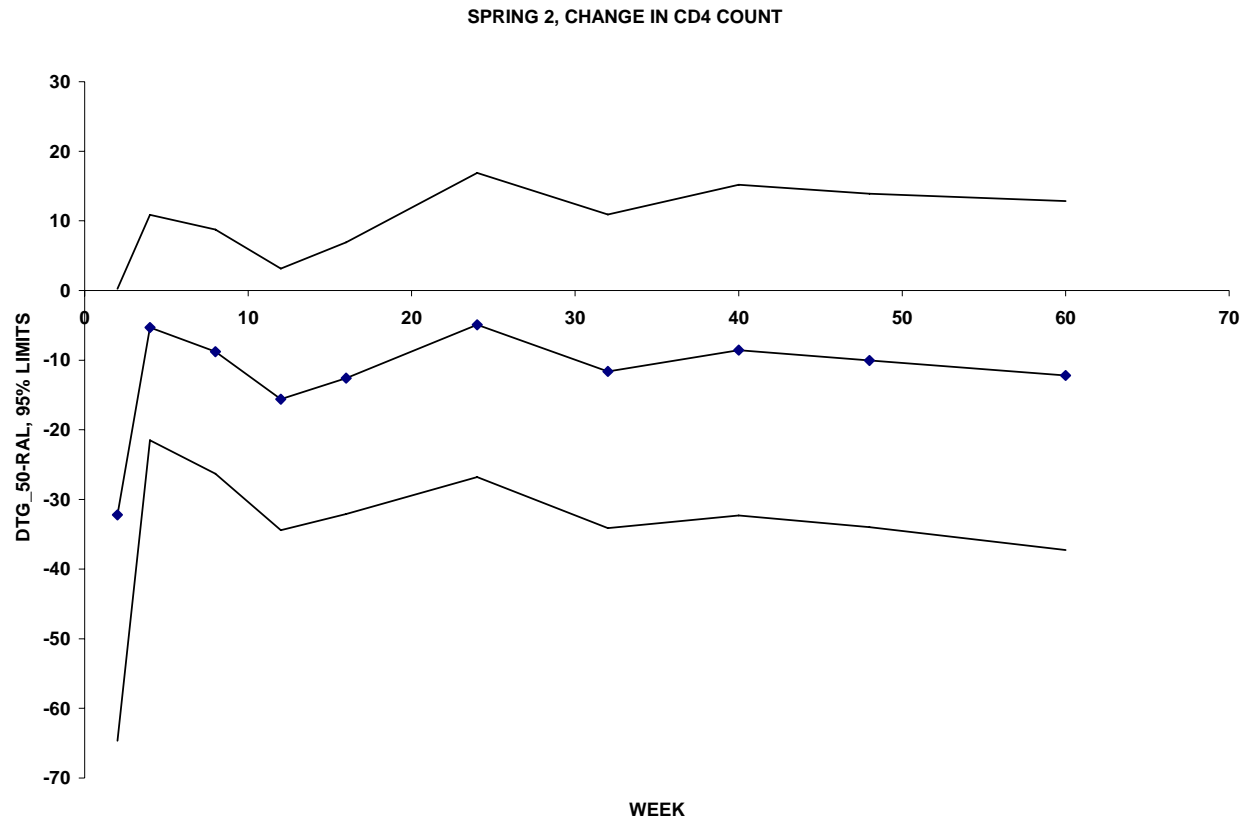
The second graph shows the 95% confidence limits for the difference DTG\_50mg - EFV on the change from baseline in CD4 count. One will notice that, as was the case with HIV, the observed superiority of DTG to EFV is close to, but not at, statistical significance.



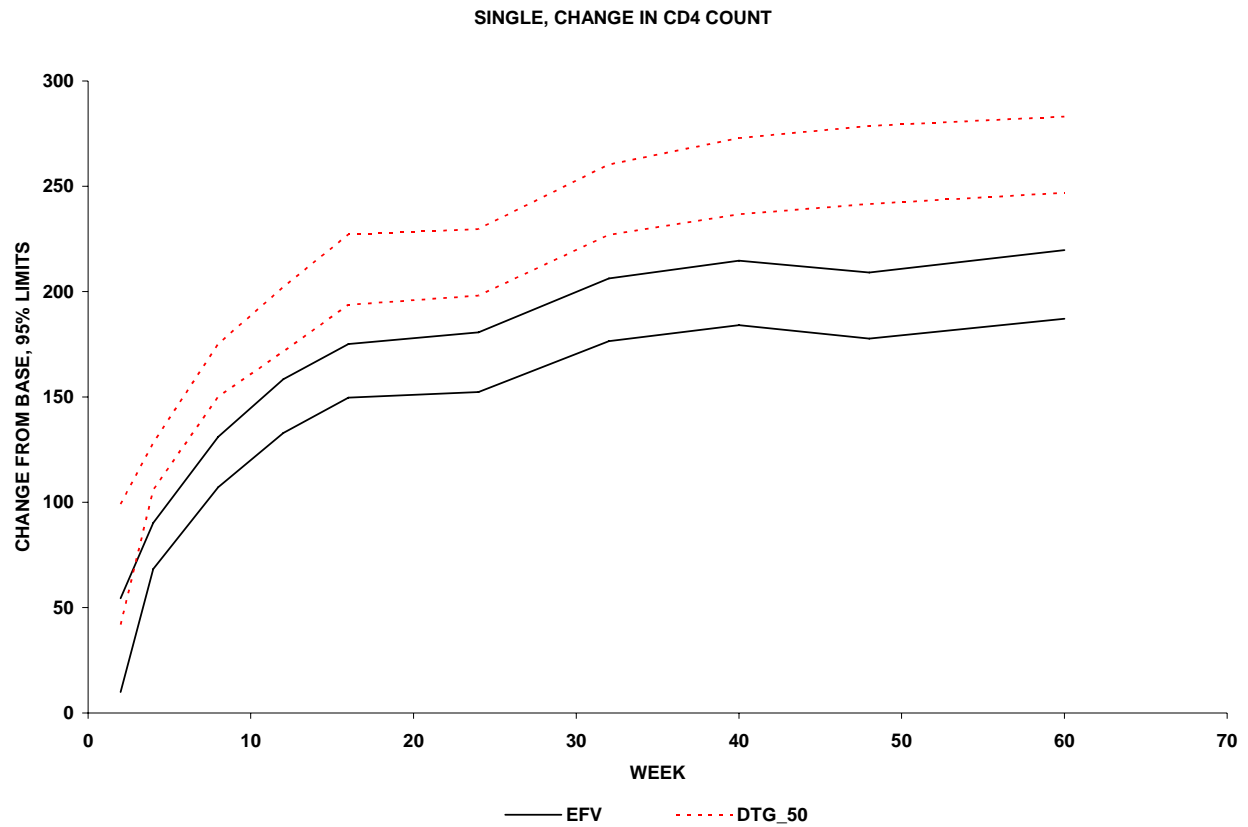
The next graph shows the 95% confidence bands for the change in CD4 count in the DTG and RAL arms of the Spring 2 trial. They nearly overlap perfectly.



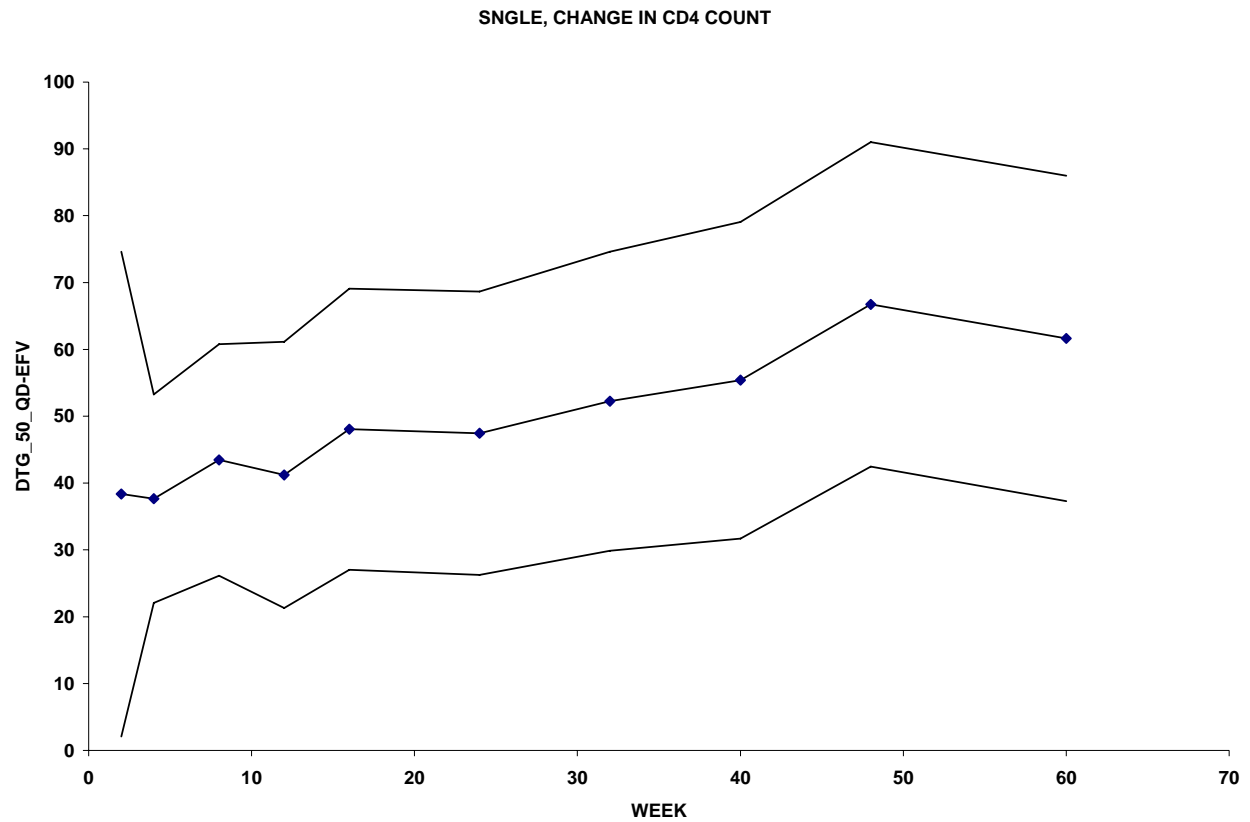
This graph shows the point estimate and 95% confidence limits for the difference, DTG-RAL, in change in CD4 count in the Spring 2 trial. One can be reasonably confident that the DTG regimen is no more than 30-35 cells/ml worse than the RAL regimen.



This graph shows the 95% confidence bounds for the change in CD4 count in the DTG and EFV arms of the Single trial. One will notice that the bands do not overlap and that the DTG regimen is superior.

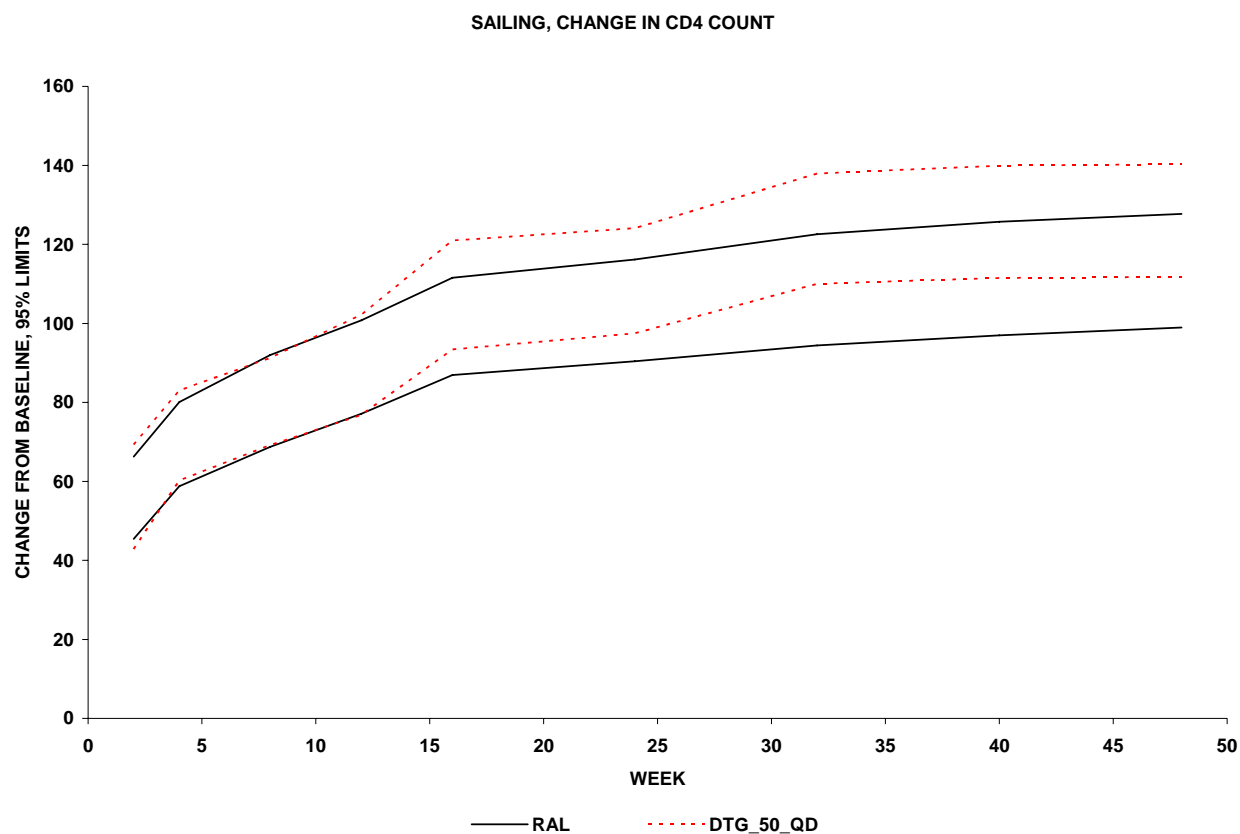


This graph gives the point estimate and 95% confidence limits for The difference, DTG-EFV, in change in CD4 count in the Single trial. The DTG regimen is statistically significantly superior throughout the trial. This confirms the findings with the HIV endpoints in this trial.

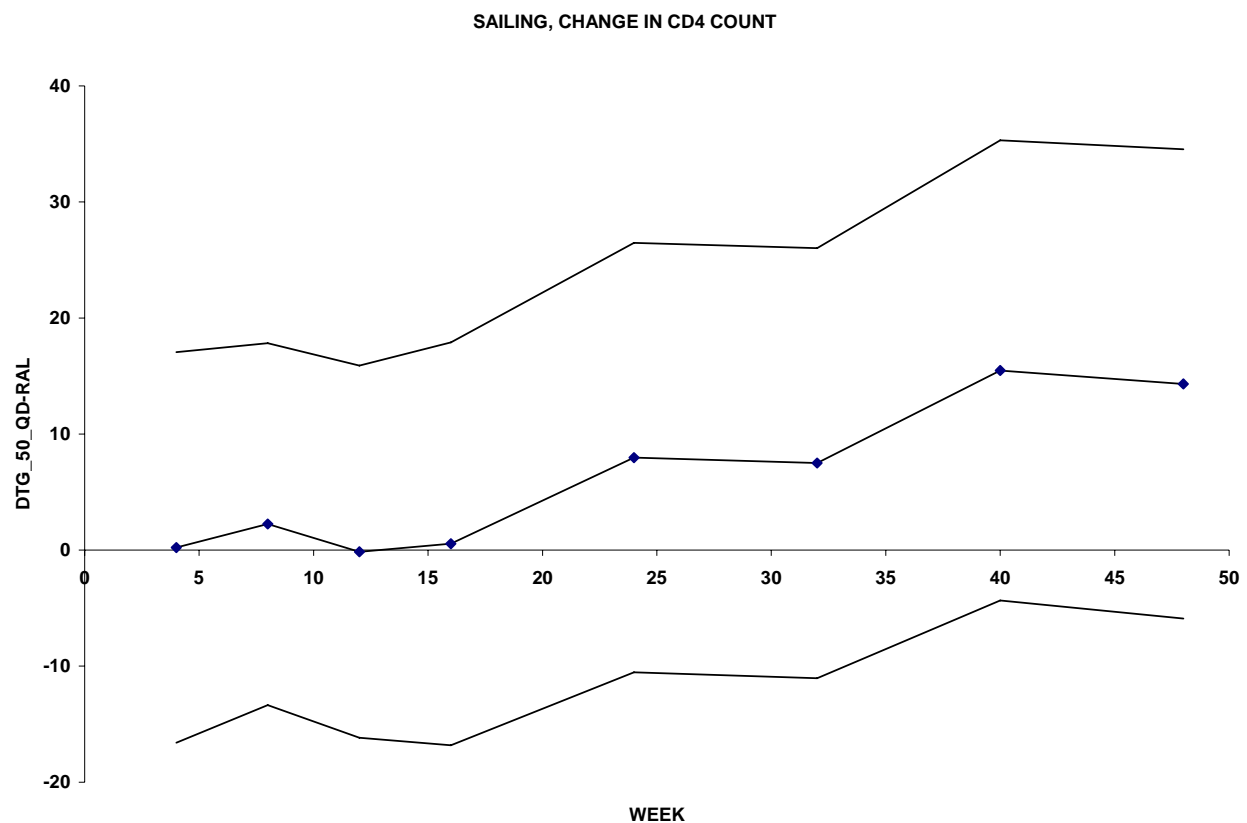


### 3.4.2 Two Class Resistant INI Naïve Trial

This graph shows the 95% confidence bounds for the change in CD4 count in the DTG and RAL arms of the Sailing trial in two class resistant subjects. As was the case with DTG and RAL in naïve subjects (Spring 2 trial), the bands nearly overlap.



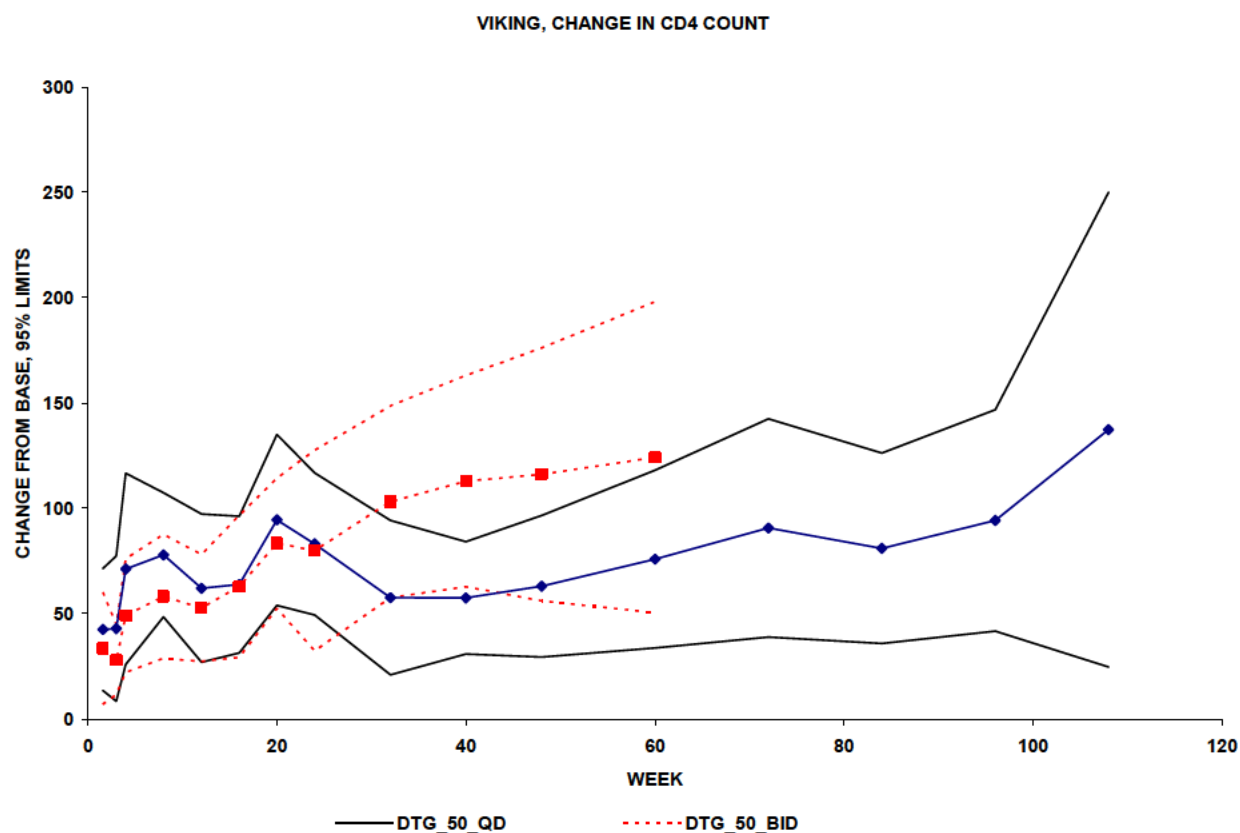
This graph shows the point estimate and 95% confidence limits for the difference, DTG-RAL, in change in CD4 count. As was the case in the Spring 2 trial and with the HIV endpoints in this trial, there is no statistically confirmed difference. Nonetheless, one can be confident that the DTG regimen is no more than 20 cells/ml worse than the RAL regimen.



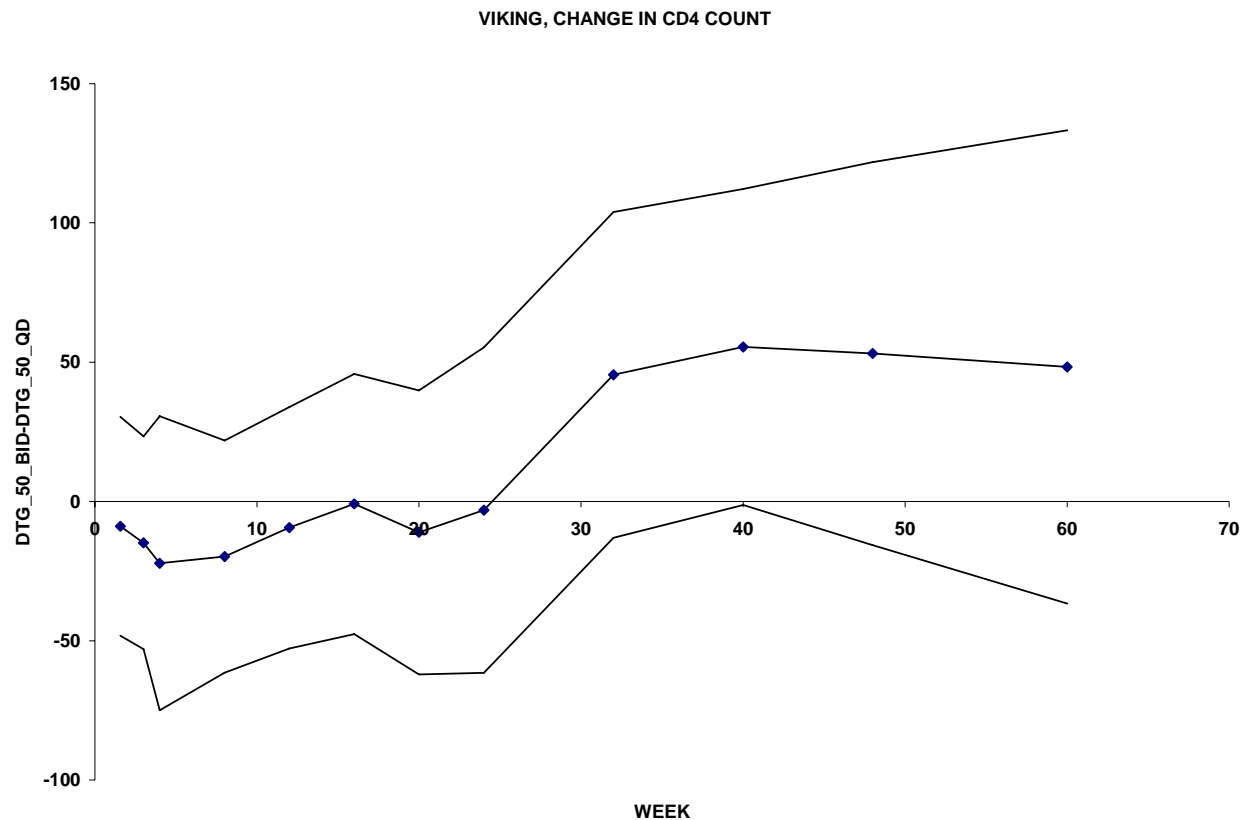


### 3.4.3 Two Class Resistant, INI Resistant Trials

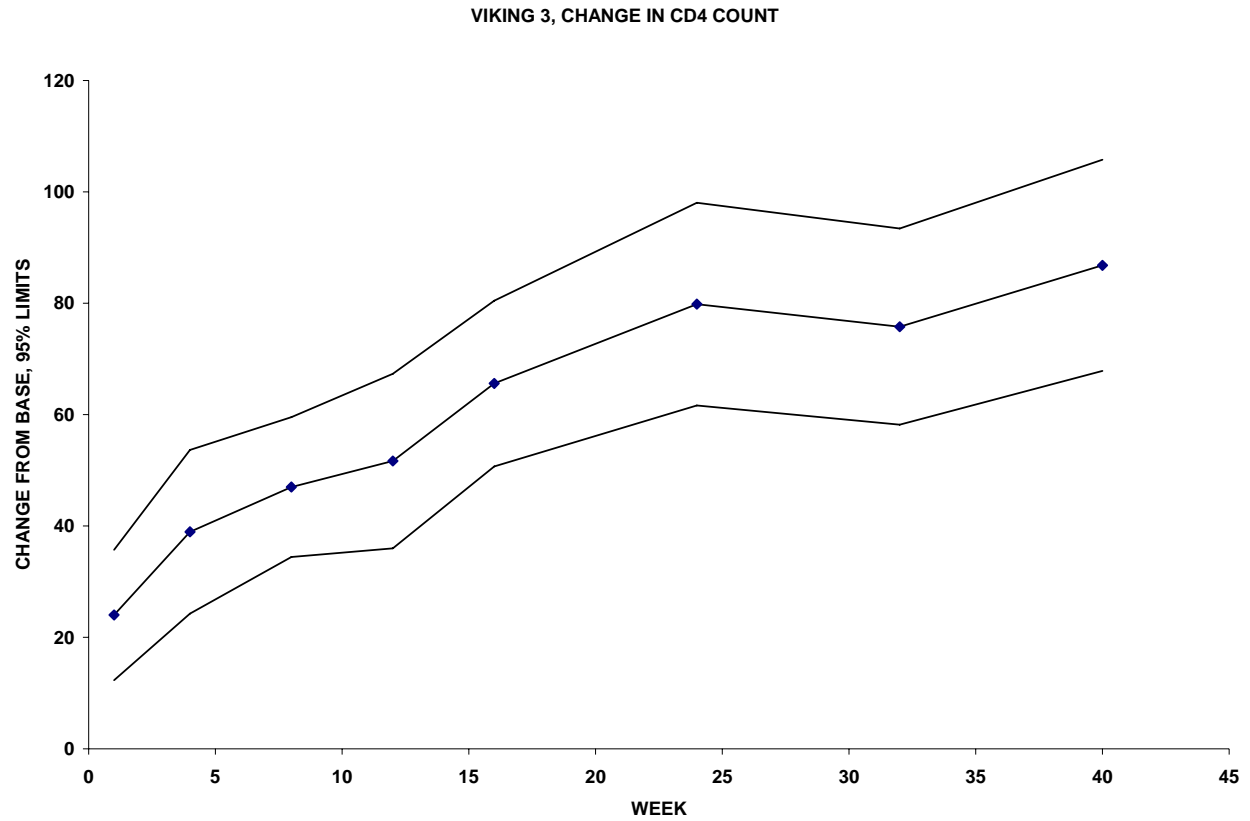
This graph shows the point estimate and the 95% confidence bounds for the two cohorts, DTG\_50mg BID and QD, in the Viking trial. Because the QD cohort was recruited earlier, the band for that cohort extends later. Looking only at the 95% bands, the separation between the two cohorts is not as clear as was the case with the HIV endpoint. Therefore, this graph also includes the point estimates where one can see the beginnings of the separation.



This graph shows the point estimate and 95% confidence bounds for the difference, BID-QD, in change in CD4 count for the Viking trial. (Notice that the x-axis in this graph stops where the BID cohort stopped in the previous graph. The x-axis in that graph extended further.) The statistical superiority of the BID regimen is less clear with the CD4 endpoint than it was with the HIV endpoint. This may be due to the fact that CD4 count responds more slowly to effective treatment than does HIV.



This last graph shows the point estimate and 95% confidence bounds for the change in CD4 count on the DTG\_50mg BID in the one arm Viking 3 trial. There is nothing (other than constant zero) to compare the DTG to in this trial. Nonetheless, one can be confident that this highly resistant population will experience a gain of at least 50-60 cells/ml in CD4 count with DTG at 50mg BID.



### 3.5 *Change in Lipids*

These tables contain the analyses of lipids for the trials Spring 2, Single, and Sailing. The site run by Kozyrev has been excluded from the Spring 2 and Sailing tables. The tables give the lipid levels for cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides, in mg/dl by visit. For each lipid and each visit, the FDA reviewer computed the mean lipid level for each arm (DTG or RAL in Spring 2 and Sailing, DTG or EFV in Single). Also computed were the difference mean cholesterol between the two arms (DTG-control), and the upper and lower 95% confidence limits for the difference. Finally, the sample sizes in each arm age also given.

Missing values have been dealt with in four ways. The first computation uses just the observed cases, with data collected from subjects who started a lipid lowering agent being discarded after the start of that agent. The second computation uses last observation carried forward (LOCF) from time of last visit or last visit prior to start of lipid lowering agent.

The FDA reviewer was concerned that both of these methods may be flawed. Potential problems include the possibility that subjects with the worst lipid problems may start lipid lowering agent that mask their continued worsening and that subjects dropping out for safety or lack of efficacy may also perform differently from those who continue their regimen without change. The third and fourth computations give two tentative attempts to adjust for these problems. The third computation found the change in lipid level between the last and penultimate visits and added that change to the last observation for each subsequent missed visit. The fourth computation was similar except that instead of adding the last change to the last visit, it added the average of the change between the last and the penultimate visit and the change between the penultimate and ante-penultimate visits. To clarify how this computation was done, consider the following subject. The observed data are as follows.

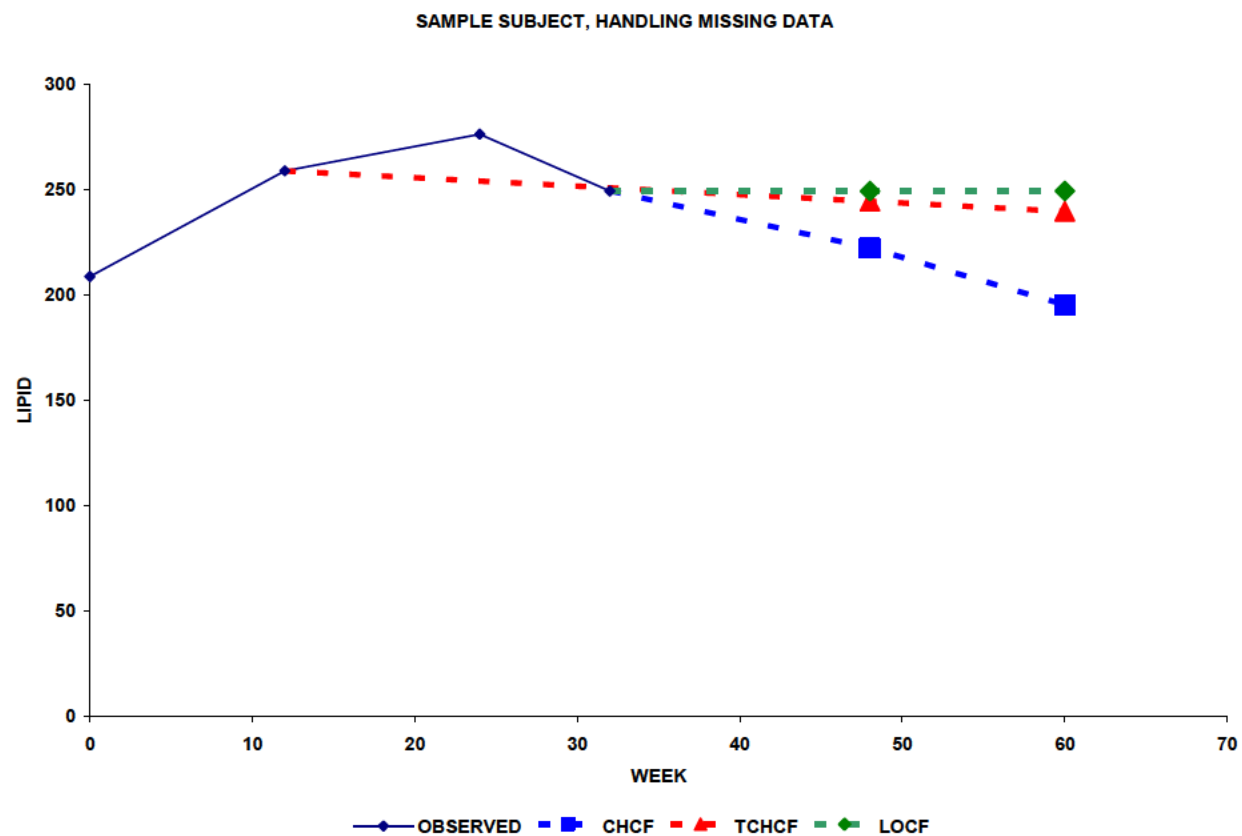
VISIT	CHOL
DAY_1	208.817
WEEK_12	259.087
WEEK_24	276.489
WEEK_32	249.420
WEEK_48	.
WEEK_60	.

The last change is  $-27.07 = 249.42 - 276.489$  and the next to last change is  $+17.4 = 276.489 - 259.087$ . The average of the last two changes is thus  $(17.4 - 27.07) / 2 = -4.83$ . This yields the following imputed values for the last two missing observations:

	LOCF	CHANGE_CF	TWO_CHANGE_CF
WEEK_48	249.420	222.351	244.586
WEEK_60	249.420	195.282	239.753

LOCF is just 249.42 for both values, the CHANGE\_CF assumes that there would have been a further change of  $-27.07$  at each of the next two visits; the TWO\_CHANGE\_CF assumes that there would have been a further change of  $-4.83$ , on average, over each of the next two visits.

The logic of these last two methods is that if lipid was changing at the time of drop-out, it would have continued to change in a similar manner if the regimen had been continued unchanged and measurements had actually been collected. One method just uses the last change observed, the second assumes that the average change over the last three visits is a better estimate of the continuing change. The three methods of extrapolating missing data for the above subject are illustrated graphically here. The solid lines are the observed data; the dotted lines and heavy squares, diamonds, triangles are the extrapolated values.



In the tables below, the four different methods of dealing with missing data are presented in succession for each of the four lipids. After that, the same computations are presented with the change from baseline. Thus the sequence of computations is weekly cholesterol, weekly HDL, weekly LDL, weekly triglycerides, change from baseline in cholesterol, change from baseline in HDL, change from baseline in LDL and change from baseline in triglycerides. This sequence is repeated for each trial: Spring 2, Single, Sailing.

# SPRING\_2\_CHOLESTEROL\_OBSERVED

VISIT	DIFF_CHOL	LOWER	UPPER	CHOL_DTG	CHOL_RAL	N_RAL	N_DTG
WEEK_12	1.78276	-3.61679	7.1823	165.534	163.751	385	386
WEEK_24	2.20548	-3.00053	7.4115	166.755	164.550	377	385
WEEK_32	1.31269	-4.20528	6.8307	166.434	165.121	364	380
WEEK_48	1.72335	-3.91819	7.3649	172.027	170.303	344	366
WEEK_60	4.34299	-3.29307	11.9790	170.364	166.021	154	169

# LOCF

VISIT	DIFF_CHOL	LOWER	UPPER	CHOL_DTG	CHOL_RAL	N_RAL	N_DTG
WEEK_12	1.01027	-4.27771	6.29825	164.866	163.856	412	408
WEEK_24	2.07183	-3.00716	7.15082	166.192	164.121	409	406
WEEK_32	1.79997	-3.47313	7.07307	166.199	164.399	412	406
WEEK_48	2.52117	-2.79650	7.83883	170.915	168.393	406	407
WEEK_60	2.69668	-2.57977	7.97313	171.327	168.630	409	405

# CHANGE\_CF

VISIT	DIFF_CHOL	LOWER	UPPER	CHOL_DTG	CHOL_RAL	N_RAL	N_DTG
WEEK_12	1.01027	-4.27771	6.2983	164.866	163.856	412	408
WEEK_24	2.13004	-3.09411	7.3542	166.523	164.393	409	406
WEEK_32	2.07190	-3.65284	7.7966	166.826	164.754	412	406
WEEK_48	3.29583	-3.03908	9.6307	171.946	168.650	406	407
WEEK_60	4.84371	-2.81332	12.5007	176.534	171.690	409	405

# TWO\_CHANGE\_CF

VISIT	DIFF_CHOL	LOWER	UPPER	CHOL_DTG	CHOL_RAL	N_RAL	N_DTG
WEEK_12	1.01027	-4.27771	6.29825	164.866	163.856	412	408
WEEK_24	2.10093	-3.03434	7.23620	166.358	164.257	409	406
WEEK_32	1.91488	-3.52690	7.35666	166.710	164.795	412	406
WEEK_48	2.68949	-3.00457	8.38355	171.794	169.105	406	407
WEEK_60	2.77626	-3.52329	9.07580	174.340	171.564	409	405



# SPRING\_2\_CHOLESTEROL\_CHANGE\_FROM\_BASELINE\_OBSERVED

VISIT	DIFF_CHOL	LOWER	UPPER	CHG_CHOL_DTG	CHG_CHOL_RAL	N_RAL	N_DTG
WEEK_12	-1.74468	-5.60540	2.11604	0.67727	2.42195	361	354
WEEK_24	-1.60716	-5.38377	2.16946	1.90808	3.51523	354	350
WEEK_32	-1.53422	-5.71354	2.64509	1.53894	3.07317	341	345
WEEK_48	-1.32853	-5.57539	2.91833	6.40302	7.73155	322	335
WEEK_60	-2.53430	-8.80285	3.73425	6.34082	8.87512	143	151

## LOCF

VISIT	DIFF_CHOL	LOWER	UPPER	CHG_CHOL_DTG	CHG_CHOL_RAL	N_RAL	N_DTG
WEEK_12	-1.63065	-5.28663	2.02533	0.64623	2.27688	384	371
WEEK_24	-1.42376	-5.08527	2.23775	2.03724	3.46099	381	369
WEEK_32	-0.91118	-4.87347	3.05111	2.35058	3.26175	384	369
WEEK_48	-0.52531	-4.47326	3.42263	6.93652	7.46183	378	370
WEEK_60	-0.85811	-4.82490	3.10868	7.15496	8.01306	381	368

## CHANGE\_CF

VISIT	DIFF_CHOL	LOWER	UPPER	CHG_CHOL_DTG	CHG_CHOL_RAL	N_RAL	N_DTG
WEEK_12	-1.63065	-5.28663	2.02533	0.6462	2.2769	384	371
WEEK_24	-1.27224	-5.23848	2.69400	2.4009	3.6731	381	369
WEEK_32	-0.50862	-5.21590	4.19866	3.0401	3.5488	384	369
WEEK_48	0.31182	-5.15731	5.78095	7.9179	7.6061	378	370
WEEK_60	1.62195	-5.50561	8.74951	12.5246	10.9026	381	368

## TWO\_CHANGE\_CF

VISIT	DIFF_CHOL	LOWER	UPPER	CHG_CHOL_DTG	CHG_CHOL_RAL	N_RAL	N_DTG
WEEK_12	-1.63065	-5.28663	2.02533	0.6462	2.2769	384	371
WEEK_24	-1.34800	-5.13917	2.44317	2.2191	3.5671	381	369
WEEK_32	-0.72708	-5.02738	3.57321	2.9128	3.6399	384	369
WEEK_48	-0.26662	-4.89451	4.36126	7.8970	8.1636	378	370
WEEK_60	-0.40763	-5.91028	5.09502	10.4818	10.8894	381	368

# SPRING\_2\_HDL\_OBSERVED

VISIT	DIFF_HDL	LOWER	UPPER	HDL_DTG	HDL_RAL	N_RAL	N_DTG
WEEK_12	0.40699	-1.31179	2.12578	45.9369	45.5299	385	386
WEEK_24	0.13305	-1.70898	1.97508	47.3358	47.2028	377	385
WEEK_32	0.38573	-1.38881	2.16027	47.2006	46.8148	364	379
WEEK_48	0.33596	-1.57245	2.24436	46.9510	46.6150	344	366
WEEK_60	-0.42569	-3.13035	2.27898	46.1337	46.5594	154	169

# LOCF

VISIT	DIFF_HDL	LOWER	UPPER	HDL_DTG	HDL_RAL	N_RAL	N_DTG
WEEK_12	-0.20227	-1.91367	1.50912	45.5810	45.7833	412	408
WEEK_24	-0.31091	-2.12956	1.50774	46.9399	47.2509	409	406
WEEK_32	0.01083	-1.74038	1.76204	46.8754	46.8646	412	405
WEEK_48	-0.12062	-1.94427	1.70303	46.6507	46.7714	406	407
WEEK_60	0.19192	-1.65088	2.03472	47.1762	46.9842	409	405

# CHANGE\_CF

VISIT	DIFF_HDL	LOWER	UPPER	HDL_DTG	HDL_RAL	N_RAL	N_DTG
WEEK_12	-0.20227	-1.91367	1.50912	45.5810	45.7833	412	408
WEEK_24	-0.24007	-2.08124	1.60111	46.9304	47.1705	409	406
WEEK_32	0.11801	-1.73681	1.97283	46.8859	46.7679	412	405
WEEK_48	0.07454	-1.98412	2.13321	46.6878	46.6133	406	407
WEEK_60	0.51748	-2.00717	3.04214	47.4989	46.9814	409	405

# TWO\_CHANGE\_CF

VISIT	DIFF_HDL	LOWER	UPPER	HDL_DTG	HDL_RAL	N_RAL	N_DTG
WEEK_12	-0.20227	-1.91367	1.50912	45.5810	45.7833	412	408
WEEK_24	-0.27549	-2.10327	1.55229	46.9352	47.2107	409	406
WEEK_32	0.05358	-1.74735	1.85451	46.9608	46.9073	412	405
WEEK_48	-0.03203	-1.96626	1.90219	46.8422	46.8742	406	407
WEEK_60	0.22599	-1.91625	2.36823	47.5662	47.3402	409	405

# SPRING\_2\_HDL\_CHANGE\_FROM\_BASELINE\_OBSERVED

VISIT	DIFF_HDL	LOWER	UPPER	CHG_HDL_DTG	CHG_HDL_RALN_RAL	N_DTG
WEEK_12	-0.12834	-1.44933	1.19266	1.50200	1.63034	361
WEEK_24	-0.49292	-1.93923	0.95340	3.07038	3.56330	354
WEEK_32	-0.03877	-1.52088	1.44334	2.73161	2.77039	341
WEEK_48	-0.00974	-1.51745	1.49797	2.68033	2.69007	322
WEEK_60	-0.46598	-2.70686	1.77491	2.33555	2.80153	143

## LOCF

VISIT	DIFF_HDL	LOWER	UPPER	CHG_HDL_DTG	CHG_HDL_RALN_RAL	N_DTG
WEEK_12	-0.09951	-1.35187	1.15285	1.43318	1.53269	384
WEEK_24	-0.33122	-1.71437	1.05193	2.88923	3.22045	381
WEEK_32	0.13573	-1.26747	1.53893	2.72580	2.59007	384
WEEK_48	0.06795	-1.32551	1.46141	2.63059	2.56264	378
WEEK_60	0.07364	-1.34744	1.49473	2.93176	2.85811	381

## CHANGE\_CF

VISIT	DIFF_HDL	LOWER	UPPER	CHG_HDL_DTG	CHG_HDL_RAL	N_RAL	N_DTG
WEEK_12	-0.09951	-1.35187	1.15285	1.43318	1.53269	384	371
WEEK_24	-0.27370	-1.69675	1.14935	2.87875	3.15245	381	369
WEEK_32	0.23490	-1.31192	1.78172	2.73736	2.50246	384	368
WEEK_48	0.21587	-1.48914	1.92087	2.61073	2.39487	378	370
WEEK_60	0.31470	-1.93530	2.56469	3.12511	2.81041	381	368

## TWO\_CHANGE\_CF

VISIT	DIFF_HDL	LOWER	UPPER	CHG_HDL_DTG	CHG_HDL_RAL	N_RAL	N_DTG
WEEK_12	-0.09951	-1.35187	1.15285	1.43318	1.53269	384	371
WEEK_24	-0.30246	-1.70253	1.09761	2.88399	3.18645	381	369
WEEK_32	0.17590	-1.31318	1.66499	2.81985	2.64394	384	368
WEEK_48	0.14979	-1.43044	1.73002	2.82394	2.67415	378	370
WEEK_60	0.09850	-1.75804	1.95503	3.30322	3.20472	381	368

# SPRING\_2\_LDL\_OBSERVED

VISIT	DIFF_LDL	LOWER	UPPER	LDL_DTG	LDL_RAL	N_RAL	N_DTG
WEEK_12	2.43742	-2.06442	6.9393	96.201	93.7635	379	383
WEEK_24	2.73322	-1.51046	6.9769	96.382	93.6489	375	381
WEEK_32	1.03000	-3.32916	5.3892	94.856	93.8264	359	375
WEEK_48	2.12039	-2.39961	6.6404	101.133	99.0128	340	362
WEEK_60	5.45418	-1.14490	12.0533	101.653	96.1992	153	169

# LOCF

VISIT	DIFF_LDL	LOWER	UPPER	LDL_DTG	LDL_RAL	N_RAL	N_DTG
WEEK_12	2.10738	-2.27299	6.48775	95.762	93.6546	409	406
WEEK_24	3.43259	-0.70389	7.56906	96.134	92.7010	407	404
WEEK_32	1.99962	-2.17765	6.17688	94.851	92.8516	411	403
WEEK_48	2.66893	-1.62977	6.96763	99.827	97.1582	406	405
WEEK_60	3.64657	-0.70762	8.00076	100.764	97.1178	409	404

# CHANGE\_CF

VISIT	DIFF_LDL	LOWER	UPPER	LDL_DTG	LDL_RAL	N_RAL	N_DTG
WEEK_12	2.16132	-2.21456	6.5372	95.762	93.6006	410	406
WEEK_24	3.72390	-0.47991	7.9277	96.340	92.6165	407	404
WEEK_32	2.59407	-1.82008	7.0082	95.180	92.5863	411	403
WEEK_48	3.57920	-1.27715	8.4355	100.100	96.5211	406	405
WEEK_60	5.69477	-0.21943	11.6090	104.270	98.5748	409	404

# TWO\_CHANGE\_CF

VISIT	DIFF_LDL	LOWER	UPPER	LDL_DTG	LDL_RAL	N_RAL	N_DTG
WEEK_12	2.16132	-2.21456	6.53721	95.762	93.6006	410	406
WEEK_24	3.57824	-0.58464	7.74112	96.237	92.6587	407	404
WEEK_32	2.16380	-2.11100	6.43860	95.142	92.9777	411	403
WEEK_48	2.70897	-1.79903	7.21697	100.229	97.5197	406	405
WEEK_60	3.33512	-1.67493	8.34517	102.705	99.3695	409	404

SPRING\_2\_LDL\_CHANGE\_FROM\_BASELINE\_OBSERVED

VISIT	DIFF_LDL	LOWER	UPPER	CHG_LDL_DTG	CHG_LDL_RAL	N_RAL	N_DTG
WEEK_12	-0.65830	-3.69383	2.37722	-1.53467	-0.87637	353	351
WEEK_24	-0.28001	-3.19905	2.63902	-1.38138	-1.10137	349	346
WEEK_32	-1.63455	-4.83466	1.56556	-3.06174	-1.42718	333	340
WEEK_48	-0.42776	-3.77288	2.91736	2.42767	2.85542	315	331
WEEK_60	0.76188	-4.37728	5.90104	4.26136	3.49948	141	151

LOCF

VISIT	DIFF_LDL	LOWER	UPPER	CHG_LDL_DTG	CHG_LDL_RAL	N_RAL	N_DTG
WEEK_12	-0.75989	-3.60400	2.08423	-1.57613	-0.81625	379	369
WEEK_24	-0.11344	-2.90771	2.68082	-1.25914	-1.14569	376	367
WEEK_32	-1.41118	-4.41508	1.59272	-2.28532	-0.87414	380	366
WEEK_48	-0.50427	-3.56919	2.56064	2.70583	3.21011	375	368
WEEK_60	0.14502	-2.98109	3.27114	3.47185	3.32683	378	367

CHANGE\_CF

VISIT	DIFF_LDL	LOWER	UPPER	CHG_LDL_DTG	CHG_LDL_RAL	N_RAL	N_DTG
WEEK_12	-0.75989	-3.60400	2.08423	-1.57613	-0.81625	379	369
WEEK_24	0.23654	-2.71014	3.18321	-1.03154	-1.26808	376	367
WEEK_32	-0.74451	-4.15189	2.66287	-1.92292	-1.17841	380	366
WEEK_48	0.38422	-3.50845	4.27688	2.90549	2.52127	375	368
WEEK_60	2.54994	-2.62945	7.72933	7.12177	4.57183	378	367

TWO\_CHANGE\_CF

VISIT	DIFF_LDL	LOWER	UPPER	CHG_LDL_DTG	CHG_LDL_RAL	N_RAL	N_DTG
WEEK_12	-0.75989	-3.60400	2.08423	-1.57613	-0.81625	379	369
WEEK_24	0.06155	-2.79728	2.92037	-1.14534	-1.20689	376	367
WEEK_32	-1.21928	-4.43084	1.99227	-1.96571	-0.74643	380	366
WEEK_48	-0.45802	-3.92689	3.01086	3.13982	3.59783	375	368
WEEK_60	-0.01531	-4.20058	4.16997	5.59078	5.60609	378	367

# SPRING\_2\_TRIGLYCERIDES\_OBSERVED

VISIT	DIFF_TRIG	LOWER	UPPER	TRIG_DTG	TRIG_RAL	N_RAL	N_DTG
WEEK_12	-7.60858	-18.5223	3.3052	116.028	123.636	385	386
WEEK_24	-5.90162	-16.0528	4.2496	113.070	118.971	377	385
WEEK_32	-2.27785	-13.4885	8.9328	120.405	122.683	364	380
WEEK_48	0.43910	-14.4513	15.3295	123.705	123.266	344	366
WEEK_60	-4.56419	-18.3786	9.2502	112.641	117.205	154	169

# LOCF

VISIT	DIFF_TRIG	LOWER	UPPER	TRIG_DTG	TRIG_RAL	N_RAL	N_DTG
WEEK_12	-8.38804	-18.9450	2.1689	115.899	124.287	412	408
WEEK_24	-7.27879	-17.2493	2.6918	113.263	120.542	409	406
WEEK_32	-3.08816	-13.9572	7.7809	120.690	123.778	412	406
WEEK_48	-0.46212	-14.3624	13.4382	123.903	124.365	406	407
WEEK_60	-8.18930	-19.8546	3.4760	116.626	124.816	409	405

# CHANGE\_CF

VISIT	DIFF_TRIG	LOWER	UPPER	TRIG_DTG	TRIG_RAL	N_RAL	N_DTG
WEEK_12	-8.38804	-18.9450	2.1689	115.899	124.287	412	408
WEEK_24	-8.09396	-18.9085	2.7205	113.928	122.022	409	406
WEEK_32	-4.24012	-17.1621	8.6819	122.120	126.360	412	406
WEEK_48	-2.01507	-19.6132	15.5830	126.968	128.983	406	407
WEEK_60	-8.91711	-31.7845	13.9503	124.287	133.204	409	405

# TWO\_CHANGE\_CF

VISIT	DIFF_TRIG	LOWER	UPPER	TRIG_DTG	TRIG_RAL	N_RAL	N_DTG
WEEK_12	-8.38804	-18.9450	2.1689	115.899	124.287	412	408
WEEK_24	-7.68637	-18.0073	2.6346	113.596	121.282	409	406
WEEK_32	-2.93970	-14.5794	8.7000	121.371	124.311	412	406
WEEK_48	0.10264	-15.2145	15.4197	125.141	125.038	406	407
WEEK_60	-5.71442	-22.3310	10.9021	121.011	126.725	409	405

SPRING\_2\_TRIGLYCERIDES\_CHANGE\_FROM\_BASELINE\_OBSERVED

VISIT	DIFF_TRIG	LOWER	UPPER	CHG_TRIG_DTG	CHG_TRIG_RAL	N_RAL	N_DTG
WEEK_12	-5.3940	-15.7114	4.9233	1.85965	7.2537	361	355
WEEK_24	-2.9305	-12.8754	7.0144	-2.14053	0.7900	354	351
WEEK_32	0.4832	-10.5674	11.5339	6.51184	6.0286	341	346
WEEK_48	2.7278	-11.0563	16.5119	9.19458	6.4668	322	336
WEEK_60	-11.7092	-26.3224	2.9039	-1.26921	10.4400	143	152

LOCF

VISIT	DIFF_TRIG	LOWER	UPPER	CHG_TRIG_DTG	CHG_TRIG_RAL	N_RAL	N_DTG
WEEK_12	-5.04456	-14.7895	4.7004	1.77467	6.81923	384	372
WEEK_24	-3.02552	-12.7163	6.6652	-1.01172	2.01380	381	370
WEEK_32	1.27164	-9.2682	11.8114	7.00311	5.73147	384	370
WEEK_48	2.69626	-9.9957	15.3882	9.31470	6.61844	378	371
WEEK_60	-4.23177	-15.7767	7.3132	3.25203	7.48380	381	369

CHANGE\_CF

VISIT	DIFF_TRIG	LOWER	UPPER	CHG_TRIG_DTG	CHG_TRIG_RAL	N_RAL	N_DTG
WEEK_12	-5.04456	-14.7895	4.7004	1.7747	6.8192	384	372
WEEK_24	-3.54565	-14.3024	7.2111	-0.2822	3.2634	381	370
WEEK_32	0.53146	-12.4647	13.5276	8.5721	8.0407	384	370
WEEK_48	1.80649	-15.2776	18.8906	12.7209	10.9145	378	371
WEEK_60	-3.84899	-27.0981	19.4001	11.7179	15.5669	381	369

TWO\_CHANGE\_CF

VISIT	DIFF_TRIG	LOWER	UPPER	CHG_TRIG_DTG	CHG_TRIG_RAL	N_RAL	N_DTG
WEEK_12	-5.04456	-14.7895	4.7004	1.7747	6.81923	384	372
WEEK_24	-3.28558	-13.4341	6.8630	-0.6470	2.63861	381	370
WEEK_32	1.67799	-9.9400	13.2959	7.7505	6.07255	384	370
WEEK_48	3.71685	-10.8735	18.3072	10.7602	7.04336	378	371
WEEK_60	-0.66739	-17.5315	16.1967	8.4934	9.16080	381	369

## SINGLE\_CHOLESTEROL\_OBSERVED

VISIT	DIFF_CHOL	LOWER	UPPER	CHOL_DTG	CHOL_RAL	N_RAL	N_DTG
WEEK_12	-5.99240	-11.7365	-0.24826	170.606	176.599	374	388
WEEK_24	-5.18100	-11.2561	0.89416	172.681	177.862	365	380
WEEK_32	-5.88852	-12.0021	0.22501	174.764	180.653	350	372
WEEK_48	-9.40432	-15.7325	-3.07614	174.743	184.147	336	359
WEEK_60	-4.57012	-12.9064	3.76613	178.222	182.792	160	169

## LOCF

VISIT	DIFF_CHOL	LOWER	UPPER	CHOL_DTG	CHOL_RAL	N_RAL	N_DTG
WEEK_12	-4.57692	-9.9998	0.84601	169.942	174.519	423	420
WEEK_24	-4.28170	-9.9421	1.37869	171.359	175.641	424	422
WEEK_32	-3.80947	-9.4305	1.81158	173.696	177.505	426	424
WEEK_48	-6.26294	-11.9785	-0.54735	174.308	180.571	426	424
WEEK_60	-4.35972	-10.1171	1.39767	174.826	179.186	419	418

## CHANGE\_CF

VISIT	DIFF_CHOL	LOWER	UPPER	CHOL_DTG	CHOL_RAL	N_RAL	N_DTG
WEEK_12	-4.57692	-9.9998	0.84601	169.942	174.519	423	420
WEEK_24	-4.54972	-10.3502	1.25080	171.770	176.320	424	422
WEEK_32	-3.89143	-9.9498	2.16693	174.800	178.692	426	424
WEEK_48	-6.41670	-13.0620	0.22864	176.359	182.775	426	424
WEEK_60	-5.57228	-13.3876	2.24302	177.975	183.548	419	418

## TWO\_CHANGE\_CF

VISIT	DIFF_CHOL	LOWER	UPPER	CHOL_DTG	CHOL_RAL	N_RAL	N_DTG
WEEK_12	-4.57692	-9.9998	0.84601	169.942	174.519	423	420
WEEK_24	-4.41571	-10.1327	1.30127	171.565	175.980	424	422
WEEK_32	-3.95428	-9.7555	1.84694	174.366	178.320	426	424
WEEK_48	-6.26885	-12.3561	-0.18164	175.659	181.928	426	424
WEEK_60	-5.03220	-11.6709	1.60653	177.085	182.117	419	418



## SINGLE\_CHOLESTEROL\_CHANGE\_FROM\_BASELINE\_OBSERVED

VISIT	DIFF_CHOL	LOWER	UPPER	CHG_CHOL_DTG	CHG_CHOL_EFV	N_EFV	N_DTG
WEEK_12	-5.36863	-9.4250	-1.31227	12.6458	18.0144	340	349
WEEK_24	-4.65882	-9.1349	-0.18274	14.0545	18.7134	331	342
WEEK_32	-5.22455	-9.6149	-0.83418	15.7877	21.0122	317	335
WEEK_48	-8.92379	-13.7218	-4.12582	15.9823	24.9061	307	324
WEEK_60	-0.03918	-7.0526	6.97422	21.9623	22.0015	144	146

## LOCF

VISIT	DIFF_CHOL	LOWER	UPPER	CHG_CHOL_DTG	CHG_CHOL_EFV	N_EFV	N_DTG
WEEK_12	-4.31525	-8.0418	-0.58873	11.7377	16.0530	386	376
WEEK_24	-3.44925	-7.4994	0.60093	13.3881	16.8374	386	378
WEEK_32	-3.70991	-7.6663	0.24649	15.0619	18.7718	388	380
WEEK_48	-6.01346	-10.2357	-1.79123	15.4995	21.5129	389	380
WEEK_60	-3.68848	-8.0637	0.68675	16.6921	20.3806	382	374

## CHANGE\_CF

VISIT	DIFF_CHOL	LOWER	UPPER	CHG_CHOL_DTG	CHG_CHOL_EFV	N_EFV	N_DTG
WEEK_12	-4.31525	-8.0418	-0.58873	11.7377	16.0530	386	376
WEEK_24	-3.73629	-8.0273	0.55470	13.8464	17.5827	386	378
WEEK_32	-3.88110	-8.5543	0.79207	16.2332	20.1143	388	380
WEEK_48	-6.46779	-12.0109	-0.92467	17.5174	23.9852	389	380
WEEK_60	-5.65095	-12.8391	1.53717	19.5138	25.1647	382	374

## TWO\_CHANGE\_CF

VISIT	DIFF_CHOL	LOWER	UPPER	CHG_CHOL_DTG	CHG_CHOL_EFV	N_EFV	N_DTG
WEEK_12	-4.31525	-8.0418	-0.58873	11.7377	16.0530	386	376
WEEK_24	-3.59277	-7.7416	0.55603	13.6173	17.2100	386	378
WEEK_32	-3.85397	-8.1519	0.44400	15.8327	19.6867	388	380
WEEK_48	-6.04259	-10.9342	-1.15094	16.9689	23.0115	389	380
WEEK_60	-4.40351	-10.2092	1.40216	19.1167	23.5202	382	374

SINGLE_HDL_OBSERVED							
VISIT	DIFF_HDL	LOWER	UPPER	HDL_DTG	HDL_EFV	N_EFV	N_DTG
WEEK_12	-1.87558	-3.88822	0.13705	47.2598	49.1354	374	388
WEEK_24	-1.60077	-3.67686	0.47533	48.5163	50.1171	365	380
WEEK_32	-2.54161	-4.62946	-0.45377	47.7644	50.3060	350	372
WEEK_48	-3.25022	-5.39042	-1.11003	48.6248	51.8750	336	359
WEEK_60	-0.98930	-4.03902	2.06043	48.3944	49.3837	160	169

LOCF							
VISIT	DIFF_HDL	LOWER	UPPER	HDL_DTG	HDL_EFV	N_EFV	N_DTG
WEEK_12	-1.17717	-3.08835	0.73401	47.0896	48.2668	423	420
WEEK_24	-1.08326	-3.02823	0.86170	47.9972	49.0805	424	422
WEEK_32	-2.05325	-4.00135	-0.10515	47.3832	49.4365	426	424
WEEK_48	-2.49175	-4.44396	-0.53953	47.9505	50.4423	426	424
WEEK_60	-1.94247	-3.92244	0.03750	48.0523	49.9947	419	418

CHANGE_CF							
VISIT	DIFF_HDL	LOWER	UPPER	HDL_DTG	HDL_EFV	N_EFV	N_DTG
WEEK_12	-1.17717	-3.08835	0.73401	47.0896	48.2668	423	420
WEEK_24	-1.08853	-3.05026	0.87320	48.0412	49.1297	424	422
WEEK_32	-2.09629	-4.12144	-0.07114	47.4963	49.5926	426	424
WEEK_48	-2.70350	-4.84512	-0.56189	48.0900	50.7935	426	424
WEEK_60	-2.55985	-5.10531	-0.01440	48.4584	51.0182	419	418

TWO_CHANGE_CF							
VISIT	DIFF_HDL	LOWER	UPPER	HDL_DTG	HDL_EFV	N_EFV	N_DTG
WEEK_12	-1.17717	-3.08835	0.73401	47.0896	48.2668	423	420
WEEK_24	-1.08589	-3.03756	0.86577	48.0192	49.1051	424	422
WEEK_32	-2.04940	-4.04207	-0.05674	47.5264	49.5758	426	424
WEEK_48	-2.54336	-4.60242	-0.48430	48.1717	50.7150	426	424
WEEK_60	-2.58998	-4.86090	-0.31907	48.2072	50.7972	419	418

## SINGLE\_HDL\_CHANGE\_FROM\_BASELINE\_OBSERVED

VISIT	DIFF_HDL	LOWER	UPPER	CHG_HDL_DTG	CHG_HDL_EFV	N_EFV	N_DTG
WEEK_12	-1.35144	-2.81602	0.11313	4.35007	5.70151	340	349
WEEK_24	-1.48316	-2.99305	0.02672	5.15145	6.63461	331	342
WEEK_32	-2.38664	-3.92431	-0.84897	4.47877	6.86541	317	335
WEEK_48	-3.20898	-4.79001	-1.62796	5.13210	8.34108	307	324
WEEK_60	-1.26232	-3.65901	1.13437	6.39375	7.65608	144	146

## LOCF

VISIT	DIFF_HDL	LOWER	UPPER	CHG_HDL_DTG	CHG_HDL_EFV	N_EFV	N_DTG
WEEK_12	-0.99438	-2.33388	0.34512	4.03770	5.03208	386	376
WEEK_24	-0.98697	-2.35000	0.37607	4.77643	5.76340	386	378
WEEK_32	-1.73988	-3.11601	-0.36374	4.31473	6.05461	388	380
WEEK_48	-2.29601	-3.68779	-0.90423	4.78284	7.07885	389	380
WEEK_60	-1.60058	-3.03736	-0.16381	5.11702	6.71761	382	374

## CHANGE\_CF

VISIT	DIFF_HDL	LOWER	UPPER	CHG_HDL_DTG	CHG_HDL_EFV	N_EFV	N_DTG
WEEK_12	-0.99438	-2.33388	0.34512	4.03770	5.03208	386	376
WEEK_24	-0.99196	-2.38443	0.40051	4.82554	5.81749	386	378
WEEK_32	-1.74441	-3.23894	-0.24988	4.48162	6.22603	388	380
WEEK_48	-2.40016	-4.05537	-0.74494	5.00773	7.40789	389	380
WEEK_60	-2.05644	-4.24913	0.13624	5.68156	7.73800	382	374

## TWO\_CHANGE\_CF

VISIT	DIFF_HDL	LOWER	UPPER	CHG_HDL_DTG	CHG_HDL_EFV	N_EFV	N_DTG
WEEK_12	-0.99438	-2.33388	0.34512	4.03770	5.03208	386	376
WEEK_24	-0.98946	-2.36430	0.38538	4.80098	5.79045	386	378
WEEK_32	-1.72037	-3.16565	-0.27510	4.48722	6.20759	388	380
WEEK_48	-2.31636	-3.87619	-0.75654	5.04182	7.35819	389	380
WEEK_60	-2.18847	-4.04658	-0.33035	5.34708	7.53554	382	374

SINGLE_LDL_OBSERVED							
VISIT	DIFF_LDL	LOWER	UPPER	LDL_DTG	LDL_EFV	N_EFV	N_DTG
WEEK_12	-2.25230	-7.2685	2.76392	98.240	100.493	366	381
WEEK_24	-3.13834	-8.5581	2.28146	98.502	101.641	362	377
WEEK_32	-3.44234	-8.8367	1.95199	100.332	103.774	345	365
WEEK_48	-6.21222	-11.9037	-0.52072	100.887	107.099	329	354
WEEK_60	-4.00236	-11.2565	3.25178	102.961	106.963	158	167

LOCF							
VISIT	DIFF_LDL	LOWER	UPPER	LDL_DTG	LDL_EFV	N_EFV	N_DTG
WEEK_12	-1.58508	-6.25876	3.08860	97.875	99.460	421	418
WEEK_24	-2.78245	-7.73573	2.17083	97.491	100.274	423	420
WEEK_32	-2.37268	-7.24430	2.49893	99.549	101.922	425	422
WEEK_48	-4.76838	-9.77490	0.23815	100.185	104.953	425	421
WEEK_60	-3.11752	-8.14150	1.90646	100.588	103.705	418	417

CHANGE_CF							
VISIT	DIFF_LDL	LOWER	UPPER	LDL_DTG	LDL_EFV	N_EFV	N_DTG
WEEK_12	-1.48458	-6.1576	3.18842	97.976	99.460	421	419
WEEK_24	-2.78055	-7.8171	2.25602	97.630	100.411	423	420
WEEK_32	-2.40303	-7.5645	2.75840	99.956	102.359	425	421
WEEK_48	-5.43492	-11.0891	0.21924	100.754	106.189	425	420
WEEK_60	-5.27189	-11.9051	1.36133	101.579	106.851	418	416

TWO_CHANGE_CF							
VISIT	DIFF_LDL	LOWER	UPPER	LDL_DTG	LDL_EFV	N_EFV	N_DTG
WEEK_12	-1.48458	-6.15757	3.18842	97.976	99.460	421	419
WEEK_24	-2.78150	-7.76993	2.20692	97.561	100.342	423	420
WEEK_32	-2.16609	-7.17963	2.84746	99.948	102.114	425	421
WEEK_48	-4.47928	-9.78520	0.82664	100.854	105.334	425	420
WEEK_60	-3.30799	-9.08406	2.46809	101.747	105.055	418	416

## SINGLE\_LDL\_CHANGE\_FROM\_BASELINE\_OBSERVED

VISIT	DIFF_LDL	LOWER	UPPER	CHG_LDL_DTG	CHG_LDL_EFV	N_EFV	N_DTG
WEEK_12	-2.32926	-5.7986	1.14012	5.1811	7.5103	332	339
WEEK_24	-3.16611	-7.0806	0.74838	5.2014	8.3675	329	335
WEEK_32	-3.46204	-7.2248	0.30068	6.4204	9.8824	313	325
WEEK_48	-6.31539	-10.4563	-2.17452	7.3424	13.6577	301	316
WEEK_60	1.11134	-4.8284	7.05107	11.5631	10.4517	142	143

## LOCF

VISIT	DIFF_LDL	LOWER	UPPER	CHG_LDL_DTG	CHG_LDL_EFV	N_EFV	N_DTG
WEEK_12	-1.77607	-4.86933	1.31719	4.73418	6.5103	383	371
WEEK_24	-2.19125	-5.67990	1.29739	4.96366	7.1549	384	372
WEEK_32	-2.41447	-5.78746	0.95852	6.28022	8.6947	386	374
WEEK_48	-4.56742	-8.17839	-0.95644	6.90561	11.4730	387	373
WEEK_60	-2.79058	-6.53522	0.95405	7.68994	10.4805	380	369

## CHANGE\_CF

VISIT	DIFF_LDL	LOWER	UPPER	CHG_LDL_DTG	CHG_LDL_EFV	N_EFV	N_DTG
WEEK_12	-1.77607	-4.8693	1.31719	4.73418	6.5103	383	371
WEEK_24	-2.18534	-5.8111	1.44037	5.12062	7.3060	384	372
WEEK_32	-2.37514	-6.2247	1.47437	6.67519	9.0503	386	374
WEEK_48	-4.95426	-9.5131	-0.39539	7.45404	12.4083	387	373
WEEK_60	-4.84666	-10.8118	1.11853	8.41198	13.2586	380	369

## TWO\_CHANGE\_CF

VISIT	DIFF_LDL	LOWER	UPPER	CHG_LDL_DTG	CHG_LDL_EFV	N_EFV	N_DTG
WEEK_12	-1.77607	-4.86933	1.31719	4.73418	6.5103	383	371
WEEK_24	-2.18830	-5.73427	1.35767	5.04214	7.2304	384	372
WEEK_32	-2.20710	-5.85690	1.44270	6.71499	8.9221	386	374
WEEK_48	-4.33608	-8.51791	-0.15425	7.59659	11.9327	387	373
WEEK_60	-3.15466	-8.15702	1.84770	8.84060	11.9953	380	369

## SINGLE\_TRIGLYCERIDES\_OBSERVED

VISIT	DIFF_TRIG	LOWER	UPPER	TRIG_DTG	TRIG_EFV	N_EFV	N_DTG
WEEK_12	-13.8519	-28.3402	0.6365	129.714	143.566	374 388	
WEEK_24	-1.5007	-12.7208	9.7195	130.498	131.999	365 380	
WEEK_32	1.1659	-10.8785	13.2102	135.072	133.906	350 372	
WEEK_48	2.3605	-11.3059	16.0270	131.656	129.296	336 359	
WEEK_60	0.7207	-14.9571	16.3986	133.696	132.976	160 169	

## LOCF

VISIT	DIFF_TRIG	LOWER	UPPER	TRIG_DTG	TRIG_EFV	N_EFV	N_DTG
WEEK_12	-12.9883	-26.6553	0.6787	127.935	140.923	423 420	
WEEK_24	-1.2843	-12.8597	10.2911	131.701	132.985	424 422	
WEEK_32	2.6604	-9.3230	14.6438	136.584	133.923	426 424	
WEEK_48	6.0024	-7.3681	19.3730	136.922	130.919	426 424	
WEEK_60	2.0245	-10.0701	14.1191	134.090	132.065	419 418	

## CHANGE\_CF

VISIT	DIFF_TRIG	LOWER	UPPER	TRIG_DTG	TRIG_EFV	N_EFV	N_DTG
WEEK_12	-12.9883	-26.6553	0.6787	127.935	140.923	423 420	
WEEK_24	-3.6564	-18.2272	10.9144	133.251	136.907	424 422	
WEEK_32	0.5720	-18.4226	19.5665	140.856	140.284	426 424	
WEEK_48	6.8900	-18.4180	32.1980	146.769	139.879	426 424	
WEEK_60	6.4639	-25.9953	38.9230	149.064	142.600	419 418	

## TWO\_CHANGE\_CF

VISIT	DIFF_TRIG	LOWER	UPPER	TRIG_DTG	TRIG_EFV	N_EFV	N_DTG
WEEK_12	-12.9883	-26.6553	0.6787	127.935	140.923	423 420	
WEEK_24	-2.4704	-15.3567	10.4160	132.476	134.946	424 422	
WEEK_32	0.6668	-14.2459	15.5795	138.488	137.821	426 424	
WEEK_48	4.5547	-13.5394	22.6488	141.162	136.607	426 424	
WEEK_60	2.5856	-17.9411	23.1122	142.195	139.610	419 418	

## SINGLE\_TRIGLYCERIDES\_CHANGE\_FROM\_BASELINE\_OBSERVED

VISIT	DIFF_TRIG	LOWER	UPPER	CHG_TRIG_DTG	CHG_TRIG_EFV	N_EFV	N_DTG
WEEK_12	-14.5880	-27.0869	-2.0890	14.1289	28.7168	340	349
WEEK_24	-2.2782	-13.8083	9.2519	16.3406	18.6188	331	342
WEEK_32	0.5886	-10.7299	11.9071	20.8533	20.2646	317	335
WEEK_48	1.6635	-11.4065	14.7335	18.4748	16.8113	307	324
WEEK_60	-0.6108	-15.8576	14.6359	17.8749	18.4857	144	146

## LOCF

VISIT	DIFF_TRIG	LOWER	UPPER	CHG_TRIG_DTG	CHG_TRIG_EFV	N_EFV	N_DTG
WEEK_12	-12.8681	-24.2551	-1.4811	13.1143	25.9824	386	376
WEEK_24	-2.2817	-13.0291	8.4656	16.5660	18.8477	386	378
WEEK_32	0.6630	-9.6746	11.0005	20.6497	19.9868	388	380
WEEK_48	4.7344	-6.8302	16.2989	21.0503	16.3159	389	380
WEEK_60	2.1033	-7.9864	12.1931	18.3546	16.2512	382	374

## CHANGE\_CF

VISIT	DIFF_TRIG	LOWER	UPPER	CHG_TRIG_DTG	CHG_TRIG_EFV	N_EFV	N_DTG
WEEK_12	-12.8681	-24.2551	-1.4811	13.1143	25.9824	386	376
WEEK_24	-4.8595	-18.2380	8.5190	18.2961	23.1556	386	378
WEEK_32	-2.0194	-19.6270	15.5881	24.9558	26.9752	388	380
WEEK_48	4.4278	-19.6318	28.4874	30.5123	26.0846	389	380
WEEK_60	6.2977	-25.2255	37.8209	32.6842	26.3865	382	374

## TWO\_CHANGE\_CF

VISIT	DIFF_TRIG	LOWER	UPPER	CHG_TRIG_DTG	CHG_TRIG_EFV	N_EFV	N_DTG
WEEK_12	-12.8681	-24.2551	-1.4811	13.1143	25.9824	386	376
WEEK_24	-3.5706	-15.3453	8.2041	17.4311	21.0017	386	378
WEEK_32	-1.6339	-14.7223	11.4544	22.6351	24.2690	388	380
WEEK_48	2.9620	-13.2728	19.1968	25.5647	22.6028	389	380
WEEK_60	2.9765	-15.8513	21.8042	27.1367	24.1602	382	374

## SAILING\_CHOLESTEROL\_OBSERVED

VISIT	DIFF_CHOL	LOWER	UPPER	CHOL_DTG	CHOL_RAL	N_RAL	N_DTG
WEEK_12	3.01973	-4.0876	10.1270	179.806	176.787	341	335
WEEK_24	2.28919	-5.2257	9.8041	182.682	180.393	315	318
WEEK_32	0.21482	-7.8651	8.2948	184.727	184.512	235	247
WEEK_48	-2.07597	-12.6098	8.4579	181.175	183.251	123	141

## LOCF

VISIT	DIFF_CHOL	LOWER	UPPER	CHOL_DTG	CHOL_RAL	N_RAL	N_DTG
WEEK_12	3.12828	-3.69852	9.95508	179.479	176.351	367	360
WEEK_24	2.60927	-4.51207	9.73062	181.829	179.220	372	362
WEEK_32	0.41343	-6.55829	7.38515	182.030	181.616	367	361
WEEK_48	-0.19423	-7.14102	6.75257	181.197	181.391	364	355

## CHANGE\_CF

VISIT	DIFF_CHOL	LOWER	UPPER	CHOL_DTG	CHOL_RAL	N_RAL	N_DTG
WEEK_12	3.28403	-3.5497	10.1177	179.635	176.351	367	360
WEEK_24	1.76616	-5.7987	9.3310	182.522	180.756	372	362
WEEK_32	-1.16258	-9.6375	7.3123	183.594	184.756	367	361
WEEK_48	-3.67532	-14.0552	6.7045	183.999	187.675	364	355

## TWO\_CHANGE\_CF

VISIT	DIFF_CHOL	LOWER	UPPER	CHOL_DTG	CHOL_RAL	N_RAL	N_DTG
WEEK_12	3.20616	-3.6224	10.0347	179.557	176.351	367	360
WEEK_24	2.26866	-5.0534	9.5908	182.306	180.037	372	362
WEEK_32	-1.01569	-8.7230	6.6917	184.103	185.119	367	361
WEEK_48	-2.89697	-11.6151	5.8212	185.962	188.859	364	355



## SAILING\_CHOLESTEROL\_CHANGE\_FROM\_BASELINE\_OBSERVED

VISIT	DIFF_CHOL	LOWER	UPPER	CHG_CHOL_DTG	CHG_CHOL_RAL	N_RAL	N_DTG
WEEK_12	-2.18052	-7.4797	3.11864	12.4834	14.6639	316	312
WEEK_24	0.98925	-4.8089	6.78738	16.5218	15.5326	293	295
WEEK_32	-1.05997	-7.8656	5.74562	17.4821	18.5421	219	230
WEEK_48	-5.61293	-14.3776	3.15174	15.2964	20.9093	112	133

## LOCF

VISIT	DIFF_CHOL	LOWER	UPPER	CHG_CHOL_DTG	CHG_CHOL_RAL	N_RAL	N_DTG
WEEK_12	-1.72589	-6.68328	3.23149	11.8232	13.5491	342	334
WEEK_24	0.21908	-5.02508	5.46325	15.1595	14.9404	346	336
WEEK_32	-2.69011	-8.06988	2.68965	15.4610	18.1511	343	336
WEEK_48	-3.60723	-8.81984	1.60539	15.2406	18.8478	339	330

## CHANGE\_CF

VISIT	DIFF_CHOL	LOWER	UPPER	CHG_CHOL_DTG	CHG_CHOL_RAL	N_RAL	N_DTG
WEEK_12	-1.5580	-6.5435	3.42750	11.9911	13.5491	342	334
WEEK_24	-0.8825	-6.7946	5.02961	15.7913	16.6738	346	336
WEEK_32	-4.8607	-12.2826	2.56129	16.8823	21.7430	343	336
WEEK_48	-8.2134	-17.9499	1.52313	17.8619	26.0753	339	330

## TWO\_CHANGE\_CF

VISIT	DIFF_CHOL	LOWER	UPPER	CHG_CHOL_DTG	CHG_CHOL_RAL	N_RAL	N_DTG
WEEK_12	-1.64195	-6.6107	3.32679	11.9072	13.5491	342	334
WEEK_24	-0.24440	-5.7846	5.29581	15.6158	15.8602	346	336
WEEK_32	-4.61590	-11.1537	1.92195	17.3853	22.0012	343	336
WEEK_48	-7.05958	-14.8930	0.77387	19.8587	26.9183	339	330

SAILING_HDL_OBSERVED							
VISIT	DIFF_HDL	LOWER	UPPER	HDL_DTG	HDL_RAL	N_RAL	N_DTG
WEEK_12	0.48156	-1.68326	2.64639	45.8658	45.3842	341	335
WEEK_24	-0.53051	-3.00371	1.94268	46.2858	46.8163	314	318
WEEK_32	-0.16299	-2.98358	2.65759	46.1798	46.3428	235	247
WEEK_48	-1.20524	-4.85374	2.44326	45.3588	46.5641	123	141

LOCF							
VISIT	DIFF_HDL	LOWER	UPPER	HDL_DTG	HDL_RAL	N_RAL	N_DTG
WEEK_12	0.66447	-1.41521	2.74415	45.5541	44.8896	367	360
WEEK_24	0.29195	-2.05344	2.63734	46.4080	46.1160	371	362
WEEK_32	0.55775	-1.71736	2.83287	45.7814	45.2236	367	361
WEEK_48	0.65741	-1.66727	2.98210	46.0954	45.4380	364	355

CHANGE_CF							
VISIT	DIFF_HDL	LOWER	UPPER	HDL_DTG	HDL_RAL	N_RAL	N_DTG
WEEK_12	0.67521	-1.40473	2.75515	45.5648	44.8896	367	360
WEEK_24	0.39328	-2.15197	2.93853	46.6750	46.2818	371	362
WEEK_32	1.16374	-1.75604	4.08352	46.4980	45.3342	367	361
WEEK_48	2.16549	-1.53556	5.86654	46.9789	44.8134	364	355

TWO_CHANGE_CF							
VISIT	DIFF_HDL	LOWER	UPPER	HDL_DTG	HDL_RAL	N_RAL	N_DTG
WEEK_12	0.66984	-1.40995	2.74962	45.5594	44.8896	367	360
WEEK_24	0.32553	-2.10165	2.75271	46.5463	46.2208	371	362
WEEK_32	0.62604	-1.90547	3.15755	46.1879	45.5618	367	361
WEEK_48	0.89612	-2.05599	3.84823	47.1134	46.2173	364	355

## SAILING\_HDL\_CHANGE\_FROM\_BASELINE\_OBSERVED

VISIT	DIFF_HDL	LOWER	UPPER	CHG_HDL_DTG	CHG_HDL_RAL	N_RAL	N_DTG
WEEK_12	0.03345	-1.68161	1.74851	0.99897	0.96552	316	312
WEEK_24	0.00608	-1.90084	1.91299	2.24416	2.23808	292	295
WEEK_32	-0.35208	-2.53717	1.83300	0.89277	1.24485	219	230
WEEK_48	-2.76158	-5.47607	-0.04709	0.32855	3.09013	112	133

## LOCF

VISIT	DIFF_HDL	LOWER	UPPER	CHG_HDL_DTG	CHG_HDL_RAL	N_RAL	N_DTG
WEEK_12	0.05842	-1.53631	1.65315	0.95054	0.89212	342	334
WEEK_24	-0.07987	-1.86511	1.70537	2.13719	2.21707	345	336
WEEK_32	-0.25886	-1.98260	1.46489	1.12672	1.38557	343	336
WEEK_48	-0.27253	-1.95764	1.41257	1.55031	1.82284	339	330

## CHANGE\_CF

VISIT	DIFF_HDL	LOWER	UPPER	CHG_HDL_DTG	CHG_HDL_RAL	N_RAL	N_DTG
WEEK_12	0.06999	-1.52514	1.66513	0.96211	0.89212	342	334
WEEK_24	-0.03543	-2.16105	2.09020	2.38003	2.41546	345	336
WEEK_32	0.09658	-2.57823	2.77139	1.69410	1.59752	343	336
WEEK_48	0.68053	-2.92152	4.28258	2.04481	1.36428	339	330

## TWO\_CHANGE\_CF

VISIT	DIFF_HDL	LOWER	UPPER	CHG_HDL_DTG	CHG_HDL_RAL	N_RAL	N_DTG
WEEK_12	0.06421	-1.53069	1.65910	0.95632	0.89212	342	334
WEEK_24	-0.07601	-2.01277	1.86076	2.26379	2.33980	345	336
WEEK_32	-0.24914	-2.44615	1.94786	1.51974	1.76889	343	336
WEEK_48	-0.18956	-2.86632	2.48719	2.48424	2.67380	339	330

## SAILING\_LDL\_OBSERVED

VISIT	DIFF_LDL	LOWER	UPPER	LDL_DTG	LDL_RAL	N_RAL	N_DTG
WEEK_12	2.53824	-3.1152	8.19169	96.597	94.059	321	311
WEEK_24	0.69805	-5.2949	6.69102	97.032	96.334	300	294
WEEK_32	0.23535	-6.3756	6.84628	100.859	100.624	221	235
WEEK_48	-2.16261	-10.7301	6.40485	98.795	100.958	116	134

## LOCF

VISIT	DIFF_LDL	LOWER	UPPER	LDL_DTG	LDL_RAL	N_RAL	N_DTG
WEEK_12	3.59706	-1.66608	8.86020	96.803	93.2059	362	352
WEEK_24	1.63996	-3.88356	7.16348	97.208	95.5682	366	355
WEEK_32	1.42430	-4.02161	6.87021	98.967	97.5431	361	356
WEEK_48	0.72902	-4.63075	6.08879	98.474	97.7448	358	352

## CHANGE\_CF

VISIT	DIFF_LDL	LOWER	UPPER	LDL_DTG	LDL_RAL	N_RAL	N_DTG
WEEK_12	3.51382	-1.7592	8.78680	96.746	93.232	363	355
WEEK_24	0.39436	-5.5277	6.31645	97.458	97.063	366	356
WEEK_32	-1.05586	-7.8232	5.71151	99.701	100.757	361	357
WEEK_48	-4.26397	-12.5317	4.00381	100.121	104.385	358	352

## TWO\_CHANGE\_CF

VISIT	DIFF_LDL	LOWER	UPPER	LDL_DTG	LDL_RAL	N_RAL	N_DTG
WEEK_12	3.30426	-1.9614	8.56992	96.591	93.286	363	355
WEEK_24	0.95121	-4.7616	6.66404	97.382	96.431	366	356
WEEK_32	-0.16465	-6.2455	5.91617	100.135	100.299	361	357
WEEK_48	-2.15388	-8.9547	4.64692	101.280	103.434	358	352

## SAILING\_LDL\_CHANGE\_FROM\_BASELINE\_OBSERVED

VISIT	DIFF_LDL	LOWER	UPPER	CHG_LDL_DTG	CHG_LDL_RAL	N_RAL	N_DTG
WEEK_12	-1.21664	-5.4288	2.99552	7.2853	8.5019	285	287
WEEK_24	-1.39577	-5.9132	3.12170	7.2337	8.6295	266	269
WEEK_32	-0.14813	-5.1296	4.83329	10.9719	11.1200	197	217
WEEK_48	-3.73686	-10.8495	3.37576	9.8358	13.5727	101	124

## LOCF

VISIT	DIFF_LDL	LOWER	UPPER	CHG_LDL_DTG	CHG_LDL_RAL	N_RAL	N_DTG
WEEK_12	-0.89714	-4.62498	2.83070	6.5584	7.4555	325	325
WEEK_24	-1.61456	-5.57132	2.34219	7.0938	8.7084	327	325
WEEK_32	-2.42485	-6.39326	1.54356	8.8550	11.2799	324	327
WEEK_48	-3.78904	-7.74250	0.16442	8.6250	12.4141	321	322

## CHANGE\_CF

VISIT	DIFF_LDL	LOWER	UPPER	CHG_LDL_DTG	CHG_LDL_RAL	N_RAL	N_DTG
WEEK_12	-0.8186	-4.5544	2.91714	6.6369	7.4555	325	325
WEEK_24	-2.7428	-7.3773	1.89162	7.4639	10.2067	327	325
WEEK_32	-5.3808	-11.3257	0.56417	9.5823	14.9630	324	327
WEEK_48	-10.1583	-18.0893	-2.22730	10.2343	20.3926	321	322

## TWO\_CHANGE\_CF

VISIT	DIFF_LDL	LOWER	UPPER	CHG_LDL_DTG	CHG_LDL_RAL	N_RAL	N_DTG
WEEK_12	-0.8579	-4.5889	2.87313	6.5977	7.4555	325	325
WEEK_24	-2.0335	-6.3025	2.23557	7.4329	9.4664	327	325
WEEK_32	-4.3592	-9.4336	0.71522	9.9779	14.3371	324	327
WEEK_48	-7.7572	-13.9821	-1.53218	11.1218	18.8789	321	322

## SAILING\_TRIGLYCERIDES\_OBSERVED

VISIT	DIFF_TRIG	LOWER	UPPER	TRIG_DTG	TRIG_RAL	N_RAL	N_DTG
WEEK_12	4.5768	-18.4189	27.5724	193.890	189.313	341	335
WEEK_24	14.5049	-8.4236	37.4334	201.762	187.257	315	318
WEEK_32	0.0419	-29.6030	29.6868	196.303	196.261	235	247
WEEK_48	29.8762	-31.3317	91.0840	217.429	187.553	123	141

## LOCF

VISIT	DIFF_TRIG	LOWER	UPPER	TRIG_DTG	TRIG_RAL	N_RAL	N_DTG
WEEK_12	-2.48196	-25.6474	20.6835	193.768	196.250	367	360
WEEK_24	4.04394	-18.6460	26.7339	199.196	195.152	372	362
WEEK_32	-8.16119	-33.0809	16.7586	196.088	204.249	367	361
WEEK_48	-2.86906	-32.9151	27.1770	199.105	201.974	364	355

## CHANGE\_CF

VISIT	DIFF_TRIG	LOWER	UPPER	TRIG_DTG	TRIG_RAL	N_RAL	N_DTG
WEEK_12	-2.1132	-25.2935	21.0670	194.137	196.250	367	360
WEEK_24	2.3718	-21.8962	26.6397	201.415	199.044	372	362
WEEK_32	-13.4235	-43.8687	17.0216	201.346	214.769	367	361
WEEK_48	-13.7083	-55.5411	28.1244	209.685	223.393	364	355

## TWO\_CHANGE\_CF

VISIT	DIFF_TRIG	LOWER	UPPER	TRIG_DTG	TRIG_RAL	N_RAL	N_DTG
WEEK_12	-2.2976	-25.4676	20.8725	193.953	196.250	367	360
WEEK_24	3.1146	-20.2034	26.4326	200.243	197.129	372	362
WEEK_32	-11.4393	-38.9876	16.1091	200.520	211.959	367	361
WEEK_48	-8.1915	-43.7245	27.3414	208.176	216.368	364	355

## SAILING\_TRIGLYCERIDES\_CHANGE\_FROM\_BASELINE\_OBSERVED

VISIT	DIFF_TRIG	LOWER	UPPER	CHG_TRIG_DTG	CHG_TRIG_RAL	N_RAL	N_DTG
WEEK_12	-0.4775	-18.2753	17.3204	25.1106	25.5881	316	312
WEEK_24	15.9670	-5.8744	37.8084	36.0522	20.0852	293	295
WEEK_32	7.7947	-19.7681	35.3575	36.2870	28.4923	219	230
WEEK_48	34.8289	-14.9003	84.5581	52.5517	17.7228	112	133

## LOCF

VISIT	DIFF_TRIG	LOWER	UPPER	CHG_TRIG_DTG	CHG_TRIG_RAL	N_RAL	N_DTG
WEEK_12	0.0894	-16.4731	16.6519	23.7322	23.6428	342	334
WEEK_24	13.4153	-5.9836	32.8142	34.0813	20.6660	346	336
WEEK_32	2.3857	-18.1274	22.8987	32.1955	29.8099	343	336
WEEK_48	9.2736	-14.7017	33.2489	35.8353	26.5617	339	330

## CHANGE\_CF

VISIT	DIFF_TRIG	LOWER	UPPER	CHG_TRIG_DTG	CHG_TRIG_RAL	N_RAL	N_DTG
WEEK_12	0.4868	-16.1241	17.0977	24.1296	23.6428	342	334
WEEK_24	11.7622	-9.6444	33.1688	36.6177	24.8555	346	336
WEEK_32	-1.7897	-29.0303	25.4509	38.9802	40.7699	343	336
WEEK_48	0.4322	-38.0203	38.8848	49.1231	48.6908	339	330

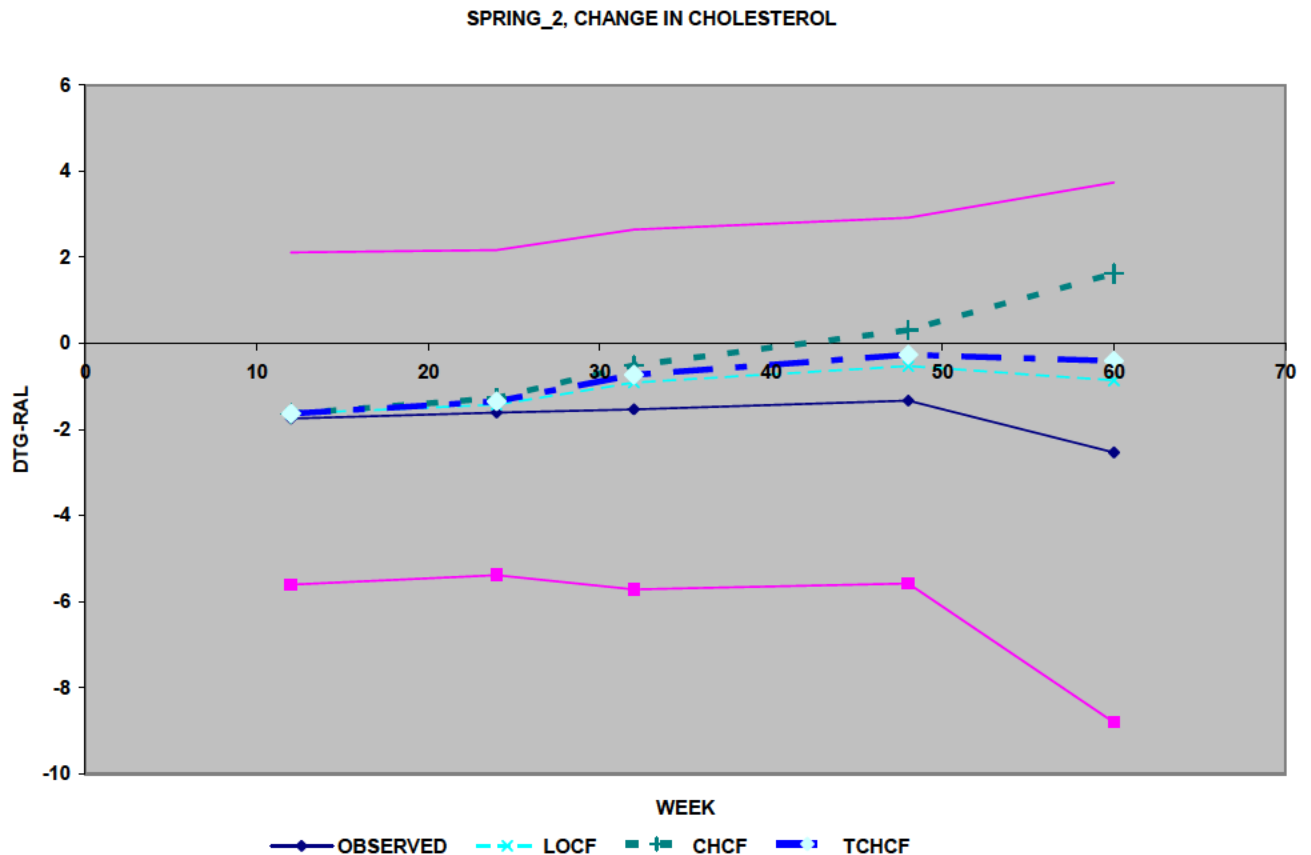
## TWO\_CHANGE\_CF

VISIT	DIFF_TRIG	LOWER	UPPER	CHG_TRIG_DTG	CHG_TRIG_RAL	N_RAL	N_DTG
WEEK_12	0.2881	-16.2940	16.8702	23.9309	23.6428	342	334
WEEK_24	12.4883	-7.7204	32.6971	35.2823	22.7940	346	336
WEEK_32	-0.3624	-24.4878	23.7630	37.4249	37.7874	343	336
WEEK_48	5.8573	-25.6344	37.3489	47.0743	41.2170	339	330

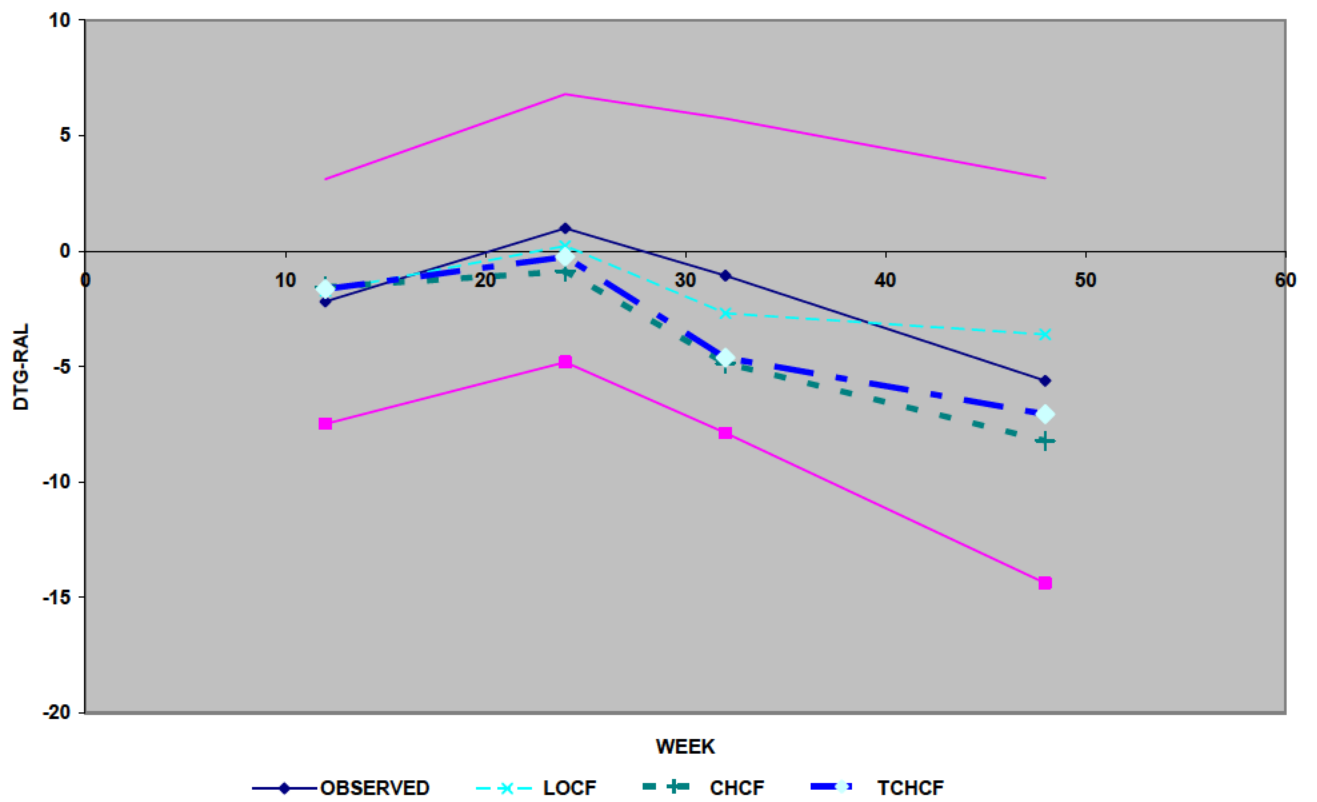
There are a lot of numbers in these tables that are hard to absorb all at once. The following graphs show the differences between DTG and control in change from baseline in each of the four lipids in each of the three trials. The four curves in the middle of each graph represent the four methods of handling missing data: observed, LOCF, change carried forward (CHCF), and average of last two changes carried forward (TCHCF). The two outermost curves show the upper and lower 95% confidence limits based on the observed data.



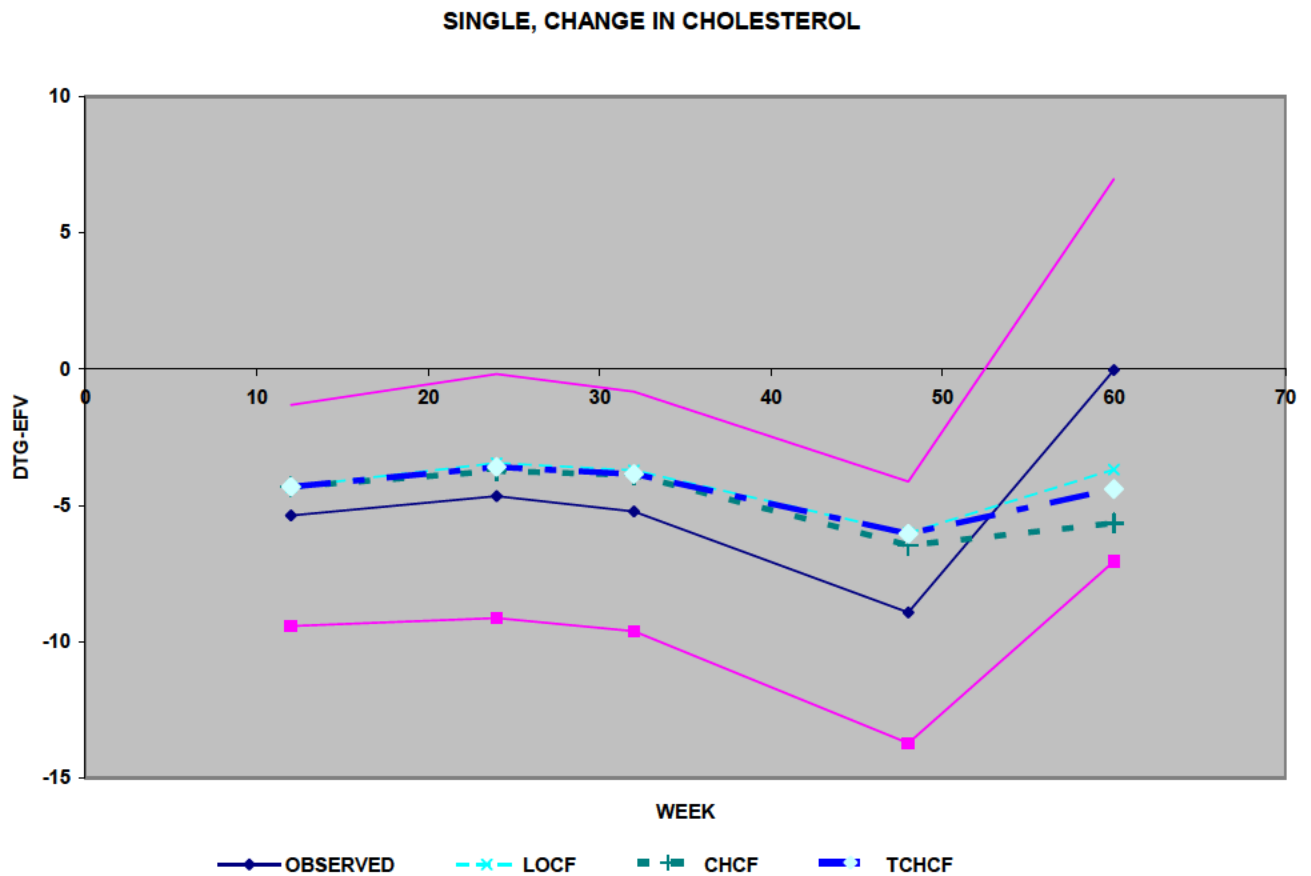
The two graphs of change from baseline in cholesterol in Spring 2 and Sailing show that there is a slight, but not statistically significant decrease of 2-5 mg/dl in DTG compared to RAL. The method of handling missing data does not move the estimated difference between the arms outside the confidence limits obtained using observed data.



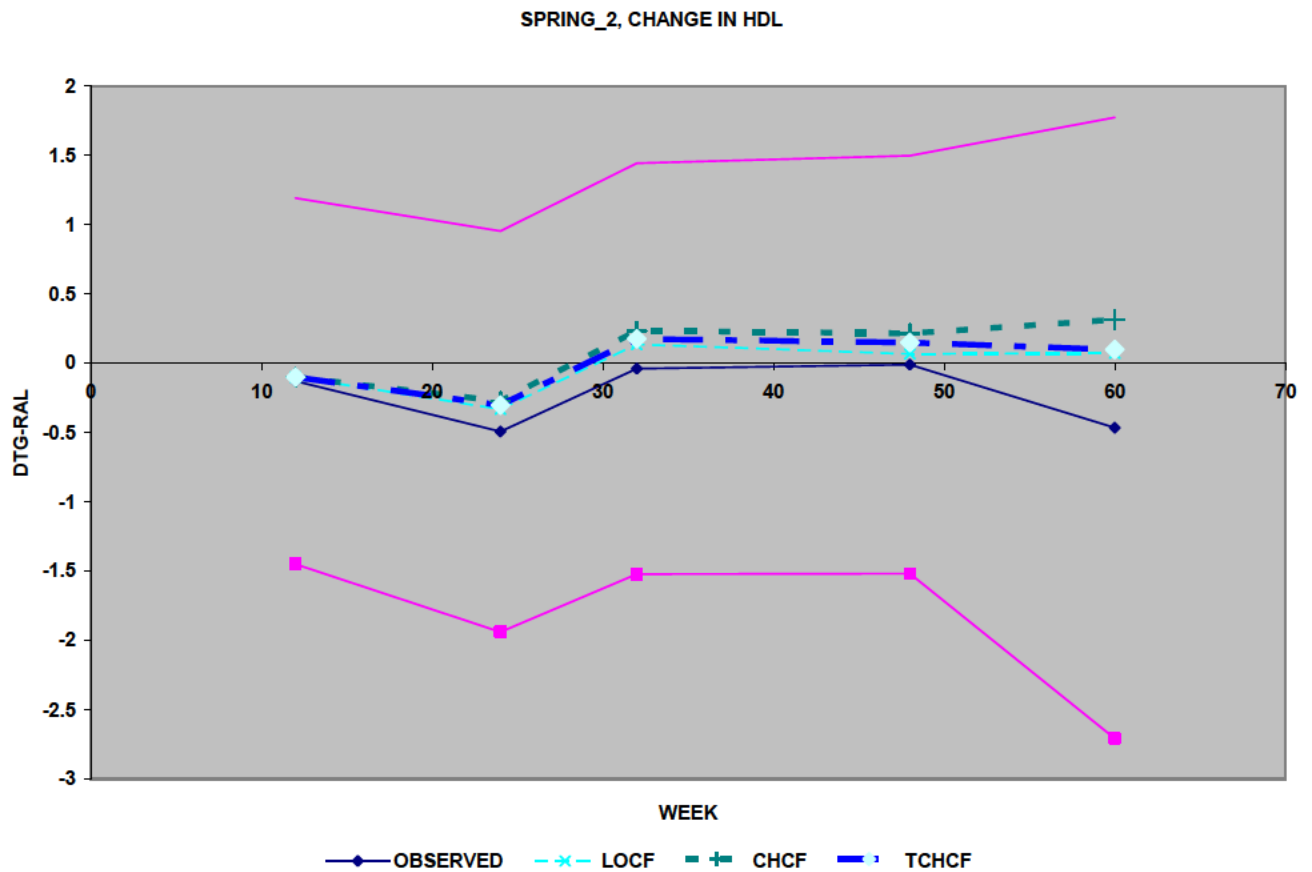
# SAILING, CHANGE IN CHOLESTEROL



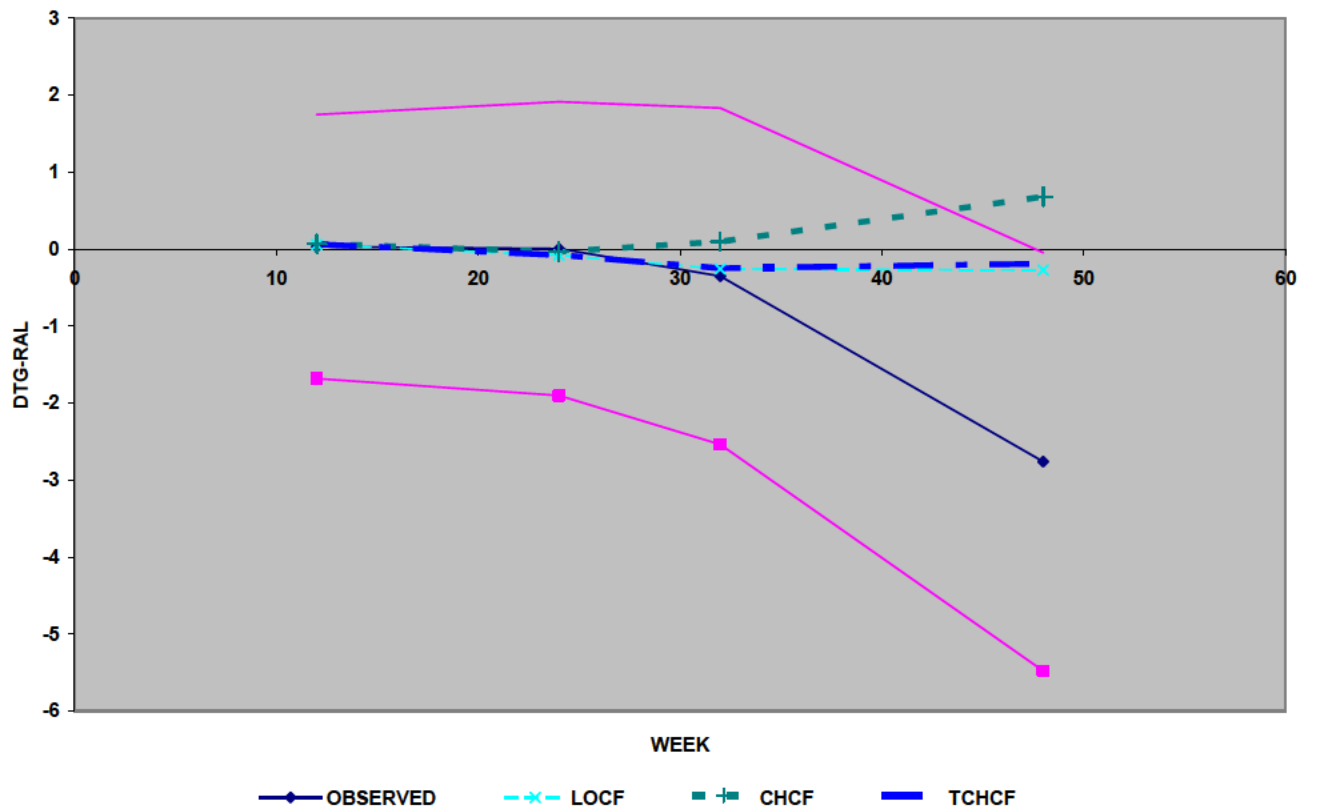
The difference between DTG and EFV in change from baseline on cholesterol in Single is statistically significant with a decrease of about 5 mg/dl, at least out to 48 weeks. At 60 weeks, dependence of results on the method of handling missing data is too great to allow trustworthy conclusions.



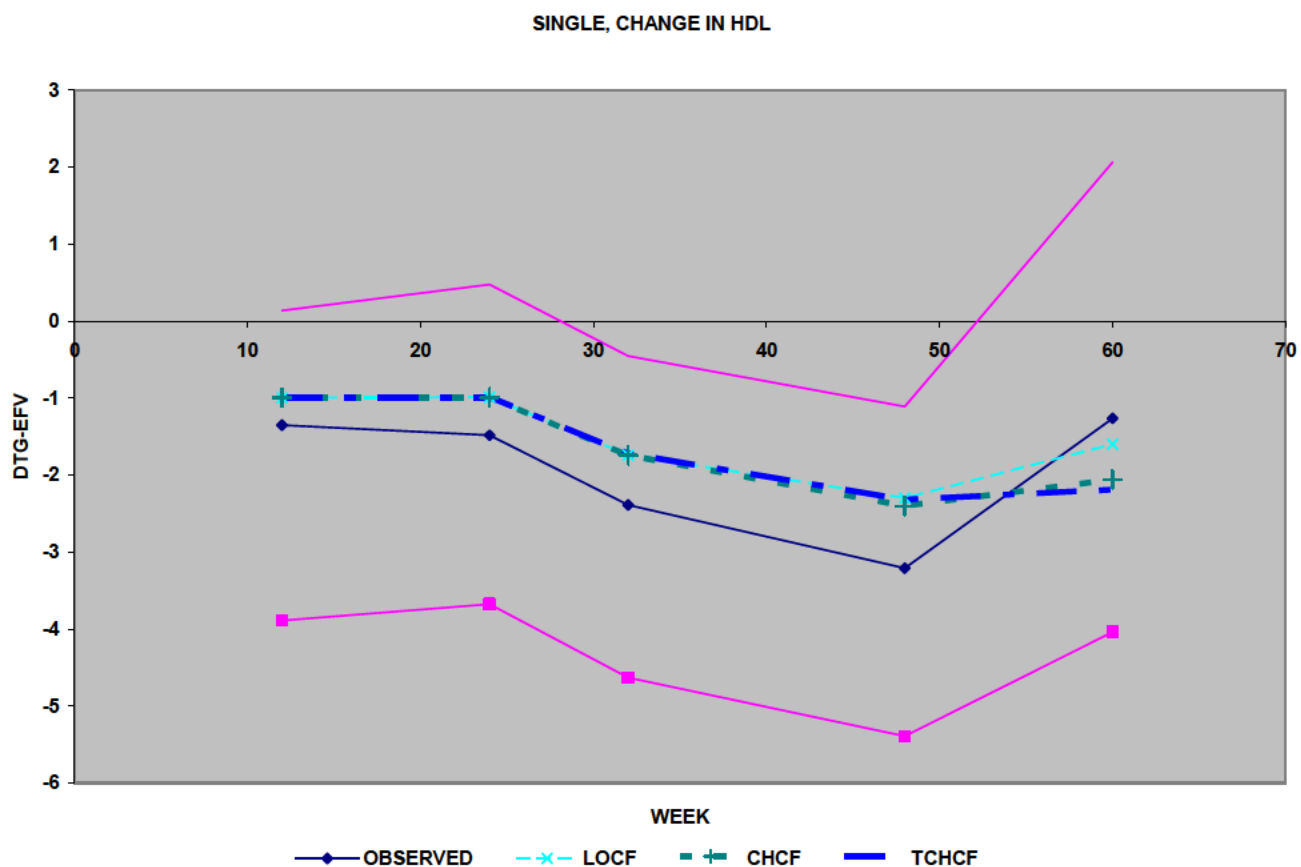
There was no statistically significant difference between DTG and RAL with respect to change from baseline in HDL. In fact, the point estimates for the DTG-RAL difference are nearly zero with the upper and lower 95% confidence bounds symmetric about zero.



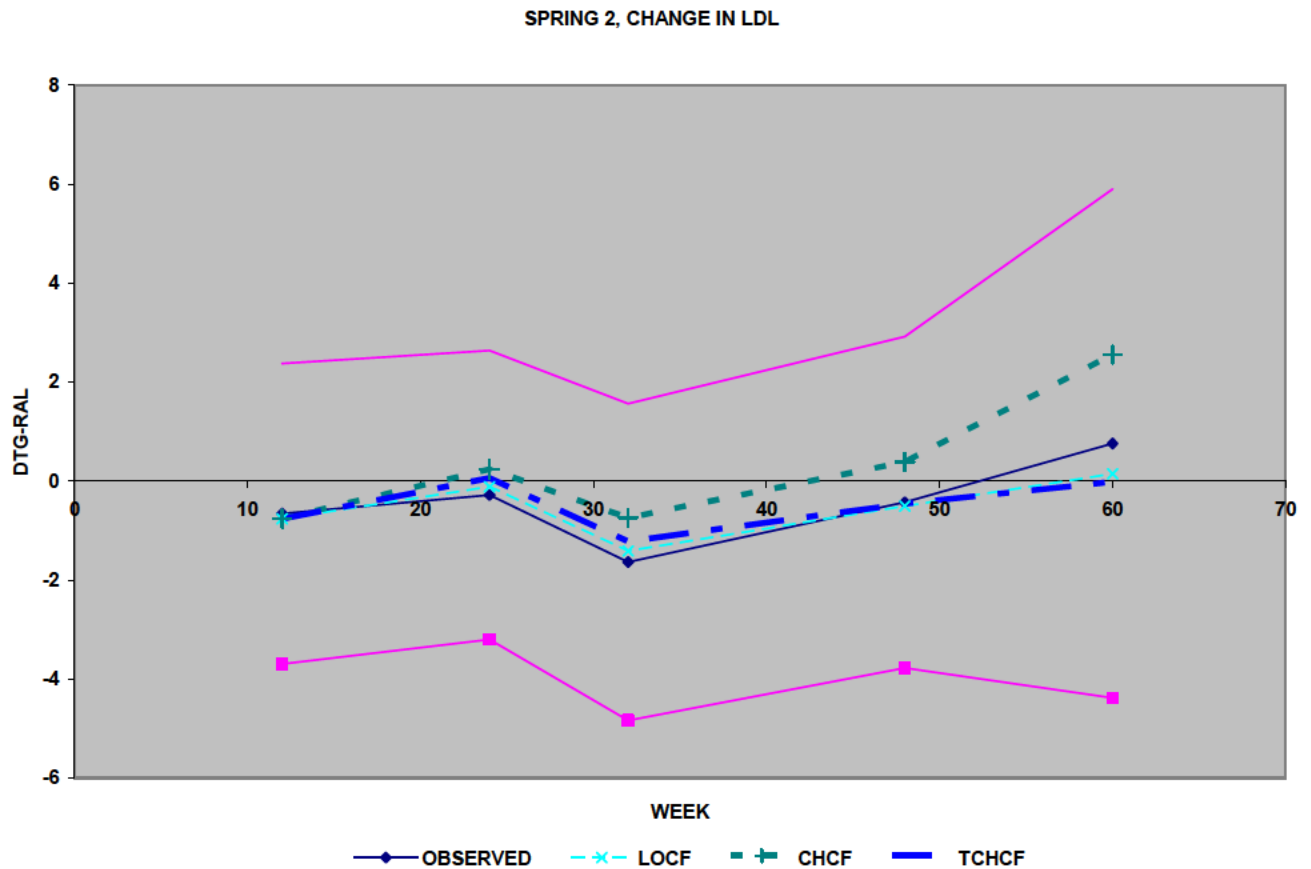
# SAILING, CHANGE IN HDL



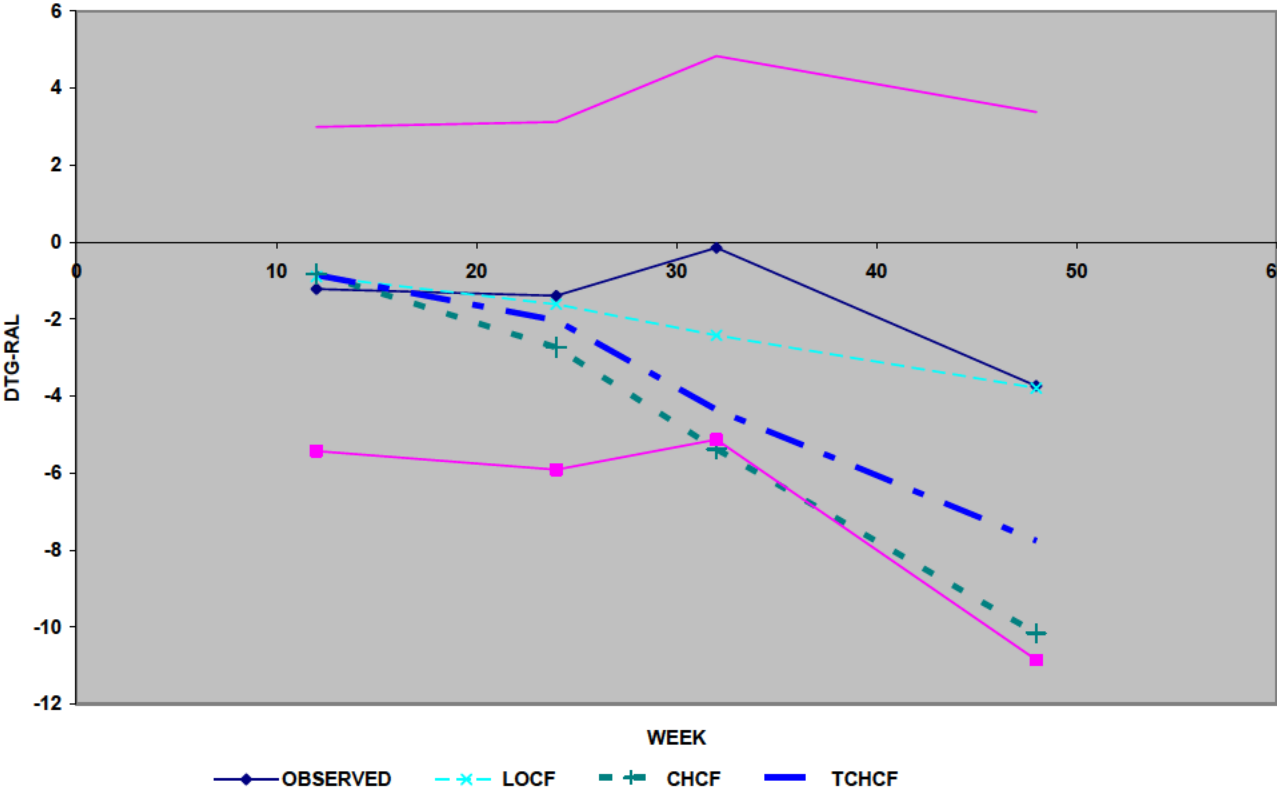
In contrast, there was a statistically significant decrease in change from baseline in HDL when DTG was compared to EFV in Single. The DTG arm showed about a 2 mg/dl greater decrease in HDL.



There is no statistically significant difference between DTG and RAL with respect to change from baseline in LDL either. Again, the point estimates are nearly zero, the method of handling missing data is of little consequence, and the 95% confidence limits are nearly symmetric about zero.



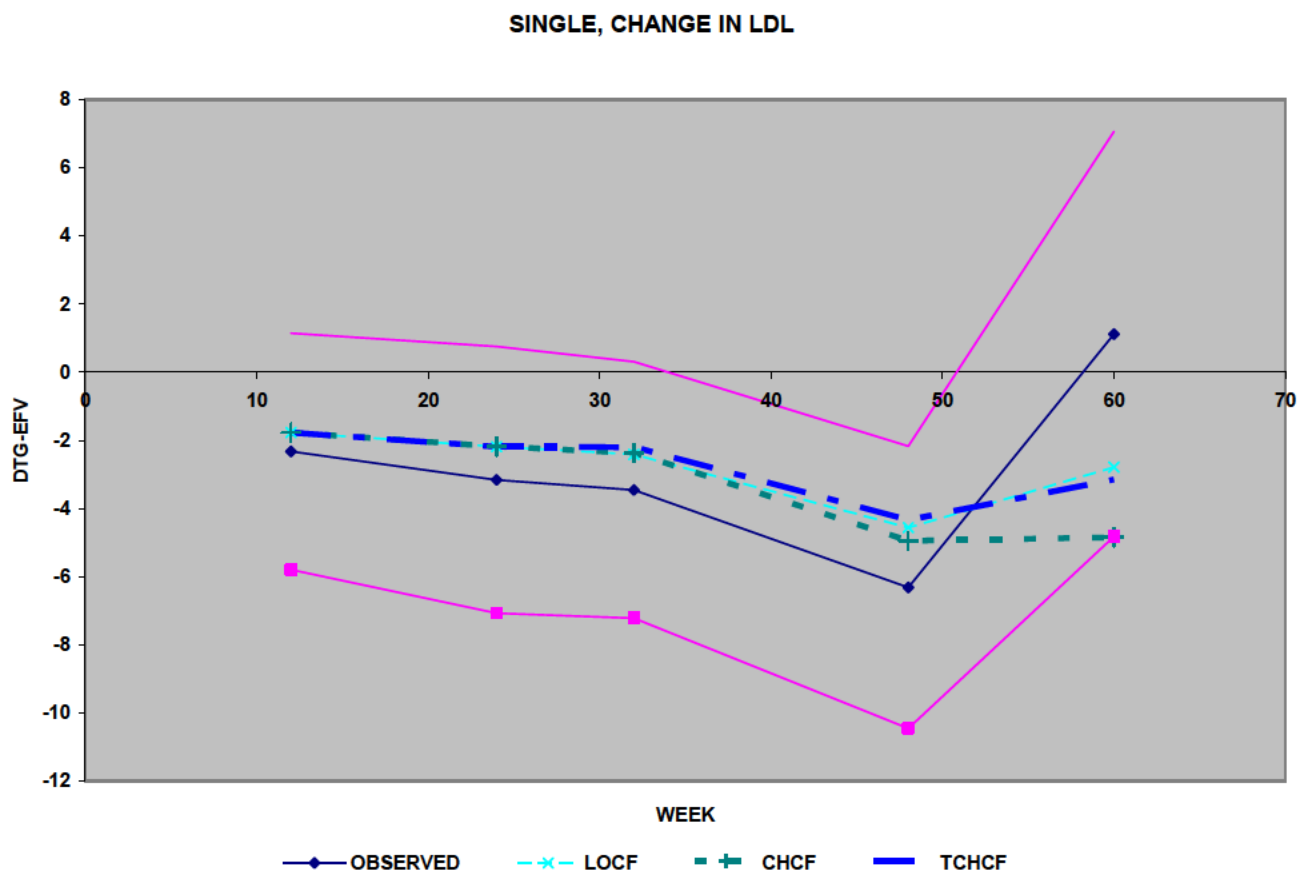
SAILING, CHANGE IN LDL



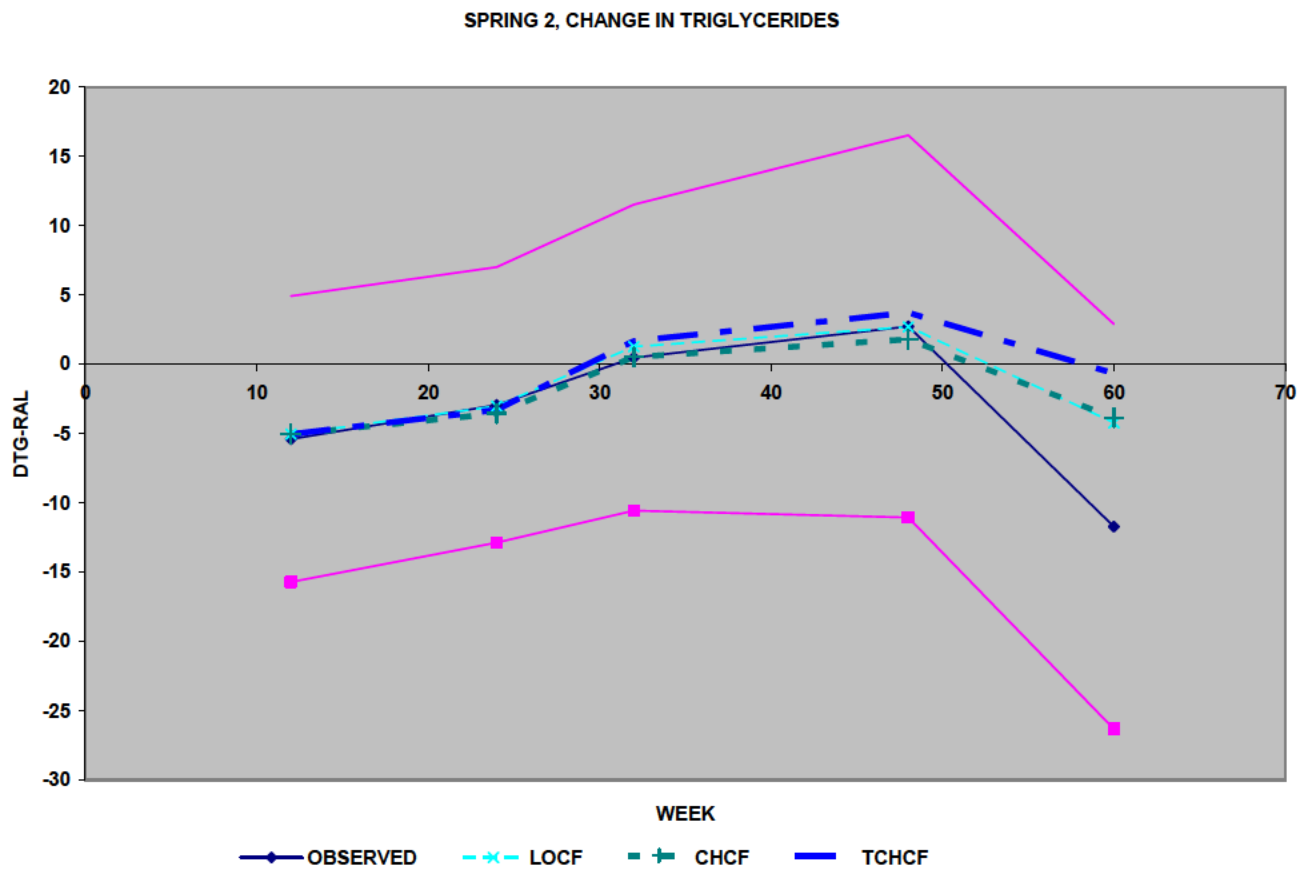




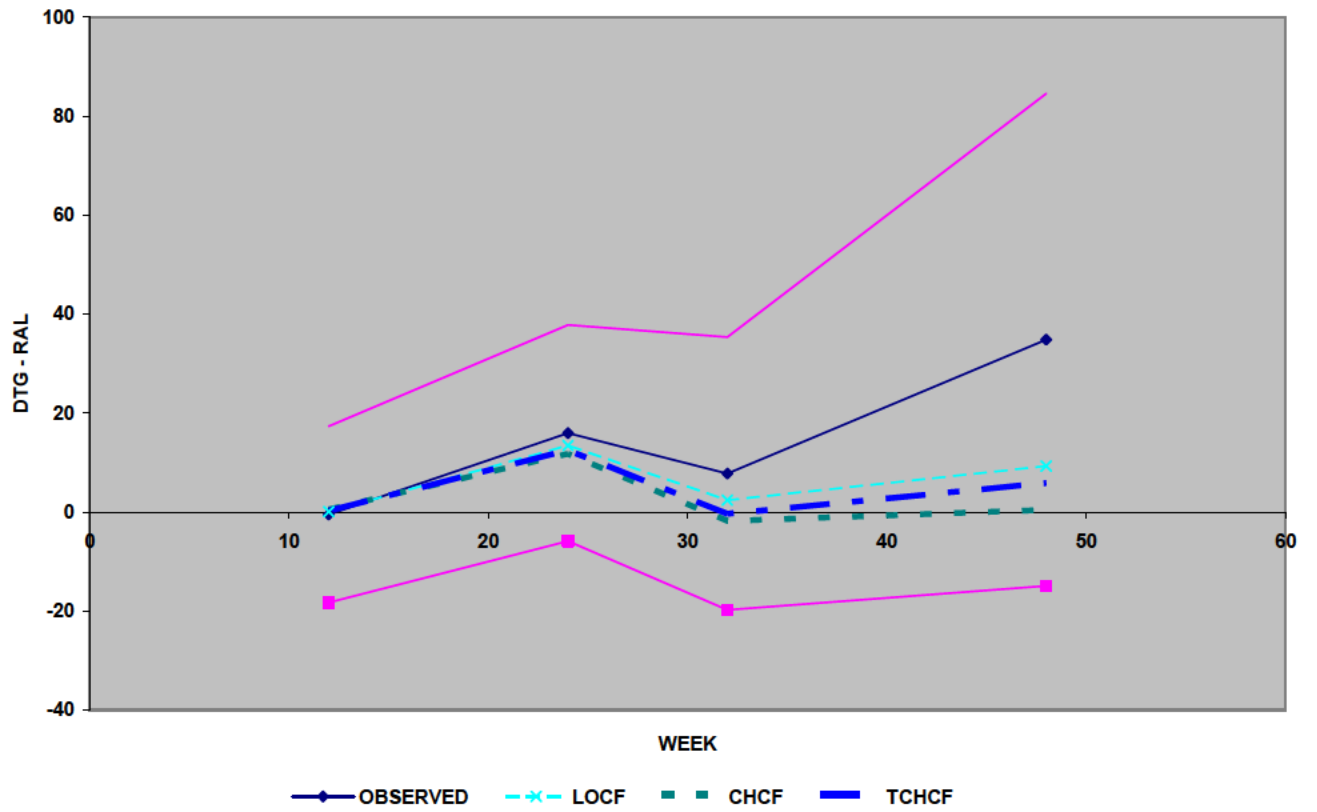
The difference between DTG and EFV was statistically significant, or nearly so, for change from baseline in LDL, estimated to be about 2 to 4 mg/dl.



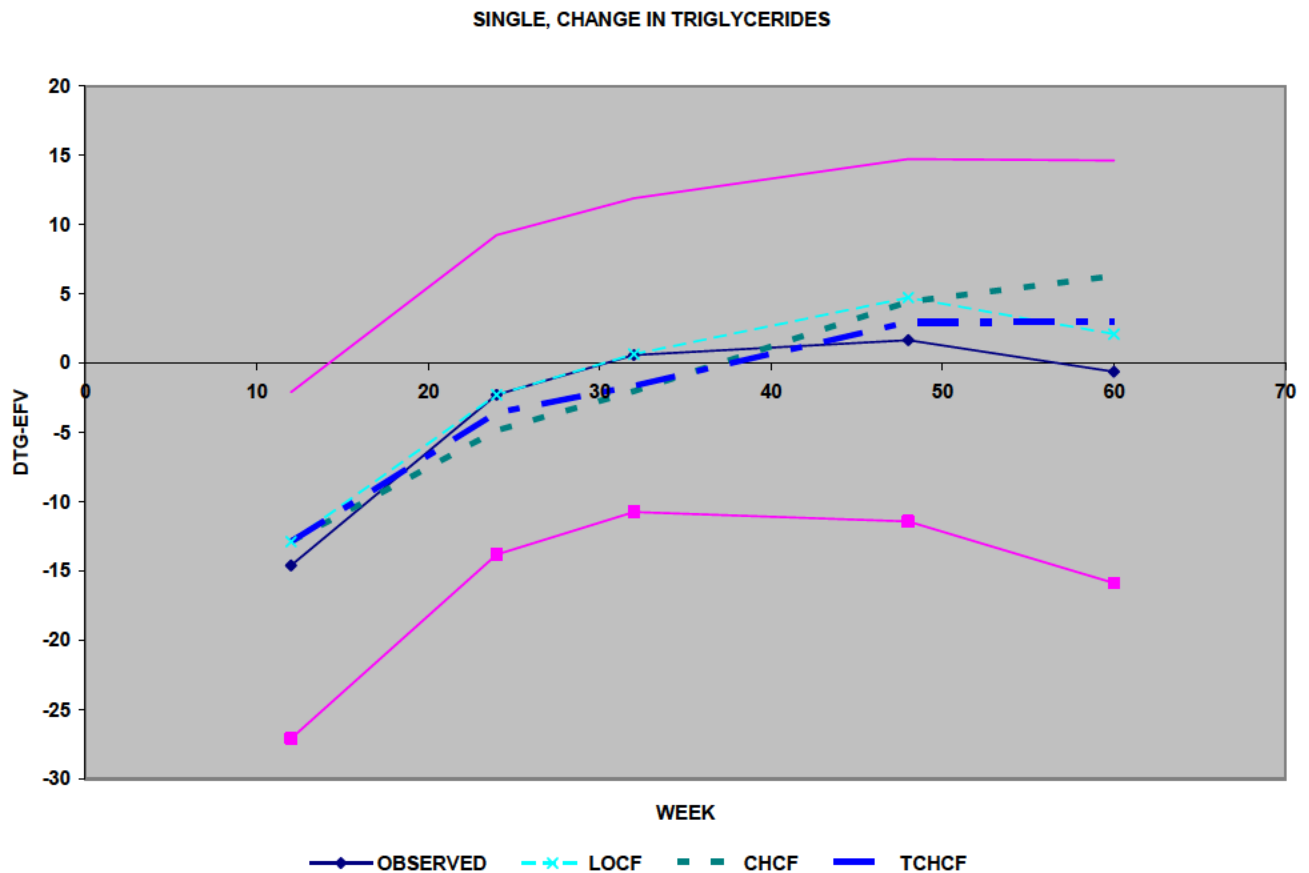
There doesn't appear to be any difference between DTG and RAL with respect to change from baseline in triglycerides. The confidence limits straddle zero although the point estimates show a slightly higher level in the DTG arm of about 3 mg/dl in Spring 2 and about 10 mg/dl in Sailing.



# SAILING, CHANGE IN TRIGLYCERIDES



There was no statistically significant difference between DTG and EFV with respect to change from baseline in triglycerides. Confidence limits are nearly symmetric about zero.



A summary of the above observations is as follows. There appears to be no statistically significant difference between DTG and RAL with respect to any of the four lipids studied. There were statistically significant differences between DTG and EFV. Change from baseline in cholesterol was significant with DTG being about 5 mg/dl lower; change from baseline in HDL was significant with DTG being about 2 mg/dl lower; change from baseline in LDL was nearly significant with DTG being about 2 to 4 mg/dl lower.

There was no real difference between DTG and either RAL or EFV with respect to change from baseline in triglycerides.

## 4. Results in Special Populations

There was little evidence of interactions between treatment and any interesting covariates.

### 4.1 Gender, Race, and Age

The following tables give the results of analyzing the primary endpoints of all seven trials by age, sex, race and the stratum variable used at randomization. For each trial, the tables give the mean difference in the estimated parameter, the lower and upper 95% confidence intervals for the difference, the mean values in the DTG and control arms, and the p-value for testing homogeneity across the sub-groups under consideration. The analyses in this section are all conducted by simple normal approximation without using the protocol specified Mantel-Haenszel weighting based on the randomization strata.

When the parameter being estimated is the change in log, the tables also give the N's in the two arms. For percent BLQ, the arm means are presented as ratios of counts and as percents. There are three tables for trial 1521, one for each of the doses of DTG; for Spring\_1 there are six tables, one for each dose of DTG for change in log and for percent BLQ. For Spring 2, Single, and Sailing there is one table each. For Viking there are two tables, one for percent BLQ in week 24 and week 48; for Viking 3, there are two tables, one for log change at day 11 and one for percent BLQ at week 24. For Viking 3, the control is zero change (i.e., it is a one sample comparison). Notice that each table takes several pages because of the number of sub-groups.

### 4.1.1 Treatment Naïve Trials

TRIAL\_1521\_LOGCHG\_DAY\_11\_DTG\_2MG\_VS\_PLACEBO

	MEAN DIFF	95% LIMITS LOWER	UPPER	DTG	PLAC	N_P	N_D	PVALUE
ALL	-1.580	-2.001	-1.159	-1.452	0.129	7	9	0
AGECAT								
<=32	-1.551			-1.498	0.053	1	2	
32-41	-1.333	-1.957	-0.710	-1.287	0.046	4	3	0
>43	-1.883	-2.342	-1.424	-1.552	0.331	2	4	0
RACE								
Black	-1.788	-3.377	-0.199	-1.545	0.243	2	2	0.0274
White	-1.508	-1.937	-1.079	-1.425	0.083	5	7	0
ETHNCITY								
Hispanic	-1.495			-1.441	0.053	1	1	
Not	-1.594	-2.075	-1.113	-1.453	0.141	6	8	0

TRIAL\_1521\_LOGCHG\_DAY\_11\_DTG\_10MG\_VS\_PLACEBO

	MEAN	95% LIMITS						
	DIFF	LOWER	UPPER	DTG	PLAC	N_P	N_D	PVALUE
ALL	-2.091	-2.451	-1.730	-1.962	0.129	7	9	0
AGECAT								
<=32	-2.237			-2.183	0.053	1	1	
32-41	-1.742	-2.360	-1.124	-1.696	0.046	4	4	0
41-43				-2.253		0	3	
>43	-2.265			-1.933	0.331	2	1	
.	-1.742	-2.360	-1.124			7	9	0
RACE								
Black					0.243	2	0	
White	-2.045	-2.440	-1.650	-1.962	0.083	5	9	0
ETHNCITY								
Hispanic	-1.477			-1.423	0.053	1	1	
Not	-2.171	-2.555	-1.786	-2.029	0.141	6	8	0

TRIAL\_1521\_LOGCHG\_DAY\_11\_DTG\_50MG\_VS\_PLACEBO

	MEAN	95% LIMITS						
	DIFF	LOWER	UPPER	DTG	PLAC	N_P	N_D	PVALUE
ALL	-2.546	-2.856	-2.237	-2.418	0.129	7	10	0
AGECAT								
<=32	-2.405			-2.351	0.053	1	6	
32-41	-2.197			-2.151	0.046	4	1	
41-43	-2.737					0	2	
>43	-2.776			-2.445	0.331	2	1	
RACE								
Black	-2.441	-3.095	-1.787	-2.198	0.243	2	3	0
White	-2.595	-2.943	-2.246	-2.512	0.083	5	7	0
ETHNCITY								
Hispanic					0.053	1	0	
Not	-2.559	-2.892	-2.226	-2.418	0.141	6	10	0



SPRING\_1\_2276\_%BLQ\_WEEK\_16\_DTG\_10mg\_VS\_EFV

	MEAN	95% LIMITS				
	DIFF	LOWER	UPPER	DTG_10mg	EFV	PVALUE
ALL	32.2%	18.0%	46.5%	51/53=96.2%	32/50=64.0%	
STRATUM						
<100_K_ABC/3TC	38.5%	12.0%	64.9%	13/13=100%	8/13=61.5%	0.98
<100_K_TDF/FTC	20.8%	4.6%	37.1%	26/26=100%	19/24=79.2%	
>100_K_ABC/3TC	33.3%	-20.0%	86.7%	4/4=100%	2/3=66.7%	
>100_K_TDF/FTC	50.0%	12.3%	87.7%	8/10=80.0%	3/10=30.0%	
AGECAT						
<=29	17.5%	-11.2%	46.1%	20/21=95.2%	7/9=77.8%	0.99
29-37	30.4%	-5.8%	66.5%	13/14=92.9%	5/8=62.5%	
37-44	50.0%	26.9%	73.1%	10/10=100%	9/18=50.0%	
>44	26.7%	4.3%	49.0%	8/8=100%	11/15=73.3%	
SEX						
F	50.0%	10.0%	90.0%	11/11=100%	3/6=50.0%	0.27
M	29.3%	13.9%	44.7%	40/42=95.2%	29/44=65.9%	
RACE						
Black	0.0%	0.0%	0.0%	8/8=100%	6/6=100%	0.32
White	34.7%	18.6%	50.7%	39/41=95.1%	26/43=60.5%	
Other	100%	100%	100%	4/4=100%	0/1=0.0%	
ETHNICITY						
Hispanic	17.5%	-21.8%	56.7%	8/9=88.9%	5/7=71.4%	0.44
Not	34.9%	19.8%	50.0%	43/44=97.7%	27/43=62.8%	

SPRING\_1\_2276\_%BLQ\_WEEK\_16\_DTG\_25mg\_VS\_EFV

	MEAN	95% LIMITS				
	DIFF	LOWER	UPPER	DTG_10mg	EFV	PVALUE
ALL	30.0%	15.2%	44.8%	47/50=94.0%	32/50=64.0%	

STRATUM

<100_K__ABC/3TC	38.5%	12.0%	64.9%	12/12=100%	8/13=61.5%	0.32
<100_K__TDF/FTC	20.8%	4.6%	37.1%	24/24=100%	19/24=79.2%	
>100_K__ABC/3TC	-16.7%	-89.1%	55.8%	2/4=50.0%	2/3=66.7%	
>100_K__TDF/FTC	60.0%	26.1%	93.9%	9/10=90.0%	3/10=30.0%	

AGECAT

<=29	22.2%	-4.9%	49.4%	12/12=100%	7/9=77.8%	0.95
29-37	29.2%	-7.8%	66.2%	11/12=91.7%	5/8=62.5%	
37-44	36.7%	7.9%	65.5%	13/15=86.7%	9/18=50.0%	
>44	26.7%	4.3%	49.0%	11/11=100%	11/15=73.3%	

SEX

F	30.0%	-23.2%	83.2%	4/5=80.0%	3/6=50.0%	0.65
M	29.6%	14.4%	44.9%	43/45=95.6%	29/44=65.9%	

RACE

Black	0.0%	0.0%	0.0%	9/9=100%	6/6=100%	1
White	32.2%	15.6%	48.9%	38/41=92.7%	26/43=60.5%	

ETHNICITY

Hispanic	14.3%	-28.0%	56.6%	6/7=85.7%	5/7=71.4%	0.43
Not	32.6%	16.8%	48.3%	41/43=95.3%	27/43=62.8%	

SPRING\_1\_2276\_%BLQ\_WEEK\_16\_DTG\_50mg\_VS\_EFV

	MEAN	95% LIMITS				
	DIFF	LOWER	UPPER	DTG_10mg	EFV	PVALUE
ALL	26.0%	10.3%	41.7%	45/50=90.0%	32/50=64.0%	

STRATUM

<100_K__ABC/3TC	30.1%	-0.6%	60.9%	11/12=91.7%	8/13=61.5%	0.57
<100_K__TDF/FTC	12.5%	-7.2%	32.2%	22/24=91.7%	19/24=79.2%	
>100_K__ABC/3TC	8.3%	-59.8%	76.5%	3/4=75.0%	2/3=66.7%	
>100_K__TDF/FTC	60.0%	26.1%	93.9%	9/10=90.0%	3/10=30.0%	

AGECAT

<=29	13.9%	-17.5%	45.2%	11/12=91.7%	7/9=77.8%	0.92
29-37	30.8%	-5.0%	66.7%	14/15=93.3%	5/8=62.5%	
37-44	31.8%	-0.6%	64.3%	9/11=81.8%	9/18=50.0%	
>44	18.3%	-9.0%	45.6%	11/12=91.7%	11/15=73.3%	

SEX

F	33.3%	-16.6%	83.2%	5/6=83.3%	3/6=50.0%	0.99
M	25.0%	8.6%	41.4%	40/44=90.9%	29/44=65.9%	

RACE

Black	-9.1%	-26.1%	7.9%	10/11=90.9%	6/6=100%	0.24
White	29.0%	11.4%	46.6%	34/38=89.5%	26/43=60.5%	

ETHNICITY

Hispanic	28.6%	-4.9%	62.0%	8/8=100%	5/7=71.4%	0.49
Not	25.3%	7.9%	42.8%	37/42=88.1%	27/43=62.8%	

SPRING_2_3086_%BLQ_WEEK_48						
	MEAN	95% LIMITS				
	DIFF	LOWER	UPPER	DTG_50mg	RAL	PVALUE
ALL	2.7%	-2.0%	7.3%	355/403=88.1%	346/405=85.4%	
STRATUM						
<100_K__ABC/3TC		-0.8%	-8.3%	6.7%	111/124=89.5%	112/124=90.3%
<100_K__TDF/FTC		1.0%	-4.9%	6.9%	152/165=92.1%	154/169=91.1%
>100_K__ABC/3TC		-4.7%	-23.8%	14.5%	27/35=77.1%	27/33=81.8%
>100_K__TDF/FTC		16.7%	3.7%	29.7%	65/76=85.5%	53/77=68.8%
AGEGPCD						
<36	4.1%	-2.8%	11.1%	157/179=87.7%	178/213=83.6%	
>=36	1.2%	-4.9%	7.2%	198/221=89.6%	168/190=88.4%	
AGECAT						
<=30	6.3%	-3.0%	15.5%	98/113=86.7%	103/128=80.5%	0.85
30-36	0.0%	-10.2%	10.1%	70/81=86.4%	83/96=86.5%	
36-44	1.1%	-8.1%	10.3%	106/121=87.6%	77/89=86.5%	
>44	1.8%	-6.5%	10.1%	81/88=92.0%	83/92=90.2%	
SEX						
F	6.4%	-7.3%	20.0%	49/56=87.5%	43/53=81.1%	0.61
M	2.1%	-2.9%	7.1%	306/347=88.2%	303/352=86.1%	
RACE						
Black	0.6%	-13.7%	14.9%	47/56=83.9%	40/48=83.3%	0.87
White	3.2%	-1.8%	8.2%	300/338=88.8%	296/346=85.5%	
Other	-2.0%	-28.7%	24.6%	8/9=88.9%	10/11=90.9%	
ETHNICITY						
Hispanic	8.4%	-4.0%	20.8%	40/43=93.0%	44/52=84.6%	0.34
Not	1.9%	-3.1%	7.0%	315/360=87.5%	302/353=85.6%	

SINGLE_4467_%BLQ_WEEK_48						
	MEAN	95% LIMITS				
	DIFF	LOWER	UPPER	DTG_50mg	EFV	PVALUE
ALL	7.0%	2.1%	11.9%	364/414=87.9%	339/419=80.9%	
STRATUM						
<100_K_<=200	3.5%	-15.1%	22.1%	19/21=90.5%	20/23=87.0%	
<100_K_>200	6.5%	0.7%	12.3%	235/262=89.7%	218/262=83.2%	
>100_K_<=200	1.5%	-18.6%	21.6%	26/34=76.5%	27/36=75.0%	
>100_K_>200	11.3%	0.8%	21.9%	84/95=88.4%	74/96=77.1%	
AGECAT						
<=29	5.2%	-4.6%	15.0%	105/125=84.0%	93/118=78.8%	0.53
29-36	10.3%	1.7%	19.0%	94/101=93.1%	91/110=82.7%	
36-43	10.6%	-0.2%	21.4%	71/80=88.8%	75/96=78.1%	
>43	2.8%	-6.9%	12.5%	94/108=87.0%	80/95=84.2%	
SEX						
F	12.1%	-1.8%	25.9%	57/67=85.1%	46/63=73.0%	0.62
M	6.2%	1.0%	11.4%	307/347=88.5%	293/356=82.3%	
RACE						
Black	8.7%	-1.9%	19.4%	92/111=82.9%	86/116=74.1%	
White	5.6%	0.1%	11.2%	255/284=89.8%	239/284=84.2%	
Other	17.3%	-7.6%	42.1%	17/19=89.5%	13/18=72.2%	
ETHNICITY						
Hispanic	1.8%	-12.1%	15.7%	47/56=83.9%	46/56=82.1%	0.38
Not	7.8%	2.6%	13.1%	317/358=88.5%	293/363=80.7%	

### 4.1.2 Two Class Resistant INI Naïve Trial

SAILING\_1762\_%BLQ\_WEEK\_24

	MEAN	95% LIMITS		DTG_50mg	RAL	PVALUE
	DIFF	LOWER	UPPER			
ALL	9.0%	2.7%	15.3%	281/354=79.4%	254/361=70.4%	

#### STRATUM

<50_K_DRV/r_OBR<2	50.0%	1.0%	99.0%	4/4=100%	2/4=50.0%	
<50_K_DRV/r_OBR=2	-4.4%	-18.9%	10.1%	40/49=81.6%	43/50=86.0%	
<50_K_No_DRV/r_OBR<2	7.7%	-5.5%	20.9%	50/57=87.7%	48/60=80.0%	
<50_K_No_DRV/r_OBR=2	6.6%	-3.1%	16.3%	110/133=82.7%	102/134=76.1%	
>50_K_DRV/r_OBR<2				1/1=100%	0/0=.	
>50_K_DRV/r_OBR=2	-7.7%	-38.1%	22.7%	11/16=68.8%	13/17=76.5%	
>50_K_No_DRV/r_OBR<2	22.7%	-4.4%	49.8%	16/24=66.7%	11/25=44.0%	
>50_K_No_DRV/r_OBR=2	22.4%	6.4%	38.3%	49/65=75.4%	35/66=53.0%	

#### AGEGPCD

<43	10.5%	1.4%	19.5%	141/178=79.2%	121/176=68.8%	
>=43	8.0%	-0.6%	16.6%	140/171=81.9%	133/180=73.9%	

#### AGEGP3CD

<50	14.1%	6.9%	21.3%	217/265=81.9%	185/273=67.8%	
>=50	-6.9%	-19.1%	5.2%	64/84=76.2%	69/83=83.1%	

#### AGECAT

<=35	21.8%	8.7%	35.0%	74/92=80.4%	51/87=58.6%	0.007
35-42	1.0%	-11.3%	13.3%	67/86=77.9%	70/91=76.9%	
42-49	18.9%	6.8%	31.0%	76/91=83.5%	64/99=64.6%	
>49	-6.8%	-19.1%	5.4%	64/85=75.3%	69/84=82.1%	

#### SEX

F	12.4%	1.7%	23.2%	89/107=83.2%	87/123=70.7%	0.42
M	7.6%	-0.2%	15.4%	192/247=77.7%	167/238=70.2%	

#### RACE

Black	10.5%	1.5%	19.6%	125/153=81.7%	126/177=71.2%	
White	8.9%	-0.2%	18.1%	139/178=78.1%	121/175=69.1%	
Other	-14.8%	-44.3%	14.7%	16/22=72.7%	7/8=87.5%	

#### ETHNICITY

Hispanic	15.5%	4.4%	26.6%	106/135=78.5%	75/119=63.0%	0.23
Not	5.9%	-1.7%	13.6%	175/219=79.9%	179/242=74.0%	

### 4.1.3 Two Class Resistant, INI Resistant Trials

VIKING_(2961)_LOGCHANGE_DAY_11							
	MEAN	95% LIMITS					
	DIFF	LOWER	UPPER	DTG	PLAC	N_P	N_D
ALL	-0.32008	-0.71742	0.077261	-1.73798	-1.41790	26	19
AGEGPCD							
<47	-0.26732	-0.87838	0.34373	-2.08682	-1.81950	10	7
>=47	-0.36758	-0.82025	0.08508	-1.53449	-1.16690	16	12
AGECAT							
<=43	-0.33200	-0.84739	0.18340	-2.46284	-2.13084	6	3
43-47	-0.30013	-1.29585	0.69559	-1.57177	-1.27164	5	7
47-52.5	-0.87071	-1.39028	-0.35115	-1.93867	-1.06796	7	6
>52.5	0.28126	-0.28888	0.85140	-0.99955	-1.28081	8	3
SEX							
F	0.63416	-0.29414	1.56245	-1.33595	-1.97011	2	4
M	-0.47330	-0.89382	-0.05278	-1.84519	-1.37188	24	15
RACE							
Black	0.50228	-0.51387	1.51843	-1.47046	-1.97274	2	4
White	-0.43765	-0.85597	-0.01934	-1.80932	-1.37166	24	15
ETHNICITY							
Hispanic	0.24289	-0.43064	0.91642	-1.38919	-1.63208	3	5
Not	-0.47258	-0.92181	-0.02335	-1.86255	-1.38997	23	14

VIKING_2961_%BLQ_WEEK_24						
	MEAN	95% LIMITS		DTG		PVALUE
	DIFF	LOWER	UPPER	50mg_BID	50mg_QD	
ALL	26.4%	0.3%	52.5%	17/24=70.8%	12/27=44.4%	
AGEGPCD						
<47	21.2%	-21.4%	63.8%	6/9=66.7%	5/11=45.5%	0.76
>=47	29.6%	-3.5%	62.6%	11/15=73.3%	7/16=43.8%	
AGECAT						
<=43	22.9%	-27.9%	73.6%	4/5=80.0%	4/7=57.1%	0.65
43-47	26.7%	-26.2%	79.5%	6/9=66.7%	2/5=40.0%	
47-52.5	57.1%	14.8%	99.5%	5/7=71.4%	1/7=14.3%	
>52.5	4.2%	-58.8%	67.2%	2/3=66.7%	5/8=62.5%	
SEX						
F	16.7%	-62.2%	95.6%	4/6=66.7%	1/2=50.0%	0.81
M	28.2%	-0.2%	56.6%	13/18=72.2%	11/25=44.0%	
RACE						
Black	-40.0%	-82.9%	2.9%	3/5=60.0%	3/3=100%	0.046
White	36.2%	8.5%	63.9%	14/19=73.7%	9/24=37.5%	
ETHNICITY						
Hispanic	-26.7%	-95.1%	41.8%	2/5=40.0%	2/3=66.7%	0.1
Not	37.3%	10.4%	64.2%	15/19=78.9%	10/24=41.7%	
VIKING_2961_%BLQ_WEEK_48						
ALL	33.3%	7.4%	59.3%	16/24=66.7%	9/27=33.3%	
AGEGPCD						
<47	30.3%	-11.6%	72.2%	6/9=66.7%	4/11=36.4%	0.86
>=47	35.4%	2.5%	68.4%	10/15=66.7%	5/16=31.3%	
AGECAT						
<=43	57.1%	20.5%	93.8%	5/5=100%	3/7=42.9%	0.43
43-47	4.4%	-49.4%	58.3%	4/9=44.4%	2/5=40.0%	
47-52.5	57.1%	14.8%	99.5%	5/7=71.4%	1/7=14.3%	
>52.5	29.2%	-33.8%	92.2%	2/3=66.7%	3/8=37.5%	
SEX						
F	16.7%	-62.2%	95.6%	4/6=66.7%	1/2=50.0%	0.7
M	34.7%	6.2%	63.1%	12/18=66.7%	8/25=32.0%	
RACE						
Black	13.3%	-50.5%	77.2%	4/5=80.0%	2/3=66.7%	0.71
White	34.0%	5.7%	62.3%	12/19=63.2%	7/24=29.2%	
ETHNICITY						
Hispanic	-46.7%	-100%	17.2%	1/5=20.0%	2/3=66.7%	0.014
Not	49.8%	24.0%	75.6%	15/19=78.9%	7/24=29.2%	



VIKING_3_2574_LOG_CHANGE_DAY_8					
	MEAN	95% LIMITS		N	PVALUE
		LOWER	UPPER		
ALL	-1.439	-1.525	-1.352	182	0
AGEGRP					
<65	-1.436	-1.524	-1.347	178	0
>=65	-1.578	-1.861	-1.296	4	0
AGECAT					
<=43	-1.584	-1.752	-1.416	51	0
43-48	-1.414	-1.605	-1.222	50	0
48-52	-1.335	-1.510	-1.160	36	0
>52	-1.384	-1.527	-1.242	45	0
SEX					
F	-1.293	-1.461	-1.126	42	0
M	-1.482	-1.582	-1.382	140	0
RACE					
Black	-1.441	-1.626	-1.257	49	0
White	-1.443	-1.542	-1.344	129	0
Other	-1.252	-1.806	-0.698	4	0
ETHNICITY					
Hispanic	-1.476	-1.737	-1.215	19	0
Not	-1.434	-1.526	-1.342	163	0

VIKING_3_2574_%BLQ_WEEK_24					
	MEAN	95% LIMITS			PVALUE
		LOWER	UPPER		
ALL	76/114=66.7%	58.0%	75.3%		0
AGEGRP					
<65	73/111=65.8%	56.9%	74.6%		0
>=65	3/3=100%	100%	100%		.
AGECAT					
<=43	17/25=68.0%	49.7%	86.3%		0
43-48	26/34=76.5%	62.2%	90.7%		0
48-52	15/27=55.6%	36.8%	74.3%		0
>52	18/28=64.3%	46.5%	82.0%		0
SEX					
F	15/25=60.0%	40.8%	79.2%		0
M	61/89=68.5%	58.9%	78.2%		0
RACE					
Black	15/28=53.6%	35.1%	72.0%		0
White	61/85=71.8%	62.2%	81.3%		0
ETHNICITY					
Hispanic	9/11=81.8%	59.0%	104.6%		0
Not	67/103=65.0%	55.8%	74.3%		0

## 4.2 Baseline HIV, CD4, CDC Class

The following tables give the results of analyzing the primary endpoints of all seven trials by covariates reflecting baseline illness levels: baseline HIV level, baseline CD4 count, baseline CDC class, and also risk factor attributed to initial infection. The tables are laid out as in the previous section.

### 4.2.1 Treatment Naïve Trials

TRIAL\_1521\_LOGCHG\_DAY\_11

DTG\_2MG\_VS\_PLACEBO

	MEAN DIFF	95% LIMITS		DTG	PLAC	N_P	N_D
		LOWER	UPPER				
BASLINE HIV							
<=13000	-2.186	-3.013	-1.359	-1.932	0.254	4	2
13000-26250	-1.839			-1.586	0.252	1	4
26250-45800	-0.488			-0.752	-0.264	1	1
>45800	-0.946			-1.053	-0.107	1	2

DTG\_10MG\_VS\_PLACEBO

BASLINE HIV

<=13000					0.254	4	0
13000-26250	-1.868			-1.615	0.252	1	3
26250-45800	-1.803			-2.067	-0.264	1	4
>45800	-2.166			-2.273	-0.107	1	2

DTG\_50MG\_VS\_PLACEBO

BASLINE HIV

<=13000	-2.326	-2.729	-1.924	-2.072	0.254	4	3
13000-26250	-2.884			-2.632	0.252	1	1
26250-45800	-2.170			-2.433	-0.264	1	3
>45800	-2.571			-2.677	-0.107	1	3

SPRING_1_2276_%BLQ_WEEK_16_DTG_10mg_VS_EFV						
	MEAN	95% LIMITS				
RISK_FACTOR	DIFF	LOWER	UPPER	DTG_10mg	EFV	PVALUE
Drug_use	50.0%	-19.3%	119.3%	3/3=100%	1/2=50.0%	0.76
Homosexual	31.3%	12.5%	50.0%	30/32=93.8%	20/32=62.5%	
Other	31.3%	8.5%	54.0%	18/18=100%	11/16=68.8%	
NRTIGP						
ABC/3TC	33.3%	9.5%	57.2%	17/17=100%	10/15=66.7%	0.84
TDF/FTC	29.7%	12.0%	47.5%	34/36=94.4%	22/34=64.7%	
BASELINE HIV						
<=100_K	31.0%	15.5%	46.4%	41/42=97.6%	26/39=66.7%	0.77
>100_K	36.4%	2.4%	70.3%	10/11=90.9%	6/11=54.5%	
BASELINE HIV						
<=8283	21.4%	-0.1%	42.9%	16/16=100%	11/14=78.6%	0.9
8283-33580	41.7%	13.8%	69.6%	12/12=100%	7/12=58.3%	
33580-83571	25.0%	-5.9%	55.9%	11/12=91.7%	8/12=66.7%	
>83571	42.3%	10.5%	74.1%	12/13=92.3%	6/12=50.0%	
BASELINE CD4 COUNT						
<300	46.7%	25.7%	67.7%	29/30=96.7%	12/24=50.0%	0.32
>=300	18.7%	0.5%	36.9%	22/23=95.7%	20/26=76.9%	
BASELINE CD4 COUNT						
<=242	52.1%	21.8%	82.4%	15/16=93.8%	5/12=41.7%	0.67
242-305	41.7%	13.8%	69.6%	16/16=100%	7/12=58.3%	
305-393	26.7%	4.3%	49.0%	7/7=100%	11/15=73.3%	
>393	11.0%	-15.4%	37.5%	13/14=92.9%	9/11=81.8%	
BASELINE CDC GROUP						
A	33.5%	18.2%	48.8%	45/47=95.7%	28/45=62.2%	0.95
B	25.0%	-17.4%	67.4%	6/6=100%	3/4=75.0%	

SPRING_1_2276_%BLQ_WEEK_16_DTG_25mg_VS_EFV						
	MEAN	95% LIMITS				
RISK_FACTOR	DIFF	LOWER	UPPER	DTG_10mg	EFV	PVALUE
Drug_use	50.0%	-19.3%	119.3%	2/2=100%	1/2=50.0%	0.77
Homosexual	32.1%	13.8%	50.4%	35/37=94.6%	20/32=62.5%	
Other	22.2%	-6.2%	50.5%	10/11=90.9%	11/16=68.8%	
NRTIGP						
ABC/3TC	21.6%	-6.8%	49.9%	15/17=88.2%	10/15=66.7%	0.75
TDF/FTC	32.3%	15.2%	49.4%	32/33=97.0%	22/34=64.7%	
BASELINE HIV						
<=100_K	30.8%	15.3%	46.4%	39/40=97.5%	26/39=66.7%	0.38
>100_K	25.5%	-13.0%	63.9%	8/10=80.0%	6/11=54.5%	
BASELINE HIV						
<=8283	21.4%	-0.1%	42.9%	12/12=100%	11/14=78.6%	0.83
8283-33580	41.7%	13.8%	69.6%	13/13=100%	7/12=58.3%	
33580-83571	26.2%	-3.7%	56.1%	13/14=92.9%	8/12=66.7%	
>83571	31.8%	-4.5%	68.1%	9/11=81.8%	6/12=50.0%	
BASELINE CD4 COUNT						
<300	40.0%	16.1%	63.9%	18/20=90.0%	12/24=50.0%	0.97
>=300	19.7%	2.3%	37.2%	29/30=96.7%	20/26=76.9%	
BASELINE CD4 COUNT						
<=242	58.3%	30.4%	86.2%	13/13=100%	5/12=41.7%	0.38
242-305	16.7%	-24.3%	57.6%	6/8=75.0%	7/12=58.3%	
305-393	20.0%	-5.7%	45.7%	14/15=93.3%	11/15=73.3%	
>393	18.2%	-4.6%	41.0%	14/14=100%	9/11=81.8%	
BASELINE CDC GROUP						
A	31.0%	15.0%	47.0%	41/44=93.2%	28/45=62.2%	0.94
B	25.0%	-17.4%	67.4%	5/5=100%	3/4=75.0%	
C	0.0%	0.0%	0.0%	1/1=100%	1/1=100%	

SPRING_1_2276_%BLQ_WEEK_16_DTG_50mg_VS_EFV						
	MEAN	95% LIMITS				
RISK_FACTOR	DIFF	LOWER	UPPER	DTG_10mg	EFV	PVALUE
Homosexual	26.1%	6.3%	45.9%	31/35=88.6%	20/32=62.5%	
Other	24.6%	-1.4%	50.6%	14/15=93.3%	11/16=68.8%	
NRTIGP						
ABC/3TC	20.8%	-8.0%	49.7%	14/16=87.5%	10/15=66.7%	0.95
TDF/FTC	26.5%	7.8%	45.2%	31/34=91.2%	22/34=64.7%	
BASELINE HIV						
<=100_K	25.4%	8.3%	42.5%	35/38=92.1%	26/39=66.7%	0.86
>100_K	28.8%	-7.4%	65.0%	10/12=83.3%	6/11=54.5%	
BASELINE HIV						
<=8283	21.4%	-0.1%	42.9%	9/9=100%	11/14=78.6%	0.48
8283-33580	41.7%	13.8%	69.6%	14/14=100%	7/12=58.3%	
33580-83571	11.9%	-22.3%	46.2%	11/14=78.6%	8/12=66.7%	
>83571	34.6%	0.2%	69.0%	11/13=84.6%	6/12=50.0%	
BASELINE CD4 COUNT						
<300	41.7%	18.8%	64.5%	22/24=91.7%	12/24=50.0%	0.21
>=300	11.5%	-8.8%	31.9%	23/26=88.5%	20/26=76.9%	
BASELINE CD4 COUNT						
<=242	58.3%	30.4%	86.2%	10/10=100%	5/12=41.7%	0.25
242-305	29.2%	-3.1%	61.4%	14/16=87.5%	7/12=58.3%	
305-393	3.6%	-28.4%	35.6%	10/13=76.9%	11/15=73.3%	
>393	18.2%	-4.6%	41.0%	11/11=100%	9/11=81.8%	
BASELINE CDC GROUP						
A	28.0%	11.2%	44.8%	37/41=90.2%	28/45=62.2%	0.97
B	13.9%	-33.3%	61.0%	8/9=88.9%	3/4=75.0%	

SPRING_2_3086_%BLQ_WEEK_48						
	MEAN	95% LIMITS				
	DIFF	LOWER	UPPER	DTG_50mg	RAL	PVALUE
RISK_FACTOR						
Drug_use	15.0%	-13.7%	43.7%	15/20=75.0%	12/20=60.0%	
Homosexual	1.3%	-3.7%	6.3%	242/265=91.3%	226/251=90.0%	
Other	3.4%	-5.8%	12.6%	98/115=85.2%	108/132=81.8%	
NRTIGP						
ABC/3TC	-1.6%	-8.8%	5.7%	139/160=86.9%	138/156=88.5%	
TDF/FTC	5.8%	-0.1%	11.7%	216/240=90.0%	208/247=84.2%	
BASELINE HIV						
<=100_K	1.0%	-3.6%	5.7%	263/287=91.6%	260/287=90.6%	
>100_K	7.3%	-3.4%	18.0%	92/113=81.4%	86/116=74.1%	
BASELINE HIV						
<=12.8_K	-4.5%	-10.7%	1.7%	96/104=92.3%	91/94=96.8%	0.16
12.8-35.8_K	3.5%	-5.2%	12.1%	95/105=90.5%	87/100=87.0%	
35.8-115_K	-0.9%	-10.0%	8.3%	81/93=87.1%	95/108=88.0%	
>115_K	11.3%	-0.2%	22.8%	83/101=82.2%	73/103=70.9%	
BASELINE CD4 COUNT						
<350	7.3%	-0.1%	14.7%	170/195=87.2%	151/189=79.9%	
>=350	-0.9%	-6.4%	4.7%	185/205=90.2%	195/214=91.1%	
BASELINE CD4 COUNT						
<=274	11.7%	1.2%	22.3%	85/98=86.7%	81/108=75.0%	
274-361	0.2%	-8.9%	9.3%	93/106=87.7%	84/96=87.5%	
361-470	-3.7%	-12.3%	4.9%	84/96=87.5%	93/102=91.2%	
>470	2.3%	-5.4%	9.9%	93/100=93.0%	88/97=90.7%	
BASELINE CDC GROUP						
A	2.0%	-2.7%	6.7%	314/349=90.0%	299/340=87.9%	
B	2.6%	-14.2%	19.5%	33/42=78.6%	41/54=75.9%	
C	22.2%	-14.8%	59.2%	8/9=88.9%	6/9=66.7%	

SINGLE_4467_%BLQ_WEEK_48						
	MEAN	95% LIMITS				
	DIFF	LOWER	UPPER	DTG_50mg	EFV	PVALUE
RISK_FACTOR						
Drug_use	12.3%	-23.6%	48.1%	15/19=78.9%	6/9=66.7%	
Homosexual	6.1%	0.4%	11.7%	235/262=89.7%	240/287=83.6%	
Other	10.2%	0.7%	19.6%	114/131=87.0%	93/121=76.9%	
BASELINE HIV						
<=100_K	7.7%	2.2%	13.2%	253/279=90.7%	239/288=83.0%	
>100_K	5.9%	-3.6%	15.5%	111/133=83.5%	100/129=77.5%	
BASELINE HIV						
<=14.7_K	11.0%	1.3%	20.8%	94/105=89.5%	84/107=78.5%	0.87
14.7-48.3_K	4.5%	-4.2%	13.2%	97/107=90.7%	87/101=86.1%	
48.3-143_K	4.8%	-4.4%	14.0%	84/94=89.4%	93/110=84.5%	
>143_K	8.1%	-3.0%	19.3%	89/108=82.4%	75/101=74.3%	
BASELINE CD4 COUNT						
<=200	6.0%	-8.7%	20.8%	45/55=81.8%	47/62=75.8%	
>200	7.1%	2.0%	12.2%	319/357=89.4%	292/355=82.3%	
BASELINE CD4 COUNT						
<=246	2.4%	-8.5%	13.3%	80/99=80.8%	87/111=78.4%	
246-339	11.5%	1.7%	21.3%	98/109=89.9%	80/102=78.4%	
339-438	6.0%	-3.3%	15.4%	96/107=89.7%	82/98=83.7%	
>438	7.9%	-0.7%	16.4%	90/97=92.8%	90/106=84.9%	
BASELINE CD4 COUNT						
<50	-9.3%	-42.4%	23.7%	9/13=69.2%	11/14=78.6%	
50-200	10.7%	-5.5%	26.9%	36/42=85.7%	36/48=75.0%	
200-350	7.9%	-0.2%	15.9%	143/163=87.7%	127/159=79.9%	
350-500	4.4%	-4.0%	12.8%	116/131=88.5%	106/126=84.1%	
>=500	11.0%	0.9%	21.0%	60/63=95.2%	59/70=84.3%	
BASELINE CDC GROUP						
A	7.2%	2.1%	12.4%	307/342=89.8%	288/349=82.5%	
B	8.5%	-7.2%	24.2%	44/53=83.0%	38/51=74.5%	
C	0.0%	-28.5%	28.5%	13/17=76.5%	13/17=76.5%	

## 4.2.2 Two Class Resistant INI Naïve Trials

SAILING_1762_%BLQ_WEEK_24						
	MEAN	95% LIMITS				
	DIFF	LOWER	UPPER	DTG_50mg	RAL	PVALUE
RISK_FACTOR						
Drug_use	30.7%	8.7%	52.7%	20/23=87.0%	18/32=56.3%	
Homosexual	3.7%	-6.9%	14.4%	100/127=78.7%	87/116=75.0%	
Other	9.3%	1.1%	17.5%	161/199=80.9%	149/208=71.6%	
BASELINE HIV						
<=50_K	7.5%	0.6%	14.3%	208/246=84.6%	195/253=77.1%	
>50_K	13.6%	0.6%	26.6%	73/103=70.9%	59/103=57.3%	
BASELINE HIV						
<=2801	5.0%	-5.2%	15.1%	77/87=88.5%	76/91=83.5%	0.97
2801-15259	5.9%	-6.0%	17.7%	76/92=82.6%	66/86=76.7%	
15259-67283	10.3%	-2.4%	23.0%	70/88=79.5%	63/91=69.2%	
>67283	14.0%	-0.2%	28.2%	58/87=66.7%	49/93=52.7%	
BASELINE HIV						
<1_K	-1.9%	-16.4%	12.6%	37/44=84.1%	43/50=86.0%	
1-10_K	7.5%	-2.5%	17.5%	95/109=87.2%	82/103=79.6%	
10-50_K	11.7%	-0.2%	23.7%	76/93=81.7%	70/100=70.0%	
50-100_K	2.5%	-18.9%	24.0%	26/36=72.2%	23/33=69.7%	
100-500_K	10.0%	-7.9%	28.0%	37/52=71.2%	33/54=61.1%	
>=500_K	47.9%	17.3%	78.5%	10/15=66.7%	3/16=18.8%	
BASELINE CD4 COUNT						
<=200	9.9%	0.3%	19.4%	128/171=74.9%	117/180=65.0%	
>200	8.1%	0.1%	16.1%	153/178=86.0%	137/176=77.8%	
BASELINE CD4 COUNT						
<=95	13.1%	-0.7%	27.0%	65/90=72.2%	52/88=59.1%	
95-201	7.1%	-5.8%	19.9%	64/82=78.0%	66/93=71.0%	
201-365	8.7%	-3.5%	20.8%	74/90=82.2%	64/87=73.6%	
>365	7.8%	-2.5%	18.1%	78/87=89.7%	72/88=81.8%	
BASELINE CD4 COUNT						
<50	13.0%	-4.4%	30.3%	41/61=67.2%	32/59=54.2%	
50-200	8.8%	-2.3%	20.0%	87/110=79.1%	85/121=70.2%	
200-350	7.0%	-5.5%	19.4%	68/82=82.9%	60/79=75.9%	
350-500	9.1%	-4.8%	22.9%	47/54=87.0%	46/59=78.0%	
>=500	8.9%	-6.3%	24.1%	38/42=90.5%	31/38=81.6%	
BASELINE CDC GROUP						
A	10.2%	-0.5%	20.9%	92/110=83.6%	83/113=73.5%	
B	1.8%	-11.8%	15.4%	52/68=76.5%	65/87=74.7%	
C	12.2%	2.7%	21.6%	137/171=80.1%	106/156=67.9%	



### 4.2.3 Two Class Resistant, INI Resistant Trials

VIKING_(2961)_LOGCHANGE_DAY_11							
	MEAN	95% LIMITS					
	DIFF	LOWER	UPPER	DTG	PLAC	N_P	N_D
RISK FACTOR							
Drug_use	0.16426	.	.	-1.57089	-1.73515	2	1
Homosexual	-0.68880	-1.17920	-0.19840	-1.93293	-1.24413	14	12
Other	0.22181	-0.50210	0.94571	-1.37592	-1.59773	10	6
BASELINE HIV							
<10_K	-0.39343	-0.90778	0.12091	-1.65041	-1.25698	8	4
>=10_K	-0.27191	-0.77528	0.23147	-1.76133	-1.48942	18	15
BASELINE HIV							
<=7434	-0.36546	-0.79147	0.06055	-1.65041	-1.28495	6	4
7434-18621	-0.56789	-1.65643	0.52065	-1.79265	-1.22476	6	5
18621-60256	0.32780	-0.47551	1.13111	-1.35263	-1.68043	7	5
>60256	-0.70383	-1.38549	-0.02217	-2.13871	-1.43488	7	5
BASELINE CD4 COUNT							
<50	-0.25087	-0.97821	0.47648	-1.52258	-1.27171	7	6
>=50	-0.36563	-0.83737	0.10610	-1.83739	-1.47176	19	13
BASELINE CD4 COUNT							
<=44	-0.25087	-0.97821	0.47648	-1.52258	-1.27171	7	6
44-122	-0.35861	-1.38849	0.67128	-2.11297	-1.75436	8	3
122-380	-0.20793	-0.96553	0.54968	-1.61711	-1.40918	7	6
>380	-0.94507	-1.67098	-0.21915	-1.96114	-1.01608	4	4

VIKING_2961_%BLQ_WEEK_24						
	MEAN	95% LIMITS		DTG		
	DIFF	LOWER	UPPER	50mg_BID	50mg_QD	PVALUE
RISK_FACTOR						
Drug_use	-50.0%	-100%	19.3%	0/1=0.0%	1/2=50.0%	0.25
Homosexual	16.7%	-20.7%	54.0%	8/12=66.7%	7/14=50.0%	
Other	45.5%	9.0%	81.9%	9/11=81.8%	4/11=36.4%	
BASELINE HIV						
<10_K	-1.8%	-36.4%	32.8%	6/7=85.7%	7/8=87.5%	0.3
>=10_K	38.4%	8.3%	68.5%	11/17=64.7%	5/19=26.3%	
BASELINE HIV						
<=7434	16.7%	-13.2%	46.5%	6/6=100%	5/6=83.3%	0.75
7434-18621	7.1%	-47.1%	61.4%	4/7=57.1%	3/6=50.0%	
18621-60256	42.5%	-6.0%	91.0%	4/5=80.0%	3/8=37.5%	
>60256	35.7%	-12.0%	83.4%	3/6=50.0%	1/7=14.3%	
BASELINE CD4 COUNT						
<50	14.3%	-35.4%	63.9%	3/7=42.9%	2/7=28.6%	0.54
>=50	32.4%	3.9%	60.8%	14/17=82.4%	10/20=50.0%	
BASELINE CD4 COUNT						
<=44	14.3%	-35.4%	63.9%	3/7=42.9%	2/7=28.6%	0.29
44-122	37.5%	-16.6%	91.6%	3/4=75.0%	3/8=37.5%	
122-380	57.1%	14.8%	99.5%	6/7=85.7%	2/7=28.6%	
>380	-16.7%	-46.5%	13.2%	5/6=83.3%	5/5=100%	

VIKING_2961_%BLQ_WEEK_48						
	MEAN	95% LIMITS		DTG		
	DIFF	LOWER	UPPER	50mg_BID	50mg_QD	PVALUE
RISK FACTOR						
Drug_use	-50.0%	-100%	19.3%	0/1=0.0%	1/2=50.0%	0.093
Homosexual	15.5%	-22.6%	53.6%	7/12=58.3%	6/14=42.9%	
Other	63.6%	31.4%	95.9%	9/11=81.8%	2/11=18.2%	
BASELINE HIV						
<10_K	35.7%	-7.6%	79.0%	6/7=85.7%	4/8=50.0%	0.83
>=10_K	32.5%	1.9%	63.2%	10/17=58.8%	5/19=26.3%	
BASELINE HIV						
<=7434	33.3%	-16.6%	83.2%	5/6=83.3%	3/6=50.0%	0.96
7434-18621	23.8%	-28.8%	76.4%	4/7=57.1%	2/6=33.3%	
18621-60256	42.5%	-6.0%	91.0%	4/5=80.0%	3/8=37.5%	
>60256	35.7%	-12.0%	83.4%	3/6=50.0%	1/7=14.3%	
BASELINE CD4 COUNT						
<50	14.3%	-35.4%	63.9%	3/7=42.9%	2/7=28.6%	0.42
>=50	41.5%	12.4%	70.5%	13/17=76.5%	7/20=35.0%	
BASELINE CD4 COUNT						
<=44	14.3%	-35.4%	63.9%	3/7=42.9%	2/7=28.6%	0.18
44-122	50.0%	-2.0%	100%	3/4=75.0%	2/8=25.0%	
122-380	71.4%	34.8%	100%	6/7=85.7%	1/7=14.3%	
>380	-13.3%	-64.8%	38.2%	4/6=66.7%	4/5=80.0%	

VIKING_3_2574_LOG_CHANGE_DAY_8					
	95% LIMITS				
	MEAN	LOWER	UPPER	N	PVALUE
RISK FACTOR					
Drug_use	-1.596	-1.847	-1.345	27	0
Homosexual	-1.441	-1.565	-1.317	86	0
Other	-1.374	-1.510	-1.239	69	0
BASELINE HIV					
<1_K	-0.921	-1.058	-0.784	21	.0000
1-10_K	-1.513	-1.649	-1.377	49	.0000
10-50_K	-1.493	-1.662	-1.324	52	.0000
50-100_K	-1.412	-1.667	-1.157	20	.0000
100-500_K	-1.632	-1.852	-1.412	34	.0000
>=500_K	-1.168	-1.769	-0.566	6	.0001
BASELINE HIV					
<=4716	-1.212	-1.349	-1.075	46	0
4716-24855	-1.513	-1.669	-1.356	47	0
24855-84534	-1.505	-1.692	-1.317	45	0
>84534	-1.529	-1.726	-1.332	44	0
BASELINE CD4 COUNT					
<=40	-1.256	-1.447	-1.066	49	0
40-150	-1.515	-1.714	-1.317	45	0
150-330	-1.594	-1.712	-1.475	46	0
>330	-1.400	-1.557	-1.242	42	0
BASELINE CD4 COUNT					
<50	-1.256	-1.447	-1.066	49	0
50-200	-1.554	-1.714	-1.393	60	0
200-350	-1.546	-1.675	-1.418	34	0
350-500	-1.523	-1.697	-1.350	24	0
>=500	-1.196	-1.507	-0.885	15	0
BASELINE CDC GROUP					
A	-1.448	-1.608	-1.287	44	0
B	-1.465	-1.659	-1.271	37	0
C	-1.425	-1.546	-1.304	101	0

VIKING\_3\_2574\_%BLQ\_WEEK\_24

		95% LIMITS		
	MEAN	LOWER	UPPER	PVALUE
RISK FACTOR				
Drug_use	12/18=66.7%	44.9%	88.4%	0
Homosexual	41/57=71.9%	60.3%	83.6%	0
Other	23/39=59.0%	43.5%	74.4%	0
BASELINE HIV				
<=4716	26/29=89.7%	78.6%	100.7%	0
4716-24855	20/25=80.0%	64.3%	95.7%	0
24855-84534	18/28=64.3%	46.5%	82.0%	0
>84534	12/32=37.5%	20.7%	54.3%	0
BASELINE HIV				
<1_K	11/12=91.7%	76.0%	107.3%	0.0000
1-10_K	24/30=80.0%	65.7%	94.3%	0.0000
10-50_K	22/29=75.9%	60.3%	91.4%	0.0000
50-100_K	8/13=61.5%	35.1%	88.0%	0.0000
100-500_K	10/24=41.7%	21.9%	61.4%	0.0000
>=500_K	1/6=16.7%	-13.2%	46.5%	0.2733
BASELINE CD4 COUNT				
<=40	14/36=38.9%	23.0%	54.8%	0
40-150	14/25=56.0%	36.5%	75.5%	0
150-330	24/27=88.9%	77.0%	100.7%	0
>330	24/26=92.3%	82.1%	102.6%	0
BASELINE CD4 COUNT				
<50	14/36=38.9%	23.0%	54.8%	0
50-200	22/34=64.7%	48.6%	80.8%	0
200-350	18/20=90.0%	76.9%	103.1%	0
350-500	13/15=86.7%	69.5%	103.9%	0
>=500	9/9=100%	100%	100%	.
BASELINE CDC GROUP				
A	15/21=71.4%	52.1%	90.8%	0
B	19/26=73.1%	56.0%	90.1%	0
C	42/67=62.7%	51.1%	74.3%	0

### 4.3 Demographic Covariates

The following tables give the results of analyzing the primary endpoints of all seven trials by other covariates including height and weight, country, and for the treatment experienced subjects, covariates reflecting degree of resistance. The tables are laid out as in the previous sections.

#### 4.3.1 Treatment Naïve Trials

TRIAL\_1521\_LOGCHG\_DAY\_11\_DTG\_2MG\_VS\_PLACEBO

	MEAN	95% LIMITS					
	DIFF	LOWER	UPPER	DTG	PLAC	N_P	N_D
HEIGHT							
<=173	-1.805			-1.751	0.053	1	3
173-178	-0.915	-1.615	-0.215	-1.100	-0.185	2	2
178-183	-1.472	-1.980	-0.964	-1.091	0.380	3	3
>183	-2.414			-2.338	0.075	1	1
WEIGHT							
<=74.2	-1.709	-2.322	-1.096	-1.814	-0.105	2	3
74.2-78.2	-1.935			-1.525	0.410	1	1
78.2-86	-1.726	-2.353	-1.099	-1.360	0.366	2	4
>86	-0.642			-0.658	-0.016	2	1
BMI							
<=23.92	-1.998	-3.139	-0.857	-1.890	0.108	2	2
23.92-25.5	-1.658	-2.144	-1.172	-1.426	0.232	2	3
25.5-30.49	-1.702			-1.450	0.252	1	3
>30.49	-0.642			-0.658	-0.016	2	1

TRIAL\_1521\_LOGCHG\_DAY\_11\_DTG\_10MG\_VS\_PLACEBO

	MEAN DIFF	95% LIMITS		DTG	PLAC	N_P	N_D
		LOWER	UPPER				
HEIGHT							
<=173	-2.476			-2.423	0.053	1	3
173-178	-1.149	-1.382	-0.916	-1.334	-0.185	2	2
178-183	-2.310	-2.642	-1.978	-1.930	0.380	3	3
>183	-2.009			-1.933	0.075	1	1
WEIGHT							
<=74.2	-2.507			-2.612	-0.105	2	1
74.2-78.2	-2.198			-1.787	0.410	1	3
78.2-86	-2.314	-3.367	-1.261	-1.948	0.366	2	2
>86	-1.914	-2.267	-1.560	-1.930	-0.016	2	3
BMI							
<=23.92	-2.041			-1.933	0.108	2	1
23.92-25.5	-2.160	-3.545	-0.776	-1.929	0.232	2	2
25.5-30.49	-2.056			-1.803	0.252	1	2
>30.49	-2.050	-2.436	-1.663	-2.065	-0.016	2	4

TRIAL\_1521\_LOGCHG\_DAY\_11\_DTG\_50MG\_VS\_PLACEBO

	MEAN DIFF	95% LIMITS		DTG	PLAC	N_P	N_D
		LOWER	UPPER				
HEIGHT							
<=173	-2.591			-2.537	0.053	1	3
173-178	-2.125	-2.850	-1.399	-2.310	-0.185	2	3
178-183	-2.790	-3.127	-2.452	-2.409	0.380	3	4
>183					0.075	1	0
WEIGHT							
<=74.2	-2.198	-2.895	-1.500	-2.303	-0.105	2	3
74.2-78.2	-3.001			-2.591	0.410	1	4
78.2-86	-2.489			-2.123	0.366	2	1
>86	-2.375	-2.879	-1.871	-2.391	-0.016	2	2
BMI							
<=23.92	-2.613	-3.413	-1.813	-2.505	0.108	2	4
23.92-25.5	-2.206	-2.781	-1.630	-1.974	0.232	2	2
25.5-30.49	-2.778			-2.526	0.252	1	3
>30.49	-2.616			-2.632	-0.016	2	1

SPRING_1_2276_%BLQ_WEEK_16_DTG_10mg_VS_EFV						
	MEAN	95% LIMITS				
	DIFF	LOWER	UPPER	DTG_10mg	EFV	PVALUE
ABC EXPOSURE						
No	31.9%	14.4%	49.4%	36/38=94.7%	22/35=62.9%	0.69
Yes	33.3%	9.5%	57.2%	15/15=100%	10/15=66.7%	
COUNTRY						
France	0.0%	0.0%	0.0%	4/4=100%	3/3=100%	0.67
Germany	11.1%	-9.4%	31.6%	7/7=100%	8/9=88.9%	
Italy	28.6%	-16.3%	73.5%	6/7=85.7%	4/7=57.1%	
Russia	50.0%	1.0%	99.0%	7/7=100%	2/4=50.0%	
Spain	77.8%	50.6%	104.9%	11/11=100%	2/9=22.2%	
US	21.9%	-1.6%	45.4%	16/17=94.1%	13/18=72.2%	
HEIGHT						
<=170	41.1%	13.7%	68.5%	17/18=94.4%	8/15=53.3%	0.94
170-176	30.8%	5.7%	55.9%	8/8=100%	9/13=69.2%	
176-181	20.6%	-8.6%	49.8%	14/15=93.3%	8/11=72.7%	
>181	36.4%	7.9%	64.8%	12/12=100%	7/11=63.6%	
SPRING_1_2276_%BLQ_WEEK_16_DTG_25mg_VS_EFV						
	MEAN	95% LIMITS				
	DIFF	LOWER	UPPER	DTG_10mg	EFV	PVALUE
ABC EXPOSURE						
No	34.1%	17.1%	51.2%	32/33=97.0%	22/35=62.9%	0.43
Yes	21.6%	-6.8%	49.9%	15/17=88.2%	10/15=66.7%	
COUNTRY						
France	-25.0%	-67.4%	17.4%	3/4=75.0%	3/3=100%	0.53
Germany	11.1%	-9.4%	31.6%	4/4=100%	8/9=88.9%	
Italy	32.9%	-8.2%	74.0%	9/10=90.0%	4/7=57.1%	
Russia	50.0%	1.0%	99.0%	3/3=100%	2/4=50.0%	
Spain	57.8%	13.4%	102.1%	4/5=80.0%	2/9=22.2%	
US	27.8%	7.1%	48.5%	24/24=100%	13/18=72.2%	
HEIGHT						
<=170	37.6%	7.1%	68.0%	10/11=90.9%	8/15=53.3%	0.95
170-176	23.1%	-5.9%	52.0%	12/13=92.3%	9/13=69.2%	
176-181	27.3%	1.0%	53.6%	12/12=100%	8/11=72.7%	
>181	29.2%	-2.2%	60.7%	13/14=92.9%	7/11=63.6%	



SPRING\_1\_2276\_%BLQ\_WEEK\_16\_DTG\_50mg\_VS\_EFV

	MEAN	95% LIMITS				
	DIFF	LOWER	UPPER	DTG_10mg	EFV	PVALUE
ABC EXPOSURE						
No	28.6%	10.1%	47.1%	32/35=91.4%	22/35=62.9%	0.63
Yes	20.0%	-9.4%	49.4%	13/15=86.7%	10/15=66.7%	
COUNTRY						
France	-28.6%	-62.0%	4.9%	5/7=71.4%	3/3=100%	0.15
Germany	-3.2%	-36.2%	29.9%	6/7=85.7%	8/9=88.9%	
Italy	42.9%	6.2%	79.5%	3/3=100%	4/7=57.1%	
Russia	30.0%	-30.3%	90.3%	4/5=80.0%	2/4=50.0%	
Spain	77.8%	50.6%	104.9%	8/8=100%	2/9=22.2%	
US	22.8%	0.0%	45.6%	19/20=95.0%	13/18=72.2%	
HEIGHT						
<=170	34.2%	4.2%	64.2%	14/16=87.5%	8/15=53.3%	0.94
170-176	23.1%	-5.9%	52.0%	12/13=92.3%	9/13=69.2%	
176-181	27.3%	1.0%	53.6%	8/8=100%	8/11=72.7%	
>181	21.0%	-13.6%	55.5%	11/13=84.6%	7/11=63.6%	

SPRING\_2\_3086\_%BLQ\_WEEK\_48

	MEAN	95% LIMITS				
	DIFF	LOWER	UPPER	DTG_50mg	RAL	PVALUE
ABC EXPOSURE						
No	5.9%	0.1%	11.7%	216/238=90.8%	208/245=84.9%	
Yes	-1.5%	-9.0%	5.9%	139/162=85.8%	138/158=87.3%	
COUNTRY						
Australia	-9.7%	-28.3%	8.9%	17/20=85.0%	18/19=94.7%	
Canada	6.9%	-2.3%	16.1%	32/32=100%	27/29=93.1%	
France	0.9%	-10.5%	12.4%	45/49=91.8%	40/44=90.9%	
Germany	6.1%	-5.9%	18.1%	39/42=92.9%	46/53=86.8%	
Italy	-1.0%	-19.8%	17.7%	20/23=87.0%	22/25=88.0%	
Russia	-0.6%	-19.1%	18.0%	29/37=78.4%	30/38=78.9%	
Spain	6.5%	-2.1%	15.2%	112/125=89.6%	98/118=83.1%	
UK	0.0%	0.0%	0.0%	11/11=100%	6/6=100%	
US	-1.1%	-14.1%	11.9%	50/61=82.0%	59/71=83.1%	
HEIGHT						
<=170	10.4%	1.4%	19.4%	98/108=90.7%	94/117=80.3%	
170-175	5.9%	-4.2%	16.0%	86/97=88.7%	72/87=82.8%	
175-180	-2.6%	-10.9%	5.6%	98/111=88.3%	90/99=90.9%	
>180	-4.7%	-14.8%	5.4%	71/85=83.5%	90/102=88.2%	
WEIGHT						
<=66	6.9%	-3.1%	16.8%	98/112=87.5%	79/98=80.6%	
66-74.3	8.2%	-2.1%	18.4%	86/98=87.8%	78/98=79.6%	
74.3-84	-2.9%	-11.2%	5.5%	90/102=88.2%	92/101=91.1%	
>84	-0.9%	-9.6%	7.7%	80/90=88.9%	97/108=89.8%	

## SINGLE\_4467\_%BLQ\_WEEK\_48

	MEAN	95% LIMITS				
	DIFF	LOWER	UPPER	DTG_50mg	EFV	PVALUE
COUNTRY						
Australia	22.2%	-4.9%	49.4%	8/8=100%	7/9=77.8%	
Belgium	18.2%	-4.6%	41.0%	8/8=100%	9/11=81.8%	
Canada	27.6%	11.3%	43.9%	28/28=100%	21/29=72.4%	
Denmark	33.3%	-20.0%	86.7%	2/2=100%	2/3=66.7%	
France	25.3%	-4.1%	54.7%	9/10=90.0%	11/17=64.7%	
Germany	-0.8%	-11.6%	10.0%	31/33=93.9%	36/38=94.7%	
Holland	-14.3%	-40.2%	11.6%	6/7=85.7%	3/3=100%	
Italy	5.8%	-14.7%	26.4%	14/15=93.3%	14/16=87.5%	
Romania	17.5%	-24.2%	59.2%	8/10=80.0%	5/8=62.5%	
Spain	12.1%	2.7%	21.5%	104/116=89.7%	90/116=77.6%	
UK	-10.3%	-40.0%	19.4%	11/14=78.6%	8/9=88.9%	
US	-0.3%	-8.4%	7.7%	135/161=83.9%	133/158=84.2%	
HEIGHT						
<=169	13.0%	2.5%	23.5%	95/111=85.6%	82/113=72.6%	
169-175	-2.4%	-11.5%	6.7%	101/119=84.9%	89/102=87.3%	
175-181	10.7%	0.1%	21.3%	89/101=88.1%	72/93=77.4%	
>181	8.8%	0.9%	16.7%	79/83=95.2%	95/110=86.4%	
WEIGHT						
<=66.6	13.7%	2.4%	25.0%	90/109=82.6%	73/106=68.9%	
66.6-75	8.9%	0.7%	17.1%	103/109=94.5%	83/97=85.6%	
75-85	0.9%	-9.4%	11.1%	83/100=83.0%	92/112=82.1%	
>85	4.3%	-4.2%	12.8%	88/96=91.7%	90/103=87.4%	

### 4.3.2 Two Class Resistant INI Naïve Trial

SAILING\_1762\_%BLQ\_WEEK\_24

	MEAN	95% LIMITS				
	DIFF	LOWER	UPPER	DTG_50mg	RAL	PVALUE
REGION						
Europe	15.2%	1.9%	28.5%	44/47=93.6%	40/51=78.4%	
N_America	2.1%	-8.3%	12.4%	100/131=76.3%	101/136=74.3%	
Other	13.3%	4.0%	22.5%	137/171=80.1%	113/169=66.9%	
COUNTRY						
Argentina	8.9%	-12.3%	30.1%	24/27=88.9%	16/20=80.0%	
Australia	-100%	-100%	-100%	0/1=0.0%	3/3=100%	
Belgium	0.0%	0.0%	0.0%	3/3=100%	5/5=100%	
Brazil	15.2%	-0.5%	30.9%	48/61=78.7%	40/63=63.5%	
Canada	50.0%	-19.3%	119.3%	2/2=100%	1/2=50.0%	
Chile	14.7%	-24.0%	53.4%	9/13=69.2%	6/11=54.5%	
France	10.0%	-8.6%	28.6%	8/8=100%	9/10=90.0%	
Greece	100%	100%	100%	2/2=100%	0/1=0.0%	
Italy	35.7%	-19.7%	91.1%	6/7=85.7%	2/4=50.0%	
Mexico	4.0%	-23.6%	31.5%	16/21=76.2%	13/18=72.2%	
Romania	22.2%	-4.9%	49.4%	7/7=100%	7/9=77.8%	
Russia	25.0%	-7.9%	57.9%	9/12=75.0%	10/20=50.0%	
S_Africa	11.5%	-5.1%	28.1%	42/51=82.4%	34/48=70.8%	
Spain	17.6%	-8.9%	44.2%	15/17=88.2%	12/17=70.6%	
Taiwan	-16.7%	-46.5%	13.2%	5/6=83.3%	4/4=100%	
UK	0.0%	0.0%	0.0%	2/2=100%	4/4=100%	
US	0.9%	-10.3%	12.2%	82/108=75.9%	87/116=75.0%	
HEIGHT						
<=164	10.1%	-1.9%	22.0%	75/93=80.6%	72/102=70.6%	0.98
164-170	8.5%	-4.6%	21.5%	74/99=74.7%	59/89=66.3%	
170-177	8.6%	-4.2%	21.4%	70/88=79.5%	61/86=70.9%	
>177	10.0%	-2.6%	22.6%	62/74=83.8%	62/84=73.8%	
WEIGHT						
<=62	8.8%	-4.5%	22.1%	75/101=74.3%	55/84=65.5%	0.79
62-72	6.1%	-6.5%	18.7%	71/91=78.0%	64/89=71.9%	
72-82.5	14.9%	2.3%	27.6%	72/87=82.8%	59/87=67.8%	
>82.5	8.8%	-3.1%	20.6%	63/75=84.0%	76/101=75.2%	

### 4.1.3 Two Class Resistant, INI Resistant Trials

VIKING\_(2961)\_LOGCHANGE\_DAY\_11

	MEAN	95% LIMITS		DTG	PLAC	N_P	N_D
COUNTRY	DIFF	LOWER	UPPER				
France	-0.21390	-1.65833	1.23052	-1.64977	-1.43587	17	3
Spain	0.73274	0.14290	1.32258	-1.30958	-2.04232	2	3
US	-0.45079	-1.03387	0.13228	-1.85555	-1.40475	5	12
HEIGHT							
<=170	-0.16795	-0.94029	0.60440	-1.58842	-1.42048	5	7
170-177	-0.70806	-2.08755	0.67143	-2.07197	-1.36391	8	3
177-180	-0.47506	-1.15213	0.20202	-1.78915	-1.31409	9	3
>180	0.03635	-0.41599	0.48870	-1.71988	-1.75623	4	6

VIKING\_2961\_%BLQ\_WEEK\_24

	MEAN	95% LIMITS		DTG		
COUNTRY	DIFF	LOWER	UPPER	50mg_BID	50mg_QD	PVALUE
France	14.7%	-39.3%	68.7%	2/4=50.0%	6/17=35.3%	
Italy	100%	100%	100%	4/4=100%	0/2=0.0%	
Spain	16.7%	-70.8%	104.1%	2/3=66.7%	1/2=50.0%	
US	-16.7%	-56.7%	23.3%	8/12=66.7%	5/6=83.3%	
HEIGHT						
<=170	37.8%	-13.0%	88.6%	7/9=77.8%	2/5=40.0%	0.8
170-177	26.7%	-26.2%	79.5%	3/5=60.0%	3/9=33.3%	
177-180	44.4%	12.0%	76.9%	3/3=100%	5/9=55.6%	
>180	7.1%	-54.1%	68.3%	4/7=57.1%	2/4=50.0%	

VIKING\_2961\_%BLQ\_WEEK\_48

	MEAN	95% LIMITS		DTG		
COUNTRY	DIFF	LOWER	UPPER	50mg_BID	50mg_QD	PVALUE
France	51.5%	4.5%	98.5%	3/4=75.0%	4/17=23.5%	
Italy	75.0%	32.6%	117.4%	3/4=75.0%	0/2=0.0%	
Spain	16.7%	-70.8%	104.1%	2/3=66.7%	1/2=50.0%	
US	-8.3%	-55.2%	38.6%	7/12=58.3%	4/6=66.7%	
HEIGHT						
<=170	35.6%	-12.2%	83.3%	5/9=55.6%	1/5=20.0%	0.62
170-177	46.7%	0.0%	93.3%	4/5=80.0%	3/9=33.3%	
177-180	66.7%	35.9%	97.5%	3/3=100%	3/9=33.3%	
>180	7.1%	-54.1%	68.3%	4/7=57.1%	2/4=50.0%	

VIKING\_3\_2574\_LOG\_CHANGE\_DAY\_8

	MEAN	95% LIMITS		N	PVALUE
COUNTRY		LOWER	UPPER		
Belgium	-1.467	.	.	1	.
Canada	-1.582	-2.040	-1.124	3	0
France	-1.325	-1.485	-1.164	38	0
Italy	-1.538	-1.780	-1.296	30	0
Portugal	-1.629	-1.935	-1.324	6	0
Spain	-1.674	-2.035	-1.312	6	0
US	-1.422	-1.546	-1.298	98	0
HEIGHT					
<=168	-1.297	-1.460	-1.135	52	0
168-174	-1.519	-1.673	-1.365	43	0
174-180	-1.536	-1.723	-1.349	46	0
>180	-1.424	-1.608	-1.241	41	0
WEIGHT					
<=65	-1.335	-1.493	-1.177	49	0
65-72.5	-1.564	-1.717	-1.411	42	0
72.5-86	-1.391	-1.576	-1.207	45	0
>86	-1.481	-1.671	-1.290	46	0

VIKING\_3\_2574\_%BLQ\_WEEK\_24

	MEAN	95% LIMITS			PVALUE
COUNTRY		LOWER	UPPER		
Canada	2/2=100%	100%	100%	.	
France	20/26=76.9%	60.7%	93.1%	.0000	
Italy	14/22=63.6%	43.5%	83.7%	.0000	
Spain	3/4=75.0%	32.6%	117.4%	.0005	
US	37/60=61.7%	49.4%	74.0%	.0000	
HEIGHT					
<=168	19/33=57.6%	40.7%	74.4%	0	
168-174	19/25=76.0%	59.3%	92.7%	0	
174-180	22/29=75.9%	60.3%	91.4%	0	
>180	16/27=59.3%	40.7%	77.8%	0	
WEIGHT					
<=65	24/30=80.0%	65.7%	94.3%	0	
65-72.5	16/27=59.3%	40.7%	77.8%	0	
72.5-86	18/27=66.7%	48.9%	84.4%	0	
>86	18/30=60.0%	42.5%	77.5%	0	

## 4.4 Prior ART Exposure Covariates

The following tables give the results of analyzing the primary endpoints of the three trials in treatment experienced patients by covariates that reflect the extent of exposure to previous ART regimens and the resistance of their virus. The tables are laid out as in the previous sections.

### 4.4.1 Two Class Resistant INI Naïve Trials

SAILING_1762 %BLQ WEEK 24		MEAN 95% LIMITS		DTG_50mg	RAL	PVALUE	
		DIFF	LOWER UPPER				
ABC EXPOSURE							
No		8.6%	2.1%	15.0%	260/321=81.0%	234/323=72.4%	0.72
Yes		14.4%	-8.7%	37.5%	21/28=75.0%	20/33=60.6%	
CLADE							
Unknown		16.7%	-13.2%	46.5%	1/6=16.7%	0/5=0.0%	0.72
Clade_B		6.9%	-0.6%	14.5%	191/238=80.3%	176/240=73.3%	
Clade_C		15.0%	-2.2%	32.3%	43/54=79.6%	31/48=64.6%	
Other		13.0%	-1.8%	27.9%	46/56=82.1%	47/68=69.1%	
Class resistance							
2		9.0%	0.5%	17.4%	151/182=83.0%	131/177=74.0%	
>=3		9.1%	-0.1%	18.4%	130/167=77.8%	123/179=68.7%	
DRVPI DRV use and no primary PI mutation?							
No		12.1%	5.0%	19.3%	224/278=80.6%	191/279=68.5%	
Yes		-1.5%	-14.2%	11.1%	57/71=80.3%	63/77=81.8%	
BKRECENT Recent approved ART in background reg.							
N		15.1%	6.0%	24.3%	145/185=78.4%	117/185=63.2%	
Y		2.8%	-5.5%	11.1%	136/164=82.9%	137/171=80.1%	
DRV Use of DRV in background regimen							
N		14.4%	5.8%	23.0%	164/209=78.5%	132/206=64.1%	
Y		2.2%	-6.5%	11.0%	117/140=83.6%	122/150=81.3%	
ETR Use of ETR in background regimen							
N		9.0%	2.3%	15.8%	245/305=80.3%	221/310=71.3%	
Y		10.1%	-7.2%	27.4%	36/44=81.8%	33/46=71.7%	
INDUCER Use of inducer in background regimen							
N		9.6%	3.1%	16.1%	262/323=81.1%	236/330=71.5%	
Y		3.8%	-20.8%	28.5%	19/26=73.1%	18/26=69.2%	
MVC Use of MVC in background regimen							
N		9.1%	2.4%	15.8%	247/310=79.7%	228/323=70.6%	
Y		8.4%	-9.1%	25.8%	34/39=87.2%	26/33=78.8%	

#### 4.4.2 Two Class Resistant INI Resistant Trials

VIKING\_(2961)\_LOGCHANGE\_DAY\_11

ABC EXPOSURE	MEAN	95% LIMITS		DTG	PLAC	N_P	N_D
	DIFF	LOWER	UPPER				
No	-0.26071	-0.69854	0.17712	-1.76523	-1.50452	21	17
Yes	-0.45223	-1.22284	0.31838	-1.50632	-1.05409	5	2

VIKING\_2961\_%BLQ\_WEEK\_24

ABC EXPOSURE	MEAN	95% LIMITS		DTG	50mg_QD	PVALUE
	DIFF	LOWER	UPPER	50mg_BID		
No	22.7%	-5.8%	51.2%	15/22=68.2%	10/22=45.5%	0.4
Yes	60.0%	17.1%	100%	2/2=100%	2/5=40.0%	

VIKING\_3\_2574\_LOG\_CHANGE\_DAY\_8

ABC EXPOSURE	MEAN	95% LIMITS		N	PVALUE
		LOWER	UPPER		
No	-1.492	-1.582	-1.403	160	0
Yes	-1.050	-1.300	-0.799	22	0



## 4.5 Baseline Resistance Covariates

In the following tables, it will be useful to keep in mind the following abbreviations. GSS = genotypic sensitivity score, BR = background regimen, PSS = phenotypic sensitivity score, which can be computed either fully (f) or partially (p), BL = baseline, FC = fold change in resistance, IN = integrase inhibitor.

### 4.5.1 Two Class Resistant INI Naïve Trial: Baseline Sensitivity Scores

SAILING\_1762\_%BLQ\_WEEK\_24

	MEAN	95% LIMITS				
	DIFF	LOWER	UPPER	DTG_50mg	RAL	PVALUE
BGSSG	Baseline GSS to BR group					
2	4.5%	-5.1%	14.1%	108/138=78.3%	121/164=73.8%	
<2	12.7%	4.4%	21.1%	173/211=82.0%	133/192=69.3%	
BGSSG3	Baseline GSS to BR group					
0_<1	17.9%	-12.0%	47.8%	17/24=70.8%	9/17=52.9%	
1_<2	12.6%	4.0%	21.2%	156/187=83.4%	124/175=70.9%	
2_	5.1%	-4.5%	14.6%	108/137=78.8%	121/164=73.8%	
BMPSFG	BL Max PSSf group					
<=2	8.3%	-39.9%	56.5%	6/8=75.0%	4/6=66.7%	
>2	9.2%	2.9%	15.5%	275/341=80.6%	250/350=71.4%	
BPSFG2	Baseline PSSf to BR group					
<2	12.7%	1.1%	24.4%	84/100=84.0%	67/94=71.3%	
>=2	7.7%	0.3%	15.2%	197/249=79.1%	187/262=71.4%	
BPSSFG	Baseline PSSf to BR group					
2	7.7%	0.2%	15.1%	196/248=79.0%	187/262=71.4%	
<2	12.9%	1.3%	24.5%	85/101=84.2%	67/94=71.3%	
BPSSPG	Baseline PSSp to BR group					
1	20.4%	6.0%	34.9%	55/65=84.6%	43/67=64.2%	
>1	6.6%	-0.4%	13.5%	226/284=79.6%	211/289=73.0%	

## SAILING\_1762\_%BLQ\_WEEK\_24

	MEAN	95% LIMITS				
	DIFF	LOWER	UPPER	DTG_50mg	RAL	PVALUE
BGSS42	BL GSS t o BR					
<1.00	17.7%	-9.6%	45.0%	17/29=58.6%	9/22=40.9%	0.89
1.00	12.0%	-2.3%	26.4%	49/59=83.1%	49/69=71.0%	
1.25	15.1%	-1.6%	31.9%	45/53=84.9%	30/43=69.8%	
1.50	7.3%	-11.4%	25.9%	34/43=79.1%	28/39=71.8%	
1.75	16.7%	-4.8%	38.2%	28/32=87.5%	17/24=70.8%	
2.00	5.1%	-4.5%	14.6%	108/137=78.8%	121/164=73.8%	
BPSSF42G	BL PSSf t o BR					
0	52.4%	-6.9%	111.7%	6/7=85.7%	1/3=33.3%	
1	11.5%	-0.3%	23.3%	79/94=84.0%	66/91=72.5%	
2	8.3%	0.9%	15.7%	196/246=79.7%	187/262=71.4%	
BPSSF42N	BL PSSf t o BR					
0	52.4%	-6.9%	111.7%	6/7=85.7%	1/3=33.3%	
1	11.5%	-0.3%	23.3%	79/94=84.0%	66/91=72.5%	
2	8.3%	0.9%	15.7%	196/246=79.7%	187/262=71.4%	
BPSMF42N	BL PSS to BR full sens. inc mis.					
1	12.3%	0.3%	24.3%	78/93=83.9%	63/88=71.6%	
2	8.4%	1.1%	15.7%	203/254=79.9%	191/267=71.5%	
BPSSP42N	BL PSSp t o BR					
0.0	52.4%	-6.9%	111.7%	6/7=85.7%	1/3=33.3%	
1.0	18.9%	4.0%	33.8%	49/58=84.5%	42/64=65.6%	
1.5	-6.0%	-23.2%	11.2%	29/35=82.9%	24/27=88.9%	
2.0	8.2%	0.8%	15.7%	195/245=79.6%	187/262=71.4%	
BMPSSFNO	BL Max PSSf					
<=7	12.5%	-8.8%	33.8%	29/40=72.5%	21/35=60.0%	0.17
8	30.0%	1.6%	58.4%	10/10=100%	7/10=70.0%	
9	-9.1%	-37.5%	19.3%	9/11=81.8%	10/11=90.9%	
10	-4.6%	-32.8%	23.6%	12/15=80.0%	11/13=84.6%	
11	1.1%	-17.9%	20.1%	24/28=85.7%	22/26=84.6%	
12	9.4%	-9.0%	27.8%	27/32=84.4%	30/40=75.0%	
13	8.6%	-6.8%	24.1%	40/47=85.1%	39/51=76.5%	
14	3.1%	-13.2%	19.4%	45/53=84.9%	27/33=81.8%	
15	-5.9%	-23.5%	11.8%	32/49=65.3%	42/59=71.2%	
16	44.3%	19.3%	69.3%	22/24=91.7%	9/19=47.4%	
>=17	12.6%	-5.5%	30.8%	31/45=68.9%	36/64=56.3%	

## 4.5.2 Two Class Resistant, INI Resistant Trial: Small Trial

### 4.5.2.1 Baseline Mutations

VIKING\_(2961) LOGCHANGE DAY 11

	MEAN	95% LIMITS		DTG	PLAC	N_P	N_D
	DIFF	LOWER	UPPER				
SPATH	Screening	INI Mutation	Pathway				
Mixture	-1.05273	.	.	-1.34711	-0.29438	2	1
N155	-0.07756	-0.88708	0.73196	-1.50736	-1.42980	4	4
Q148+1	-0.28213	-1.00586	0.44159	-1.59939	-1.31726	5	7
Q148+2	-0.49821	.	.	-0.89680	-0.39860	3	1
Y143	-0.36080	-0.77380	0.05220	-2.25875	-1.89795	12	6

BPATH1 Baseline INI Mutation Pathway (8 cat)

Mixture	-1.05273	.	.	-1.34711	-0.29438	2	1
N155	0.02139	-1.02003	1.06281	-1.34713	-1.36852	3	3
Other_IN_mut	-1.15491	.	.	-2.91665	-1.76174	2	1
Q148+1	-0.47886	-1.26023	0.30252	-1.64798	-1.16912	4	8
Q148+2	-0.49821	.	.	-0.89680	-0.39860	3	1
Y143	-0.22922	-0.55852	0.10009	-2.12717	-1.89795	12	5

BPATHW Baseline INI mutation pathway

Mixture	-1.05273	.	.	-1.34711	-0.29438	2	1
N155/Y143	-0.04259	-0.53864	0.45345	-1.83465	-1.79206	15	8
Other	-1.15491	.	.	-2.91665	-1.76174	2	1
Q148_double	-0.72562	-1.32809	-0.12314	-1.56451	-0.83890	7	9

VIKING\_2961\_%BLQ\_WEEK\_24

	MEAN	95% LIMITS		DTG		PVALUE
	DIFF	LOWER	UPPER	50mg_BID	50mg_QD	
SPATH	Screening	INI Mutation	Pathway			
Mixture	100%	100%	100%	1/1=100%	0/2=0.0%	0.36
N155	5.7%	-37.9%	49.3%	6/7=85.7%	4/5=80.0%	
Q148+1	-17.5%	-66.0%	31.0%	5/8=62.5%	4/5=80.0%	
Q148+2	0.0%	0.0%	0.0%	0/1=0.0%	0/3=0.0%	
Y143	38.1%	-4.7%	80.9%	5/7=71.4%	4/12=33.3%	

BPATH1 Baseline INI Mutation Pathway (8 cat)

Mixture	100%	100%	100%	1/1=100%	0/2=0.0%	0.18
N155	8.3%	-43.5%	60.2%	5/6=83.3%	3/4=75.0%	
Other_IN_mut	50.0%	-19.3%	100%	1/1=100%	1/2=50.0%	
Q148+1	-37.5%	-71.0%	-4.0%	5/8=62.5%	4/4=100%	
Q148+2	50.0%	-19.3%	100%	1/2=50.0%	0/3=0.0%	
Y143	33.3%	-12.9%	79.5%	4/6=66.7%	4/12=33.3%	

BPATHW Baseline INI mutation pathway

Mixture	100%	100%	100%	1/1=100%	0/2=0.0%	0.4
N155_and/or_Y143	31.3%	-3.3%	65.8%	9/12=75.0%	7/16=43.8%	
Other	50.0%	-19.3%	100%	1/1=100%	1/2=50.0%	
Q148_double	2.9%	-44.7%	50.5%	6/10=60.0%	4/7=57.1%	

VIKING\_2961\_%BLQ\_WEEK\_48

	MEAN	95% LIMITS	DTG			PVALUE
	DIFF	LOWER	UPPER	50mg_BID	50mg_QD	
SPATH	Screening INI Mutation Pathway					
Mixture	100%	100%	100%	1/1=100%	0/2=0.0%	0.31
N155	40.0%	-2.9%	82.9%	7/7=100%	3/5=60.0%	
Q148+1	-10.0%	-65.2%	45.2%	4/8=50.0%	3/5=60.0%	
Q148+2	0.0%	0.0%	0.0%	0/1=0.0%	0/3=0.0%	
Y143	32.1%	-11.9%	76.2%	4/7=57.1%	3/12=25.0%	
BPATH1	Baseline INI Mutation Pathway (8 cat)					
Mixture	100%	100%	100%	1/1=100%	0/2=0.0%	0.17
N155	25.0%	-17.4%	67.4%	6/6=100%	3/4=75.0%	
Other_IN_mut	100%	100%	100%	1/1=100%	0/2=0.0%	
Q148+1	-25.0%	-79.8%	29.8%	4/8=50.0%	3/4=75.0%	
Q148+2	50.0%	-19.3%	119.3%	1/2=50.0%	0/3=0.0%	
Y143	25.0%	-21.9%	71.9%	3/6=50.0%	3/12=25.0%	
BPATHW	Baseline INI mutation pathway					
Mixture	100%	100%	100%	1/1=100%	0/2=0.0%	0.25
N155_and/or_Y143	37.5%	3.4%	71.6%	9/12=75.0%	6/16=37.5%	
Other	100%	100%	100%	1/1=100%	0/2=0.0%	
Q148_double	7.1%	-40.9%	55.1%	5/10=50.0%	3/7=42.9%	

#### 4.5.2.2 Baseline Fold Change in Resistance

VIKING_(2961)_LOGCHANGE_DAY_11							
	MEAN	95% LIMITS		DTG	PLAC	N_P	N_D
	DIFF	LOWER	UPPER				
BFC1GP	Baseline FC in IC50 for RAL group						
<=maximum	-0.38195	-0.84347	0.07958	-2.15264	-1.77070	8	7
>maximum	-0.23499	-0.73037	0.26040	-1.49609	-1.26110	18	12
BFC1CAT	Baseline FC in IC50 for RAL group						
<=5.36	-0.58996	-1.17259	-0.00734	-2.22442	-1.63446	6	5
5.356-7.271	-0.00353	-0.82841	0.82134	-1.84674	-1.84320	3	5
7.271-7.33	0.00939	-0.67435	0.69313	-1.19487	-1.20426	12	5
>7.33	-0.25726	-1.23318	0.71865	-1.67286	-1.41560	5	4
BFC2GP	Baseline FC in IC50 for IP group						
<2	-0.35613	-0.73657	0.02430	-2.17931	-1.82317	16	7
>=2	-0.71107	-1.20678	-0.21537	-1.48054	-0.76946	10	12
BFC2CAT	Baseline FC in IC50 for IP group						
<=0.275	-0.36316	-0.83457	0.10824	-2.35639	-1.99323	10	4
0.275-0.824	-0.40344	-0.93123	0.12434	-1.94319	-1.53975	6	3
0.824-2.35	0.01819	-0.54616	0.58253	-1.50754	-1.52573	3	6
>2.35	-1.00818	-1.55103	-0.46533	-1.45353	-0.44535	7	6
VIKING_2961_%BLQ_WEEK_24							
	MEAN	95% LIMITS		DTG			
	DIFF	LOWER	UPPER	50mg_BID	50mg_QD		PVALUE
BFC1GP	Baseline FC in IC50 for RAL group						
<=maximum	15.2%	-23.2%	53.5%	9/11=81.8%	6/9=66.7%		0.79
>maximum	28.2%	-6.1%	62.5%	8/13=61.5%	6/18=33.3%		
BFC1CAT	Baseline FC in IC50 for RAL group						
<=5.35755	16.7%	-38.3%	71.7%	4/6=66.7%	3/6=50.0%		0.44
5.35755-7.27118	-12.5%	-35.4%	10.4%	7/8=87.5%	4/4=100%		
7.27118-7.33405	50.0%	10.0%	90.0%	5/6=83.3%	4/12=33.3%		
>7.33405	5.0%	-50.0%	60.0%	1/4=25.0%	1/5=20.0%		
BFC2GP	Baseline FC in IC50 for IP group						
<2	29.2%	-9.7%	68.0%	6/9=66.7%	6/16=37.5%		0.77
>=2	18.8%	-18.2%	55.8%	11/15=73.3%	6/11=54.5%		
BFC2CAT	Baseline FC in IC50 for IP group						
<=0.27501	10.0%	-47.6%	67.6%	2/4=50.0%	4/10=40.0%		0.31
0.27501-0.82375	46.7%	-4.8%	98.2%	4/5=80.0%	2/6=33.3%		
0.82375-2.34767	-22.2%	-49.4%	4.9%	7/9=77.8%	4/4=100%		
>2.34767	38.1%	-12.3%	88.5%	4/6=66.7%	2/7=28.6%		

VIKING_2961_%BLQ_WEEK_48						
	MEAN	95% LIMITS		DTG		
	DIFF	LOWER	UPPER	50mg_BID	50mg_QD	PVALUE
BFC1GP	Baseline FC in IC50 for RAL group					
<=maximum	37.4%	-2.3%	77.0%	9/11=81.8%	4/9=44.4%	0.65
>maximum	26.1%	-8.0%	60.2%	7/13=53.8%	5/18=27.8%	
BFC1CAT	Baseline FC in IC50 for RAL group					
<=5.35755	33.3%	-20.0%	86.7%	4/6=66.7%	2/6=33.3%	0.37
5.35755-7.27118	37.5%	-16.6%	91.6%	7/8=87.5%	2/4=50.0%	
7.27118-7.33405	50.0%	10.0%	90.0%	5/6=83.3%	4/12=33.3%	
>7.33405	-20.0%	-55.1%	15.1%	0/4=0.0%	1/5=20.0%	
BFC2GP	Baseline FC in IC50 for IP group					
<2	41.7%	4.3%	79.1%	6/9=66.7%	4/16=25.0%	0.46
>=2	21.2%	-16.7%	59.1%	10/15=66.7%	5/11=45.5%	
BFC2CAT	Baseline FC in IC50 for IP group					
<=0.27501	20.0%	-36.6%	76.6%	2/4=50.0%	3/10=30.0%	0.21
0.27501-0.82375	63.3%	17.3%	109.4%	4/5=80.0%	1/6=16.7%	
0.82375-2.34767	-22.2%	-49.4%	4.9%	7/9=77.8%	4/4=100%	
>2.34767	35.7%	-12.0%	83.4%	3/6=50.0%	1/7=14.3%	

VIKING_(2961)_LOGCHANGE_DAY_11							
	MEAN	95% LIMITS		DTG	PLAC	N_P	N_D
	DIFF	LOWER	UPPER				
BRC1GP	Baseline RC for IN group						
<77	-0.05276	-0.79577	0.69025	-1.50611	-1.45335	13	6
>=77	-0.45367	-0.97851	0.07116	-1.83612	-1.38245	13	11
BRC1CAT	Baseline RC for IN group						
<=49	-0.69614	-1.38547	-0.00681	-1.97318	-1.27705	7	2
49-76	0.38647	-0.60814	1.38107	-1.27257	-1.65904	6	4
76-99	-0.60493	-1.26890	0.05905	-1.73360	-1.12867	7	5
>99	-0.24304	-0.99252	0.50645	-1.92156	-1.67852	6	6
BRC2GP	Baseline RC for PR/RT group						
<36.5	-0.11814	-0.75215	0.51587	-1.59317	-1.47503	13	9
>=36.5	-0.49423	-1.01984	0.03138	-1.85500	-1.36077	13	9
BRC2CAT	Baseline RC for PR/RT group						
<=9.4	-0.24461	-0.59647	0.10724	-2.00644	-1.76183	6	3
9.4-33	0.02052	-0.98991	1.03095	-1.38653	-1.40705	6	6
33-53	-1.11113	-1.95373	-0.26852	-2.04877	-0.93764	8	4
>53	0.02518	-0.60780	0.65816	-1.69999	-1.72517	6	5
VIKING_2961_%BLQ_WEEK_24							
	MEAN	95% LIMITS		DTG			
	DIFF	LOWER	UPPER	50mg_BID	50mg_QD		PVALUE
BRC1GP	Baseline RC for IN group						
<77	28.0%	-7.4%	63.4%	9/11=81.8%	7/13=53.8%		
>=77	27.9%	-10.0%	65.8%	7/11=63.6%	5/14=35.7%		
BRC1CAT	Baseline RC for IN group						
<=49	28.6%	-4.9%	62.0%	4/4=100%	5/7=71.4%		
49-76	38.1%	-12.3%	88.5%	5/7=71.4%	2/6=33.3%		
76-99	2.5%	-52.0%	57.0%	2/5=40.0%	3/8=37.5%		
>99	50.0%	1.9%	98.1%	5/6=83.3%	2/6=33.3%		
BRC2GP	Baseline RC for PR/RT group						
<36.5	5.1%	-32.4%	42.7%	8/12=66.7%	8/13=61.5%		
>=36.5	44.2%	8.8%	79.5%	8/11=72.7%	4/14=28.6%		
BRC2CAT	Baseline RC for PR/RT group						
<=9.4	-23.3%	-75.6%	28.9%	3/5=60.0%	5/6=83.3%		
9.4-33	38.1%	-12.3%	88.5%	5/7=71.4%	2/6=33.3%		
33-53	42.5%	-6.0%	91.0%	4/5=80.0%	3/8=37.5%		
>53	38.1%	-12.3%	88.5%	4/6=66.7%	2/7=28.6%		

VIKING_2961_%BLQ_WEEK_48						
	MEAN	95% LIMITS		DTG		
	DIFF	LOWER	UPPER	50mg_BID	50mg_QD	PVALUE
BRC1GP	Baseline RC for IN group					
<77	51.0%	17.2%	84.9%	9/11=81.8%	4/13=30.8%	
>=77	18.8%	-19.8%	57.5%	6/11=54.5%	5/14=35.7%	
BRC1CAT	Baseline RC for IN group					
<=49	71.4%	38.0%	104.9%	4/4=100%	2/7=28.6%	
49-76	38.1%	-12.3%	88.5%	5/7=71.4%	2/6=33.3%	
76-99	2.5%	-52.0%	57.0%	2/5=40.0%	3/8=37.5%	
>99	33.3%	-20.0%	86.7%	4/6=66.7%	2/6=33.3%	
BRC2GP	Baseline RC for PR/RT group					
<36.5	36.5%	0.5%	72.6%	9/12=75.0%	5/13=38.5%	
>=36.5	26.0%	-11.8%	63.7%	6/11=54.5%	4/14=28.6%	
BRC2CAT	Baseline RC for PR/RT group					
<=9.4	10.0%	-48.7%	68.7%	3/5=60.0%	3/6=50.0%	
9.4-33	69.0%	29.5%	108.6%	6/7=85.7%	1/6=16.7%	
33-53	22.5%	-32.0%	77.0%	3/5=60.0%	3/8=37.5%	
>53	21.4%	-30.7%	73.6%	3/6=50.0%	2/7=28.6%	



### 4.5.2.3 Baseline Sensitivity Scores

VIKING_(2961)_LOGCHANGE_DAY_11							
	MEAN	95% LIMITS					
	DIFF	LOWER	UPPER	DTG	PLAC	N_P	N_D
BGSS11G	BL GSS group to day 11 OBR						
>0_1	-0.03143	-0.54174	0.47887	-1.44741	-1.41598	16	5
>1_2	-0.31941	-1.08556	0.44674	-1.71182	-1.39241	5	11
>2	-0.37204	-1.33013	0.58606	-2.31819	-1.94615	2	3
BGSS1G	BL GSS group to day 1 failing regimen						
0	-0.43043	-1.35619	0.49533	-1.46283	-1.03240	5	3
>0_1	-0.19855	-0.65043	0.25332	-1.66713	-1.46858	20	13
>1_2	0.35754	.	.	-1.97430	-2.33184	1	1
>2	.	.	.	-2.91665	.	0	1
PSSF11G	PSS (full) to Day 11 ART group						
0	.	.	.	.	-1.40186	12	0
1	-0.34174	-1.18650	0.50302	-1.44707	-1.10533	7	7
2	-0.26665	-0.69382	0.16052	-1.94936	-1.68271	5	9
>2	0.16352	-0.72447	1.05152	-1.78263	-1.94615	2	3
PSSF1G	PSS (full) to Day 1 ART group						
0	-0.16392	-0.67109	0.34324	-1.44171	-1.27779	18	10
1	-0.23188	-0.85539	0.39163	-1.88518	-1.65330	6	6
2	-0.81749	.	.	-2.43113	-1.61364	1	3
>2	.	.	.	.	-2.33184	1	0

VIKING_2961_%BLQ_WEEK_24						
	MEAN	95% LIMITS		DTG		
	DIFF	LOWER	UPPER	50mg_BID	50mg_QD	PVALUE
BGSS11G	BL GSS group to day 11 OBR					
0	100%	100%	100%	1/1=100%	0/3=0.0%	0.051
>0_1	25.9%	-17.2%	69.0%	4/7=57.1%	5/16=31.3%	
>1_2	4.6%	-35.6%	44.8%	11/13=84.6%	4/5=80.0%	
>2	-66.7%	-100%	-13.3%	1/3=33.3%	3/3=100%	
BGSS1G	BL GSS group to day 1 failing regimen					
0	50.0%	1.0%	99.0%	2/4=50.0%	0/5=0.0%	
>0_1	31.3%	2.2%	60.3%	13/16=81.3%	10/20=50.0%	
>1_2	-100%	-100%	-100%	0/2=0.0%	1/1=100%	
>2	0.0%	0.0%	0.0%	1/1=100%	1/1=100%	
PSSF11G	PSS (full) to Day 11 ART group					
0	91.7%	76.0%	107.3%	1/1=100%	1/12=8.3%	0.028
1	9.5%	-38.4%	57.4%	6/9=66.7%	4/7=57.1%	
2	1.8%	-40.0%	43.6%	9/11=81.8%	4/5=80.0%	
>2	-66.7%	-100%	-13.3%	1/3=33.3%	3/3=100%	
PSSF1G	PSS (full) to Day 1 ART group					
0	33.3%	1.0%	65.6%	10/15=66.7%	6/18=33.3%	0.72
1	33.3%	-16.6%	83.2%	5/6=83.3%	3/6=50.0%	
2	-33.3%	-86.7%	20.0%	2/3=66.7%	1/1=100%	
>2				0/0=.	2/2=100%	

VIKING_2961_%BLQ_WEEK_48						
	MEAN	95% LIMITS		DTG		
	DIFF	LOWER	UPPER	50mg_BID	50mg_QD	PVALUE
BGSS11G	BL GSS group to day 11			OBR		
0	0.0%	0.0%	0.0%	0/1=0.0%	0/3=0.0%	0.18
>0_1	44.6%	4.6%	84.7%	4/7=57.1%	2/16=12.5%	
>1_2	-3.1%	-45.0%	38.8%	10/13=76.9%	4/5=80.0%	
>2	-33.3%	-86.7%	20.0%	2/3=66.7%	3/3=100%	
BGSS1G	BL GSS group to day 1			failing regimen		
0	50.0%	1.0%	99.0%	2/4=50.0%	0/5=0.0%	
>0_1	33.8%	2.9%	64.6%	11/16=68.8%	7/20=35.0%	
>1_2	-50.0%	-100%	19.3%	1/2=50.0%	1/1=100%	
>2	0.0%	0.0%	0.0%	1/1=100%	1/1=100%	
PSSF11G	PSS (full) to Day 11			ART group		
0	-8.3%	-24.0%	7.3%	0/1=0.0%	1/12=8.3%	0.41
1	38.1%	-7.4%	83.6%	6/9=66.7%	2/7=28.6%	
2	12.7%	-37.6%	63.1%	8/11=72.7%	3/5=60.0%	
>2	-33.3%	-86.7%	20.0%	2/3=66.7%	3/3=100%	
PSSF1G	PSS (full) to Day 1			ART group		
0	38.9%	7.3%	70.5%	10/15=66.7%	5/18=27.8%	0.97
1	33.3%	-20.0%	86.7%	4/6=66.7%	2/6=33.3%	
2	66.7%	13.3%	120.0%	2/3=66.7%	0/1=0.0%	
>2				0/0=.	2/2=100%	

### 4.5.3 Two Class Resistant, INI Resistant Trial: Pivotal Trial

#### 4.5.3.1 Baseline INI Exposure

VIKING\_3\_2574\_LOG\_CHANGE\_DAY\_8

		95% LIMITS		N	PVALUE
	MEAN	LOWER	UPPER		
INIDGP	Duration of INI taken group				
<=6 mos	-1.282	-1.633	-0.931	14	.0000
6-24 mos	-1.467	-1.624	-1.310	64	.0000
>24 mos	-1.449	-1.558	-1.340	102	.0000
INI_DUR	Duration of INI taken				
<=16.66	-1.337	-1.548	-1.126	46	.0000
16.66-27.83	-1.578	-1.727	-1.429	41	.0000
27.83-42.0	-1.504	-1.666	-1.341	48	.0000
>42.0	-1.361	-1.520	-1.202	45	.0000
INI_IP	Time to IP since INI stopped				
<=0.066	-1.265	-1.449	-1.082	36	0
0.066-13.47	-1.430	-1.552	-1.307	102	0
>13.47	-1.601	-1.748	-1.455	44	0

VIKING\_3\_2574\_%BLQ\_WEEK\_24

		95% LIMITS		PVALUE
		LOWER	UPPER	
ABC EXPOSURE				
No	68/98=69.4%	60.3%	78.5%	.0000
Yes	8/16=50.0%	25.5%	74.5%	.0001
INIDGP	Duration of	INI taken group		
<=6 mos	3/10=30.0%	1.6%	58.4%	0.0384
6-24 mos	29/45=64.4%	50.5%	78.4%	0.0000
>24 mos	44/58=75.9%	64.8%	86.9%	0.0000
INI DUR	Duration of	INI taken		
<=16.66	16/33=48.5%	31.4%	65.5%	0
16.66-27.83	23/29=79.3%	64.6%	94.1%	0
27.83-42.0	21/24=87.5%	74.3%	100.7%	0
>42.0	16/27=59.3%	40.7%	77.8%	0
INI_IP	Time to IP since	INI stopped		
<=0.066	12/19=63.2%	41.5%	84.8%	0
0.066-13.47	42/66=63.6%	52.0%	75.2%	0
>13.47	22/29=75.9%	60.3%	91.4%	0

### 4.5.3.2 Baseline Mutations

VIKING_3_2574_LOG_CHANGE_DAY_8					
	MEAN	95% LIMITS		N	PVALUE
		LOWER	UPPER		
SPATH	Screening	IN Mutation	(Q148/Other)		
>=2	-1.447	-2.055	-0.839	7	0
N155	-1.456	-1.627	-1.285	32	0
Prim_not_det	-1.566	-1.709	-1.424	61	0
Q148+1	-1.183	-1.380	-0.987	30	0
Q148+>=2	-0.993	-1.322	-0.664	20	0
T66	-1.854	.	.	1	.
Y143	-1.686	-1.838	-1.535	29	0
BPATH1	Baseline INI Mutation Pathway (8 cat)				
No	Q148	-1.592	-1.682	-1.503	126 0
Q148+>=1	-1.093	-1.258	-0.928	56	0
BPATHW	Baseline INI mutation pathway				
>=2	-1.446	-1.973	-0.920	8	0
N155	-1.430	-1.604	-1.257	33	0
Prim_not_det	-1.615	-1.753	-1.476	60	0
Q148+1	-1.125	-1.303	-0.947	32	0
Q148+>=2	-1.043	-1.380	-0.706	20	0
T66	-1.854	.	.	1	.
Y143	-1.695	-1.851	-1.539	28	0
BPATH2	BL Primary IN mut. detected/or not				
BPATH2CD					
No_IN_mut	-1.615	-1.753	-1.476	60	0
Prim_IN_mut	-1.352	-1.459	-1.245	122	0
BINSPG	No. of BL res. spec. IN mutat. grp code				
BINSPG					
0	-1.661	-1.826	-1.496	47	0
1	-1.330	-1.541	-1.118	17	0
2	-1.347	-1.500	-1.195	57	0
3	-1.344	-1.573	-1.115	34	0
4	-1.544	-1.761	-1.328	19	0
>=5	-1.166	-1.601	-0.730	8	0

VIKING\_3\_2574\_%BLQ\_WEEK\_24

		95% LIMITS		PVALUE
MEAN		LOWER	UPPER	
SPATH	Screening IN Mutation (Q148/Other)			
<2	2/2=100%	100%	100%	.
>=2_Pri_mut	3/4=75.0%	32.6%	117.4%	0.0005
N155	17/19=89.5%	75.7%	103.3%	0.0000
Prim_not_det	30/39=76.9%	63.7%	90.1%	0.0000
Q148+1	9/19=47.4%	24.9%	69.8%	0.0000
Q148+>=2	2/14=14.3%	-4.0%	32.6%	0.1266
T66	1/1=100%	100%	100%	.
Y143	12/16=75.0%	53.8%	96.2%	0.0000

BPATH1	Baseline IN Mutation (Q148/Other)			
No_Q148	63/79=79.7%	70.9%	88.6%	0
Q148+>=1	13/35=37.1%	21.1%	53.2%	0

BPATHW	Baseline IN mutation category			
>=2_Pri_mut	4/5=80.0%	44.9%	115.1%	0.0000
N155	18/21=85.7%	70.7%	100.7%	0.0000
Prim_not_det	31/40=77.5%	64.6%	90.4%	0.0000
Q148+1	10/20=50.0%	28.1%	71.9%	0.0000
Q148+>=2	1/12=8.3%	-7.3%	24.0%	0.2963
T66	1/1=100%	100%	100%	.
Y143	11/15=73.3%	51.0%	95.7%	0.0000

BPATH2	BL Primary IN mut. detected/or not			
No_IN_mut	31/40=77.5%	64.6%	90.4%	0
Prim_IN_mut	45/74=60.8%	49.7%	71.9%	0

BINSPG	No. of BL res. spec. IN mutat. grp code			
0	25/33=75.8%	61.1%	90.4%	0.0000
1	9/10=90.0%	71.4%	108.6%	0.0000
2	20/31=64.5%	47.7%	81.4%	0.0000
3	13/23=56.5%	36.3%	76.8%	0.0000
4	8/12=66.7%	40.0%	93.3%	0.0000
>=5	1/5=20.0%	-15.1%	55.1%	0.2636

### 4.5.3.3 Baseline Fold Change in Resistance

VIKING\_3\_2574\_LOG\_CHANGE\_DAY\_8

	95% LIMITS				
	MEAN	LOWER	UPPER	N	PVALUE
BFC1GP	Baseline FC in IC50 for RAL group				
0_1.5	-1.616	-1.762	-1.470	56	.0000
>1.5_4	-1.464	-1.891	-1.037	6	.0000
>4_8	-1.629	-2.427	-0.830	2	.0001
>10_20	-1.654	-2.017	-1.291	9	.0000
>20_maximum	-1.525	-1.712	-1.338	26	.0000
>maximum	-1.260	-1.405	-1.115	76	.0000

BFC1GP Baseline FC in IC50 for RAL group  
BFC1CAT Baseline FC in IC50 for RAL group

BFC1CAT					
<=0.118	-1.585	-1.763	-1.407	43	0
0.118-5.322	-1.558	-1.706	-1.410	41	0
5.322-6.78	-1.330	-1.462	-1.197	90	0
>6.78	-1.098	.	.	1	.

BFC2GP Baseline FC in IC50 for IP group

BFC2GP					
0_2.5	-1.603	-1.695	-1.512	122	0.0000
>2.5_4	-1.438	-1.752	-1.125	12	0.0000
>4_8	-1.042	-1.280	-0.803	22	0.0000
>8_10	-1.235	-1.886	-0.583	4	0.0002
>10_15	-0.774	-1.258	-0.290	8	0.0017
>15_20	-0.902	-2.102	0.299	3	0.1412
>20_25	-1.405	.	.	1	.
>25	-0.583	-1.141	-0.024	3	0.0408

BFC2CAT Baseline FC in IC50 for IP group

BFC2CAT					
<=-0.12	-1.592	-1.748	-1.437	48	0
<=0.12-0.356	-1.626	-1.761	-1.491	36	0
0.356-1.761	-1.611	-1.782	-1.441	43	0
>1.761	-1.011	-1.181	-0.841	48	0

VIKING\_3\_2574\_%BLQ\_WEEK\_24

	MEAN	95% LIMITS		PVALUE
		LOWER	UPPER	
BFC1GP	Baseline FC in IC50 for RAL group			
0_1.5	28/38=73.7%	59.7%	87.7%	0.0000
>1.5_4	2/3=66.7%	13.3%	120.0%	0.0143
>4_8	1/1=100%	100%	100%	.
>10_20	6/7=85.7%	59.8%	111.6%	0.0000
>20_max	14/15=93.3%	80.7%	106.0%	0.0000
>max	21/46=45.7%	31.3%	60.0%	0.0000

BFC1CAT	Baseline FC in IC50 for RAL group			
<=0.118	22/29=75.9%	60.3%	91.4%	0
0.118-5.322	21/26=80.8%	65.6%	95.9%	0
5.322-6.779	28/54=51.9%	38.5%	65.2%	0
>6.779	1/1=100%	100%	100%	.

BFC2GP	Baseline FC in IC50 for IP group			
0_2.5	61/78=78.2%	69.0%	87.4%	0.0000
>2.5_4	3/8=37.5%	4.0%	71.0%	0.0285
>4_8	5/11=45.5%	16.0%	74.9%	0.0025
>8_10	1/4=25.0%	-17.4%	67.4%	0.2482
>10_15	1/5=20.0%	-15.1%	55.1%	0.2636
>15_20	1/3=33.3%	-20.0%	86.7%	0.2207
>25	0/1=0.0%	0.0%	0.0%	.

BFC2CAT	Baseline FC in IC50 for IP group			
<=-0.120	23/29=79.3%	64.6%	94.1%	.0000
<=0.120-0.356	16/23=69.6%	50.8%	88.4%	.0000
0.356-1.761	24/30=80.0%	65.7%	94.3%	.0000
>1.761	9/28=32.1%	14.8%	49.4%	.0003



#### 4.5.3.4 Baseline Sensitivity Scores

VIKING_3_2574_LOG_CHANGE_DAY_8					
	95% LIMITS				
	MEAN	LOWER	UPPER	N	PVALUE
BGSS1G	BL GSS group to day 1 failing regimen				
0	-1.454	-1.650	-1.257	34	0
>0_1	-1.471	-1.580	-1.362	120	0
>1_2	-1.379	-1.622	-1.136	19	0
>2	-1.071	-1.406	-0.736	9	0
BGSS8G	BL GSS group to day 8 OBR				
0	-1.273	.	.	1	.
>0_1	-1.381	-1.560	-1.201	47	0
>1_2	-1.489	-1.608	-1.371	95	0
>2	-1.389	-1.572	-1.206	39	0
BOSSF1G	BL OSS to day 1 backg.ART full sens. grp				
0	-1.441	-1.545	-1.337	105	0
1	-1.516	-1.688	-1.345	60	0
2	-1.137	-1.456	-0.817	11	0
>2	-1.179	-1.625	-0.733	6	0
BOSSF8G	BL OSS to day 8 OBR full sens. group				
0	-1.234	-1.625	-0.844	11	0
1	-1.454	-1.583	-1.324	70	0
2	-1.470	-1.617	-1.324	74	0
>2	-1.397	-1.605	-1.188	27	0
BPSSF1G	BL PSS to day 1 b.ART full sens. group				
0	-1.441	-1.546	-1.336	96	0
1	-1.494	-1.657	-1.330	67	0
2	-1.219	-1.514	-0.925	11	0
>2	-1.258	-1.764	-0.752	8	0
BPSSF8G	BL PSS to day 8 OBR full sens. group				
0	-1.252	-1.682	-0.822	10	0
1	-1.399	-1.536	-1.262	58	0
2	-1.509	-1.643	-1.374	79	0
>2	-1.400	-1.612	-1.188	35	0
BPSSP8G	BL PSS to day 8 OBR part. sens. group				
0	-1.396	-1.638	-1.155	2	0
>0_1	-1.393	-1.579	-1.207	42	0
>1_2	-1.483	-1.613	-1.354	85	0
>2	-1.405	-1.559	-1.251	53	0

VIKING\_3\_2574\_%BLQ\_WEEK\_24

		95% LIMITS		PVALUE
		LOWER	UPPER	
BGSS1G	BL GSS group to day 1 failing regimen			
0	17/25=68.0%	49.7%	86.3%	.0000
>0_1	48/69=69.6%	58.7%	80.4%	.0000
>1_2	7/12=58.3%	30.4%	86.2%	.0000
>2	4/8=50.0%	15.4%	84.6%	.0047
BGSS8G	BL GSS group to day 8 OBR			
>0_1	22/29=75.9%	60.3%	91.4%	0
>1_2	37/62=59.7%	47.5%	71.9%	0
>2	17/23=73.9%	56.0%	91.9%	0
BOSSF1G	BL OSS to day 1 backg.ART full sens. grp			
0	44/65=67.7%	56.3%	79.1%	0.0000
1	27/38=71.1%	56.6%	85.5%	0.0000
2	3/6=50.0%	10.0%	90.0%	0.0143
>2	2/5=40.0%	-2.9%	82.9%	0.0679
BOSSF8G	BL OSS to day 8 OBR full sens. group			
0	5/6=83.3%	53.5%	113.2%	0
1	33/48=68.8%	55.6%	81.9%	0
2	26/44=59.1%	44.6%	73.6%	0
>2	12/16=75.0%	53.8%	96.2%	0
BPSSF1G	BL PSS to day 1 b.ART full sens. group			
0	43/62=69.4%	57.9%	80.8%	0.0000
1	28/39=71.8%	57.7%	85.9%	0.0000
2	3/6=50.0%	10.0%	90.0%	0.0143
>2	2/7=28.6%	-4.9%	62.0%	0.0943
BPSSF8G	BL PSS to day 8 OBR full sens. group			
0	4/5=80.0%	44.9%	115.1%	0
1	30/41=73.2%	59.6%	86.7%	0
2	29/47=61.7%	47.8%	75.6%	0
>2	13/21=61.9%	41.1%	82.7%	0
BPSSP8G	BL PSS to day 8 OBR part. sens. group			
0	1/1=100%	100%	100%	.
>0_1	20/26=76.9%	60.7%	93.1%	0
>1_2	35/54=64.8%	52.1%	77.6%	0
>2	20/33=60.6%	43.9%	77.3%	0

#### 4.5.3.5 Miscellaneous

##### VIKING\_3\_2574\_LOG\_CHANGE\_DAY\_8

	MEAN	95% LIMITS		N	PVALUE
		LOWER	UPPER		
C0AVG	C0_avg (ug/mL)				
<=1.758	-1.454	-1.639	-1.268	43	.0000
1.758-2.33	-1.361	-1.535	-1.188	45	.0000
2.33-3.46	-1.480	-1.631	-1.328	42	.0000
>3.46	-1.493	-1.677	-1.309	47	.0000

PIQC0AVG	PIQ_C0_avg				
<=9.62	-1.129	-1.303	-0.955	46	0
9.62-29.05	-1.575	-1.744	-1.406	43	0
29.05-44.3	-1.567	-1.729	-1.405	39	0
>44.3	-1.578	-1.755	-1.402	42	0

##### VIKING\_3\_2574\_%BLQ\_WEEK\_24

	MEAN	95% LIMITS		PVALUE
		LOWER	UPPER	
C0AVG	C0_avg (ug/mL)			
<=1.758	19/25=76.0%	59.3%	92.7%	0
1.758-2.33	18/31=58.1%	40.7%	75.4%	0
2.33-3.46	19/28=67.9%	50.6%	85.2%	0
>3.46	20/29=69.0%	52.1%	85.8%	0

PIQC0AVG	PIQ_C0_avg			
<=9.618	12/29=41.4%	23.5%	59.3%	0
9.618-29.05	19/27=70.4%	53.1%	87.6%	0
29.05-44.34	20/28=71.4%	54.7%	88.2%	0
>44.34	21/25=84.0%	69.6%	98.4%	0

#### **4.4 Exploratory Looks for Treatment-Covariate Interactions**

The following graphs are intended to look for any suggestions of treatment-covariate interactions. By absence of interaction, this reviewer means that the difference between DTG and control is constant across all levels of the covariate. This reviewer does not count a change in the DTG response and a change in the control response as an interaction. One would obviously expect that both DTG and control would perform better in, say, subjects with lower baseline viral load than in subjects with higher baseline viral load. The question of interest is whether both regimens improve or worsen by comparable amounts as one goes from one covariate level to another.

There are two graphs for each endpoint and trial examined. The first graph is obtained by computing the point estimate and 95% confidence intervals for the parameter of interest, either log change from baseline or percent BLQ, for each subgroup of interest. The numeric results of these computations have just been listed in the preceding tables. The graph is to provide a single overview of all the previous tables for each trial that facilitates the detection of possibly anomalous subgroups.

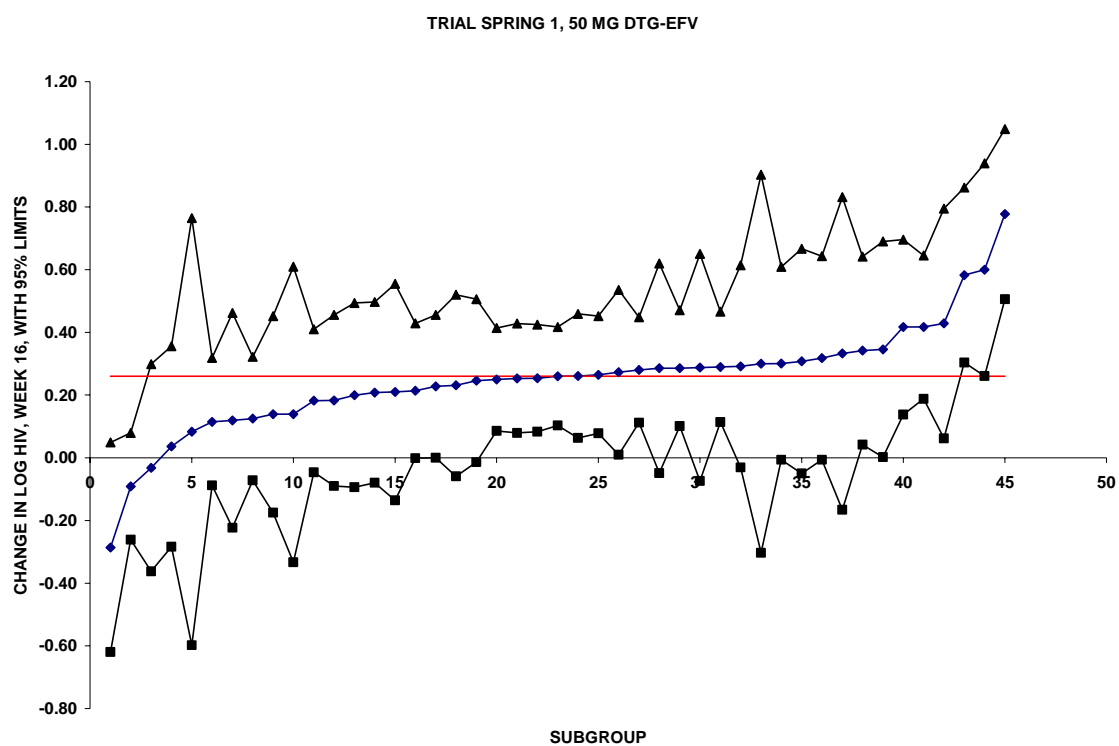
In the first graph, the subgroups are sorted by increasing value of the difference between DTG\_50mg and control. (The control in Viking 3 is a constant zero.) In this graph, the plot includes the point estimate and upper and lower bounds for each subgroup plus a horizontal line corresponding to the point estimate for all subjects taken together. One should be looking for sudden jogs upward or downward at the ends of the graph. In the absence of any treatment-covariate interactions, the point estimates by subgroup should increase smoothly.

In the second graph, the point estimates for each subgroup are sorted by increasing sample size in the subgroup. Only the point estimates are plotted so each subgroup is represented by one discrete point. Three curves are also plotted. The horizontal line is the point estimate for all subjects taken together. The upper and lower curves will be seen to converge on the line for the point estimate from above and below as the sample size increases. These two curves represent what the upper and lower 95% tolerance limits on the DTG- control difference in each subgroup would be if there were no treatment-covariate interaction. That is, if the true DTG-control difference

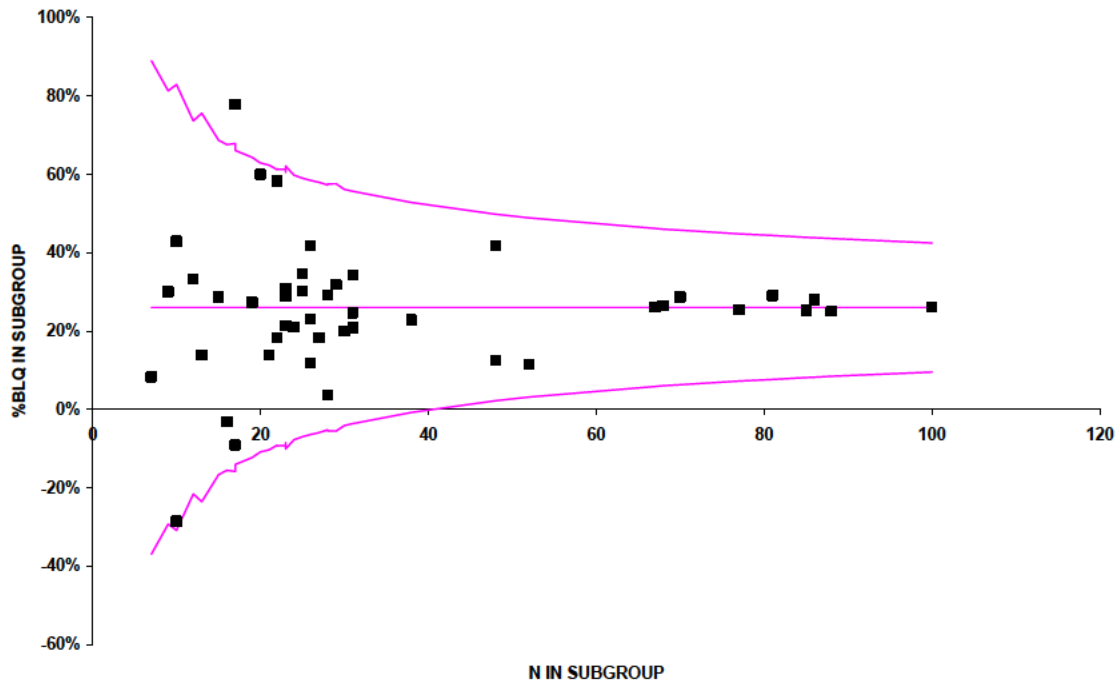
were exactly the same in, say, males and females, and any observed difference were just due to random sampling error, then the point estimate for males would lie between the upper and lower curves, as the point estimate for females. If the majority of the point representing individual subgroups lie within the tolerance limits, that would constitute evidence that none of the subgroups exhibited any treatment-covariate interaction.

One will observe that the upper and lower curves in these graphs are not smooth but rather exhibit some jerks up and down. That is because the limits on difference between two samples would depend not merely on the total sample size= sum of the sample sizes in each arm but also on the sample sizes in each of the individual arms. That is, the tolerance limits when there are 5 subjects each on DTG and control will be different from the tolerance limits when there are 7 DTG subjects and 3 control subjects.

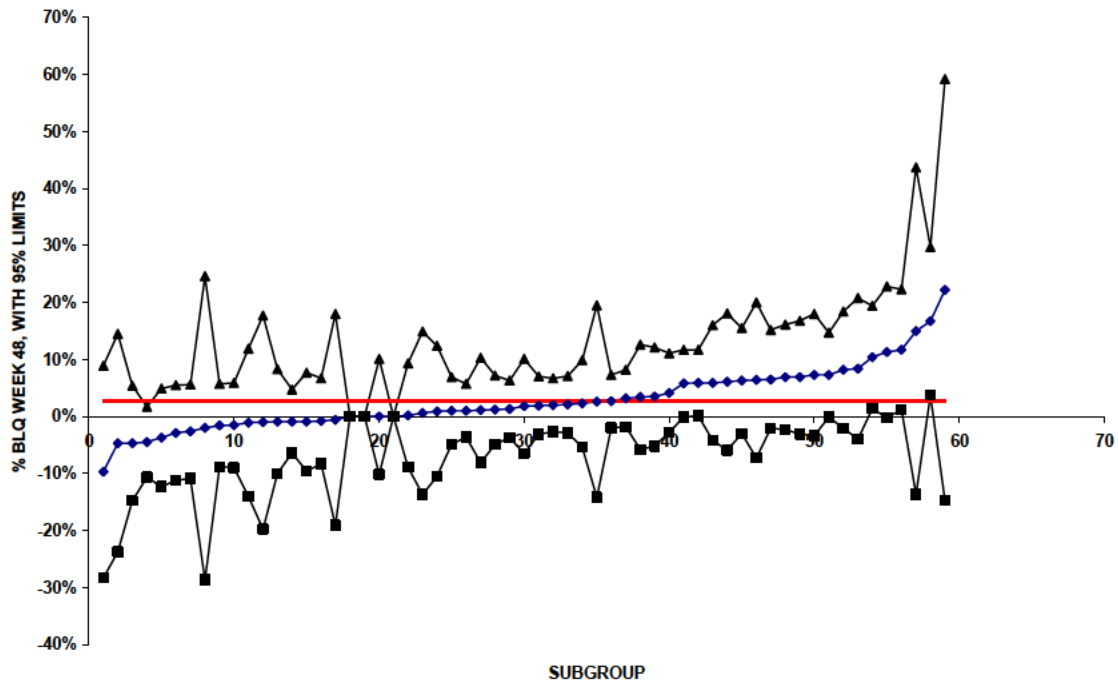
#### 4.4.1 Treatment Naïve Trials



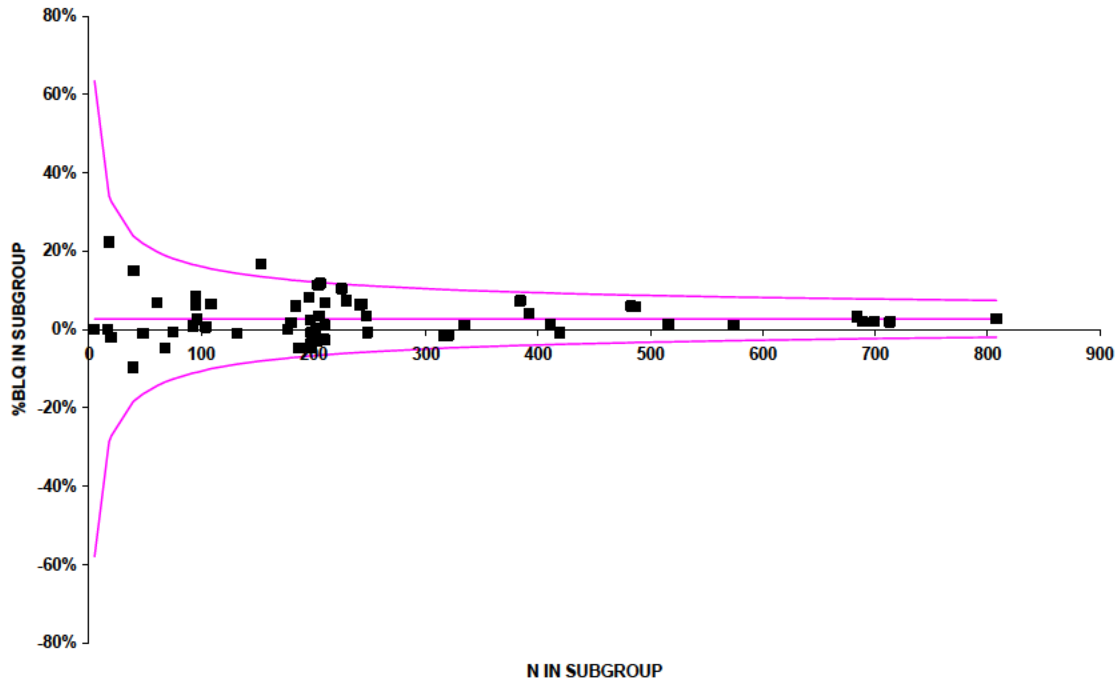
SPRING 1, DTG 50 VS EFV, WEEK 16



# TRIAL SPRING 2, DTG -RAL

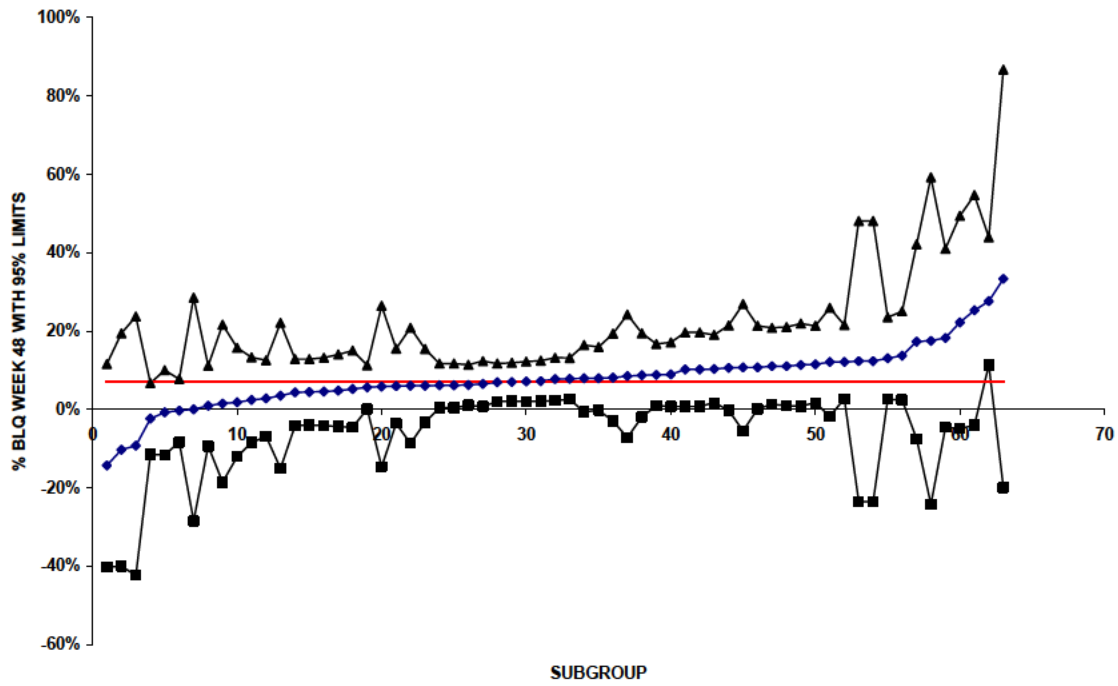


## SPRING 2, WEEK 48

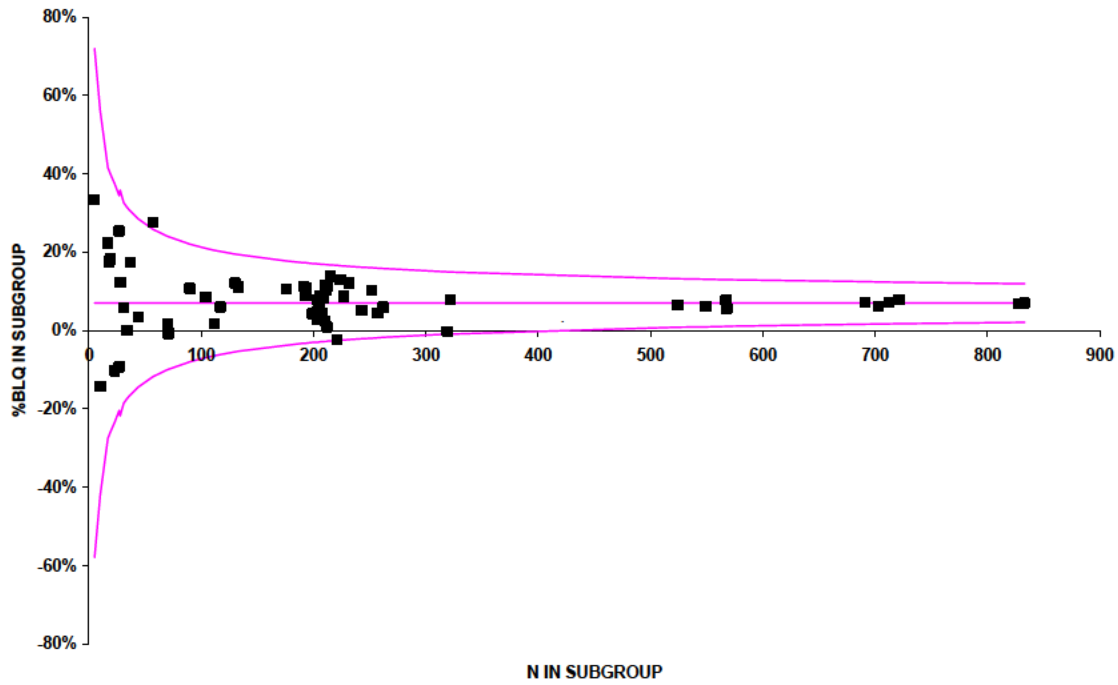




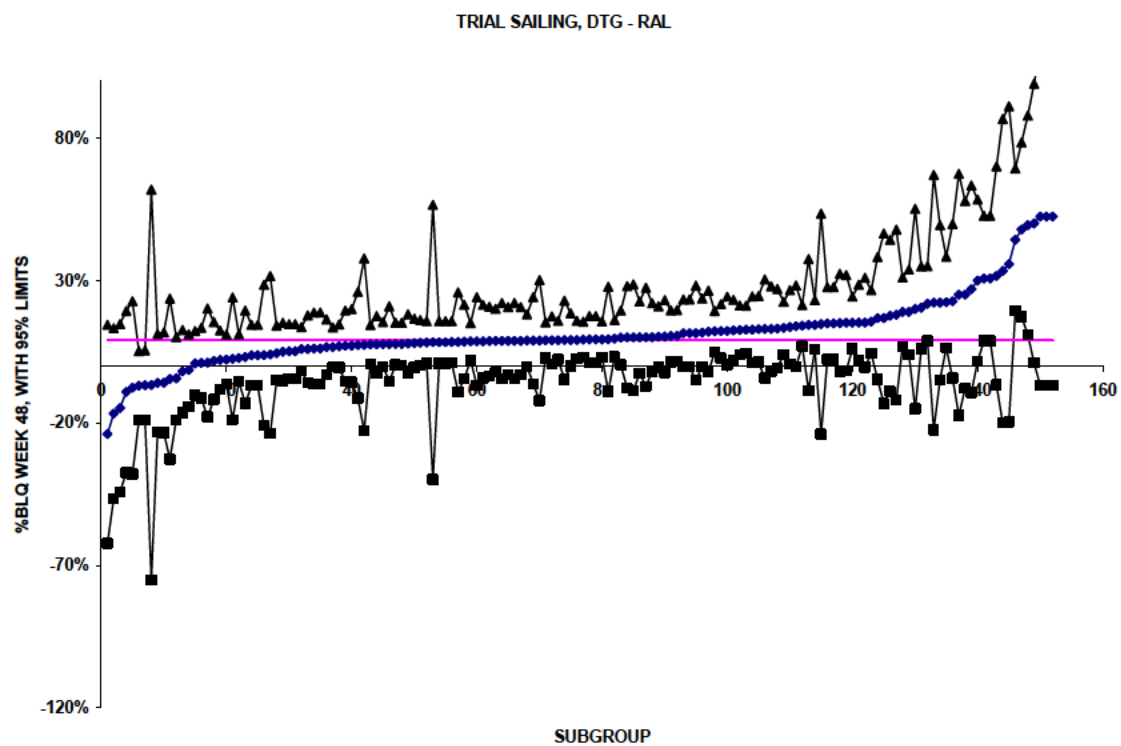
# TRIAL SINGLE, DTG - EFV



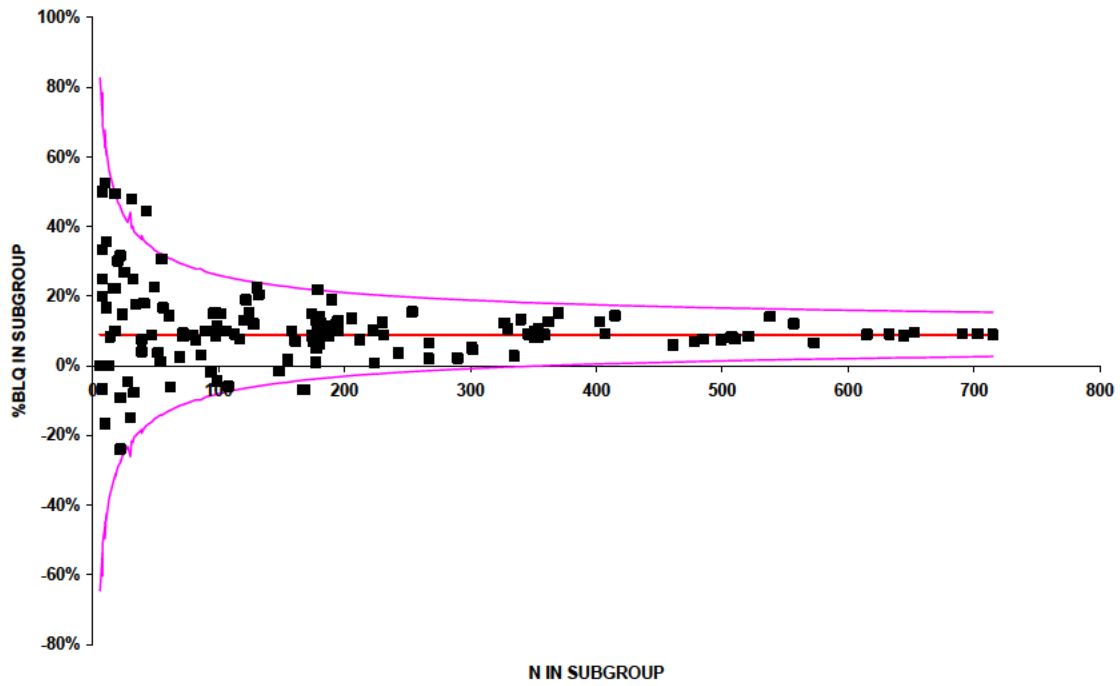
# SINGLE, WEEK 48



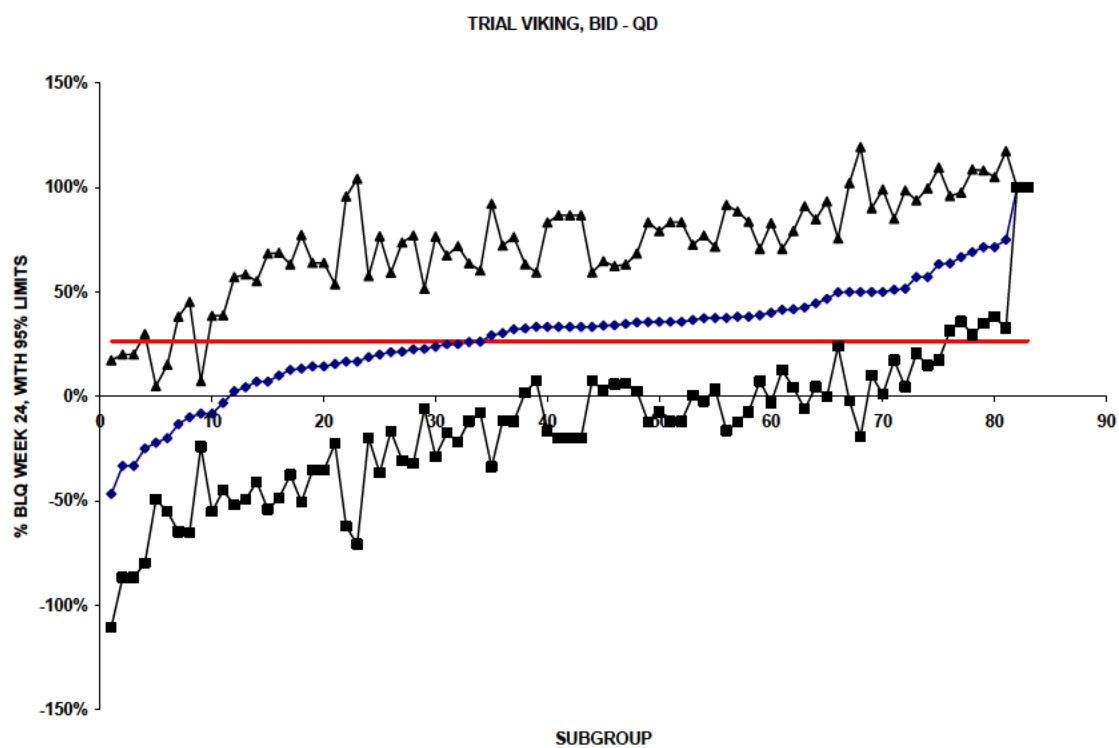
#### 4.4.2 Two Class Resistant INI Naïve Trial

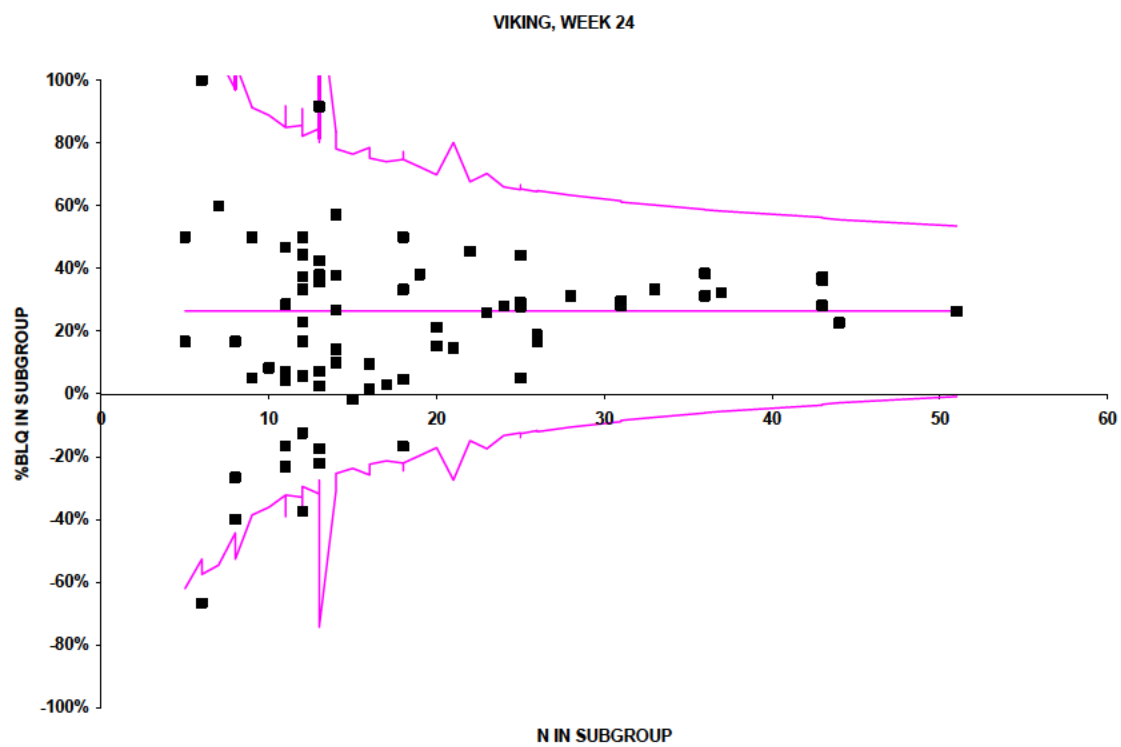


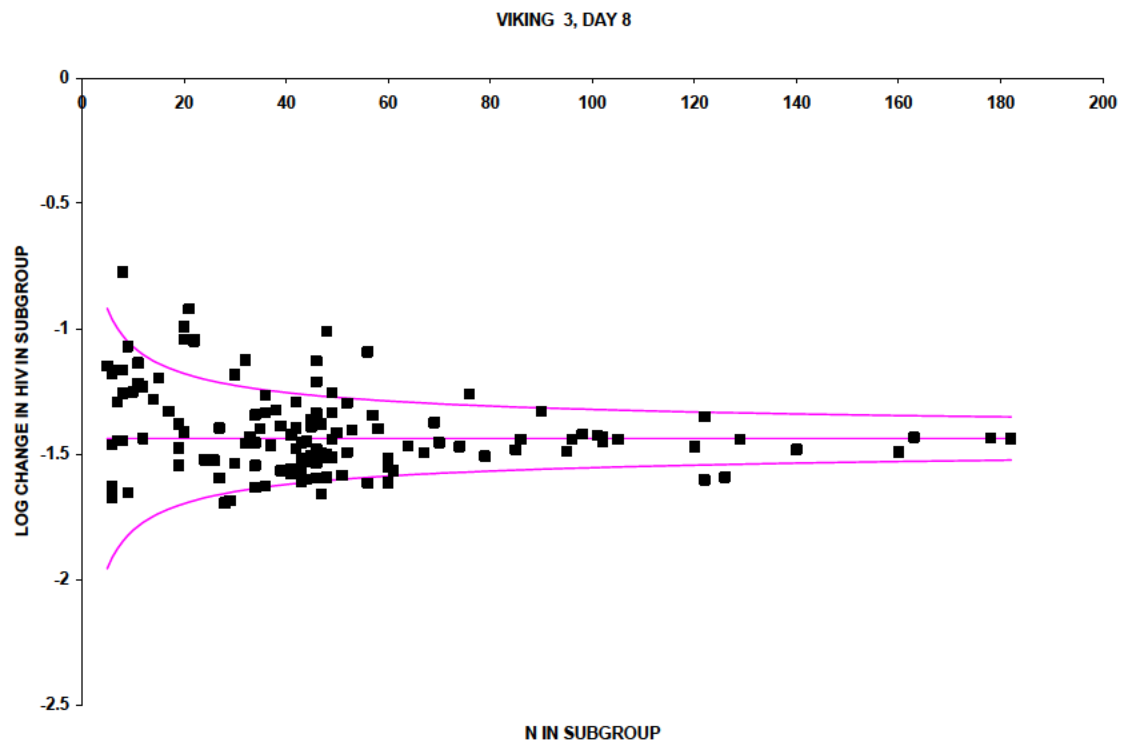
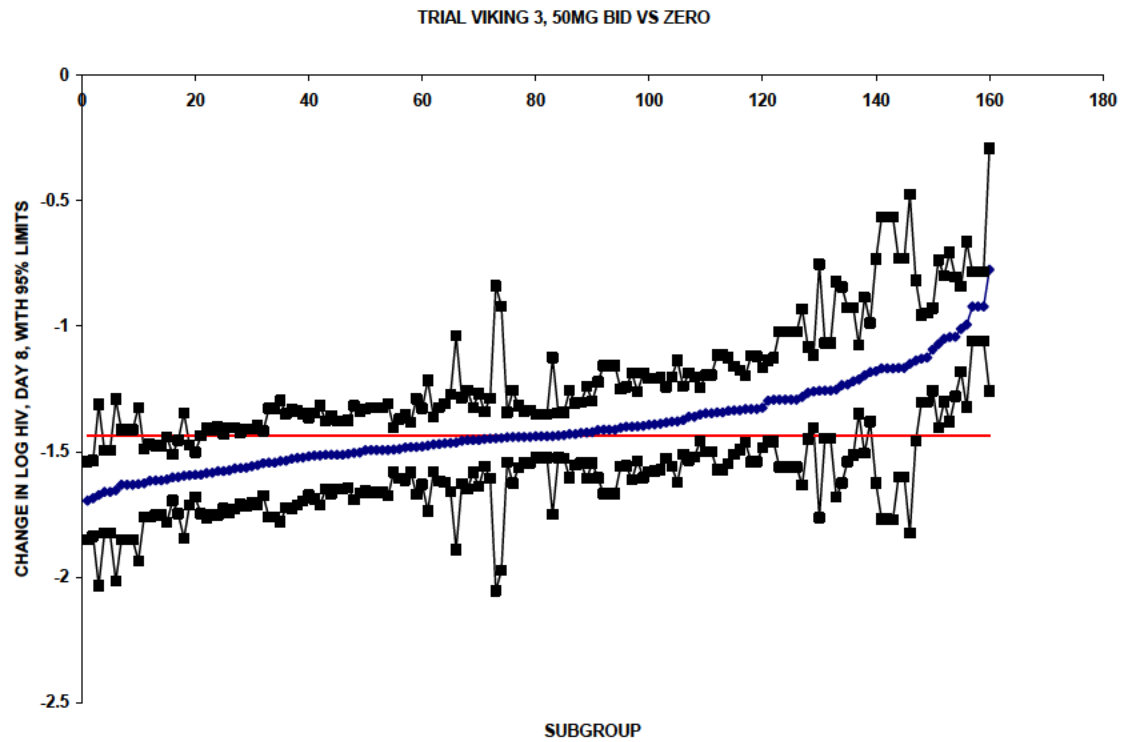
SAILING, WEEK 24

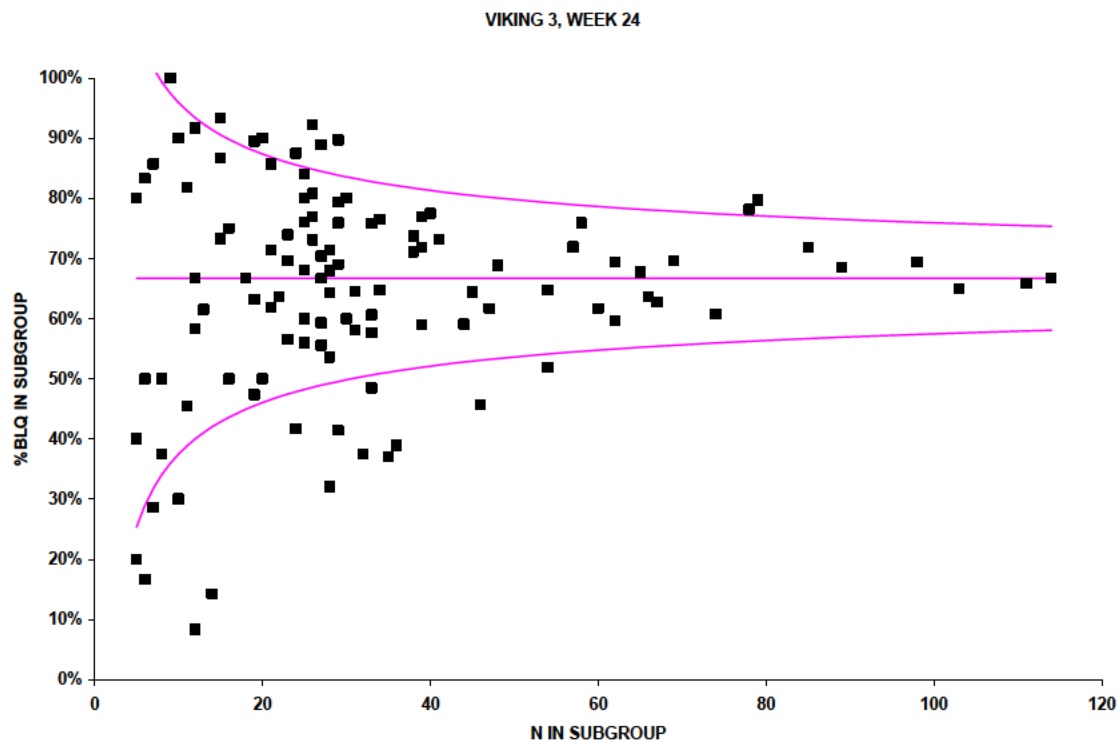
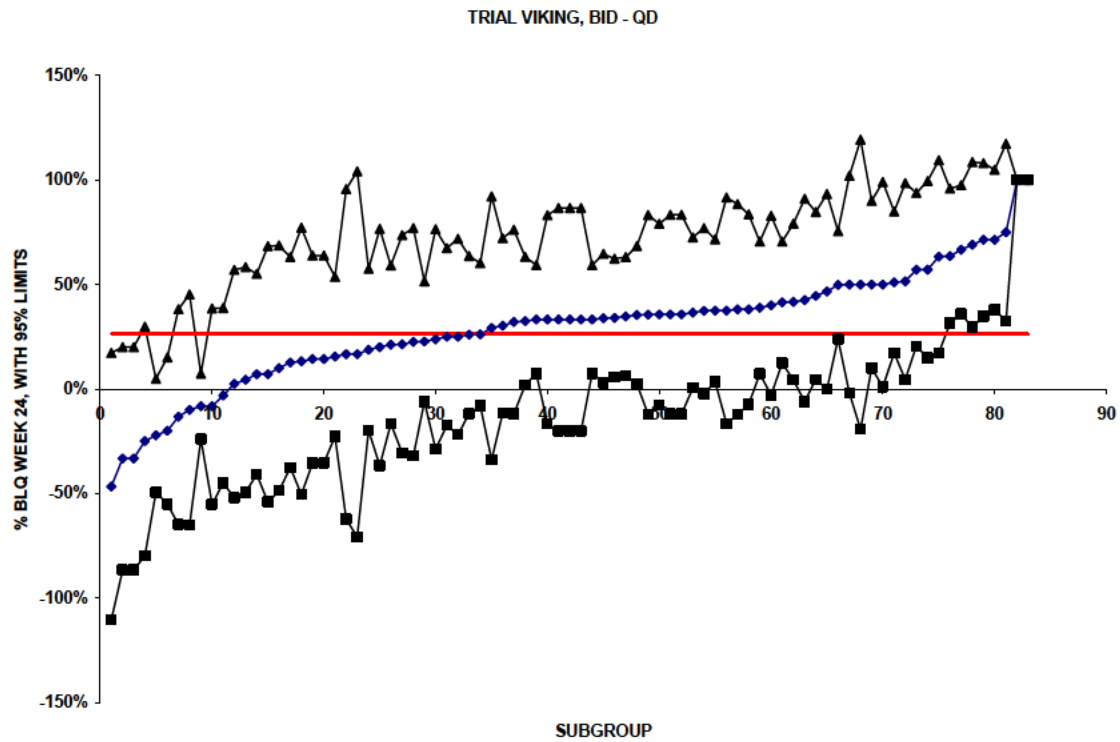


#### 4.4.3 Two Class Resistant, INI Resistant Trials









## 5. Summary and Conclusions:

The applicant has conducted seven trials to test the efficacy of dolutegravir (DTG) at 50mg QD or BID in HAART regimens among HIV-1 infected patients ranging from treatment naïve to integrase inhibitor resistant. In treatment naïve patients, the applicant conducted four trials: one short term dose ranging study, one long term dose ranging study, and two long term pivotal trials.

In the short term dose ranging study, trial 1521, DTG at 50mg QD achieved statistically significant superiority over placebo with respect to change in log HIV. In the long term dose ranging study, trial Spring 1, DTG at 50mg QD was slightly (but not statistically significantly) superior to efavirenz (EFV) with respect to both change in log HIV and percent BLQ.

In one of the two pivotal trials, trial Single, DTG at 50mg QD was statistically significantly superior to the EFV arm at 48 weeks with respect to both endpoints change in log HIV and percent BLQ.

In the second pivotal trial, trial Spring 2, DTG at 50mg QD was statistically non-inferior to raltegravir (RAL) at week 48.

The applicant conducted one pivotal trial in treatment experienced, two class resistant, integrase inhibitor (INI) naïve patients. In this trial DTG at 50mg QD was slightly, but not statistically significantly, superior to RAL arm with respect to both change in log HIV and percent BLQ. It was statistically non-inferior to RAL with respect to percent BLQ, the endpoint where there is an agreed margin of clinical non-inferiority and which was the protocol specified primary endpoint.

The applicant conducted two trials among INI resistant patients. The small dose ranging trial, the Viking trial, DTG at 50mg BID showed a clinically important and almost statistically significant superiority to DTG at 50mg QD. This comparison involved sequentially enrolled cohorts, not randomized cohorts. Nonetheless, the difference between the BID and QD doses did not diminish when the comparison was adjusted for baseline covariates.

The large trial in this population was a single arm trial because ethical constraints precluded any control arm. In this trial, DTG at



50mg BID both change in log HIV and percent BLQ were statistically significantly greater than zero. The 95% lower confidence bounds on both endpoints were comparable to what one expects from an effective three drug HAART regimen in any population.

The applicant has convincingly demonstrated the efficacy of dolutegravir at 50mg qd in treatment naïve and treatment experienced, INI naïve HIV-1 infected patients and the efficacy of dolutegravir at 50mg bid in INI resistant HIV-1 infected patients.

Thomas Hammerstrom, Ph.D.  
Mathematical Statistician

Concur: Dr. Soon

cc:

Archival NDA #21-481

HFD-530

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/s/  
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THOMAS S HAMMERSTROM  
05/08/2013

GUOXING SOON  
05/15/2013



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

### CARCINOGENICITY STUDIES

**NDA:** 204790 (IND 75382)

**Drug Name:** Dolutegravir (b) (4)

**Indications:** Treatment of HIV-1 infection in combination with other retroviral products

**Applicants:** Sponsor: VIIV Healthcare Company  
c/o Glaxo Smith Kline  
Research Triangle Park, North Carolina

**CRO:** (b) (4)

**Date:** Submitted: 10 December 2012

**Review Priority:** Standard

**Biometrics Division:** Division 6

**Statistical Reviewer:** Steve Thomson

**Concurring Reviewers:** Karl Lin, Ph.D.

**Medical Division:** Antiviral Products

**Toxicologist Team:** Mark Seaton, Ph.D.  
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**Project Manager:** Katherine Schumann, MS

**Keywords:** Carcinogenicity, Cox regression, Kaplan-Meier product limit, Survival analysis, Trend test

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## 1. EXECUTIVE SUMMARY

Reports and data from two studies, in rats and mice, were provided. Both studies were conducted (b) (4). The compound is described as S-349572 sodium with vehicle described as “Aqueous 0.5 w/w% hydroxypropyl methylcellulose (HPMC) solution with 0.1 w/w% Tween 80 (0.5% HPMC/0.1% Tween 80) [polysorbate]/solution” (page 12 of rat report). The Sponsor states that: “The purpose of this study was to assess the carcinogenicity potential and toxicokinetics of S-349572 sodium when administered orally, via gavage, to rats for up to 24-months.” (page 20 of rat report). The statement of purpose is identical in the mice report except that it applies to mice, not rats.

### 1.1. Conclusions and Recommendations

Again, the Sponsor reports that the drug vehicle is “Aqueous 0.5 w/w% hydroxypropyl methylcellulose (HPMC) solution with 0.1 w/w% Tween 80 (0.5% HPMC/0.1% Tween 80) [polysorbate]/solution” (page 12 of rat report), in sterile water. For each study, in each gender, there are three actual treatment groups. Animals were dosed once daily by oral gavage. Gross aspects of the study designs for the main study animals are summarized in Tables 1 and 2 below:

**Table 1. Design of Rat Study** (dose volume 5 mL/kg)

Treatment Group	# Main study animals (# TK <sup>a</sup> animals)/gender	Dose (mg/kg/day)	Dosing Concentration (mL/kg)
1. Water <sup>b</sup>	65 (4)	0	0
2. Vehicle	65 (4)	0	0
3. Low	65 (12)	2	0.2
4. Medium	65 (12)	10	1
5. High	65 (12)	50	5

<sup>a</sup> Toxicokinetic phase animals began dosing during Week 1 of the carcinogenicity phase and terminated during Week 52

<sup>b</sup> Sterile water alone.

**Table 2. Design of Mouse Study** (dose volume 5 mL/kg)

Treatment Group	# Main study animals (# TK <sup>a</sup> animals)/gender	Dose (mg/kg/day)	Dosing Concentration (mL/kg)
1. Water <sup>b</sup>	65 (20)	0	0
2. Vehicle	65 (20)	0	0
3. Low	65 (45)	7.5	0.75
4. Medium	65 (45)	25	2.5
5. High	65 (45)	500	50

<sup>a</sup> Toxicokinetic phase animals began dosing during Week 1 of the carcinogenicity phase and terminated during Week 52

<sup>b</sup> Sterile water.

More detailed descriptions of the studies are provided in Section 3.2.1 and 3.2.2 below. In this report both the water only group and the vehicle group are each sometimes referred to as “controls” or a “control group”, with the vehicle as the “primary control”. Groups 3-5 are sometimes referred to as “actual dose groups.” For purposes of assessing trend, the Vehicle, Low, Medium, and High dose groups (i.e., Groups 2-5) as sometimes described as “treated groups.” Simple summary life tables in mortality are presented in the study specific sections of this report.

In Appendix 1, Figures A.1.1 and A.1.2, for rats, display Kaplan-Meier estimated survival curves for each study group for each gender, as do Figures A.1.3 and A.1.4 for mice. Results of tests on survival in rats and mice are summarized in Tables 3 and 4, respectively, below:

**Table 3. Statistical Significances of Tests of Homogeneity and Trend in Survival in the Rat Study**

Hypothesis Tested	Males		Females	
	Log rank	Wilcoxon	Log rank	Wilcoxon
Homogeneity over groups 1-5	0.5260	0.4717	0.2222	0.2543
Homogeneity over groups 2-5	0.4290	0.3610	0.1269	0.1408
No Trend over dose groups 2-5	0.1285	0.0943	0.1419	0.0865
No difference between groups 1 & 5	0.1478	0.1551	0.4183	0.4111
No difference between groups 2 & 5	0.1635	0.0953	0.0427	0.0390
No difference between groups 1 & 2	0.9786	0.7620	0.2142	0.2183

From the Kaplan-Meier plots in Figures A.1.1 and A.1.2 in Appendix 1, it seems that in both genders the high dose group tends to have the highest mortality and the vehicle group generally the lowest mortality with the other treated groups and the water only group generally intertwined between these boundaries. The difference between the high dose and vehicle dose survival curves was strong enough to result in statistically significant test of differences between the vehicle and high dose in females (Logrank  $p = 0.0427$ , Wilcoxon  $p = 0.0390$ ), but not quite in males (Logrank  $p = 0.1635$ , Wilcoxon  $p = 0.0953$ ). The test of trend over treated groups 2-5 was somewhat close to statistical significance (Male: Wilcoxon  $p = 0.0943$ , Female: Wilcoxon  $p = 0.0865$ ), possibly suggestive of early, but small differences in trend in survival. No other test achieved even a 0.10 level of statistical significance, let alone the usual 0.05 level (all remaining  $p \geq 0.1269$ ).

**Table 4. Statistical Significances of Tests of Homogeneity and Trend in Survival in the Mouse Study**

Hypothesis Tested	Males		Females	
	Log rank	Wilcoxon	Log rank	Wilcoxon
Homogeneity over groups 1-5	0.2818	0.2243	0.3814	0.1883
Homogeneity over groups 2-5	0.1772	0.1423	0.2779	0.1223
No Trend over dose groups 2-5	0.3183	0.3469	0.0733	0.0321
No difference between groups 1 & 5	0.4638	0.4233	0.4407	0.1911
No difference between groups 2 & 5	0.8313	0.9633	0.0577	0.0209
No difference between groups 1 & 2	0.5953	0.3892	0.1855	0.1854

Figures A.1.3 and A.1.4 display the gender specific survival curves over the five study groups in mice. From Figure A.1.3 in male mice there seems to be a slight tendency for the low dose group to have the lowest mortality and the vehicle group to have the highest mortality, but no particular evidence of a dose related trend. This is consistent with the results of the tests above. None of the tests comparing the various survival curves in males are statistically significant (all 12  $p \geq 0.1423$ ). From Figure A.1.4, as with rats, in female mice the high dose group tends to have the highest mortality and the vehicle group generally the lowest mortality with the other dose groups generally intertwined between these boundaries. The difference between the high dose and the vehicle control survival curves was strong enough to result in a statistically significant Wilcoxon test of differences between the vehicle and high dose in females (Logrank  $p = 0.0577$ , Wilcoxon  $p = 0.0209$ ), and a test of trend over groups 2-5 (Logrank  $p = 0.0733$ , Wilcoxon  $p = 0.0321$ ). No other test was statistically significant in females (all 8 remaining  $p \geq 0.1223$ ).

An alternative Bayesian analysis of survival using an accelerate failure time (AFT) model is presented in Appendix 2. Its results are generally similar to those above, but with the proviso that one has estimates of actual probabilities that parameters have an effect of interest.

Of course in a carcinogenicity study, primary interest is on the occurrence of cancers. The statistical analysis of tumors compares tumor incidence over dose groups. The poly-k test, as used here with  $k=3$ , modifies the original Cochran-Armitage test to adjust for differences in mortality (please see section 1.3.1.4 for details). Complete tumor incidence tables for each organ tumor combination listed by the Sponsor in the submitted data sets and those combined by this reviewer are provided in Tables A.3.5 through A.3.8 in Appendix 3.

To adjust for the multiplicity of tests the so-called Haseman-Lin-Rahman (HLR) rules discussed in Section 1.3.1.5 are often applied. That is, when testing for trend over dose groups and the difference between the highest dose group with the appropriate reference, to control the overall Type I error rate to roughly 10% for a standard two species, two sex study, one compares the unadjusted significance level of the trend test to 0.005 for common tumors and 0.025 for rare tumors, and the pairwise test to 0.01 for common tumors and 0.05 for rare tumors. Using these adjustments for other tests, like testing the comparisons between the low and medium dose groups versus the vehicle or testing against the water group can be expected to increase the overall type I error rate to some value above the nominal rough 10% level, possibly considerably higher than the overall nominal 10% rate.

Table 5, below, shows those tumors that had at least one mortality adjusted statistical test significant at the usual nominal 0.05 level and were then classified as significant following the HLR rules to adjust for multiplicity. No tests of trend or pairwise comparisons in male rats or mice achieved this level of statistical significance. Tables 18 (page 19) and 24 (pages 25-26), below, in the study specific sections show those organ-tumor combinations that had a non-multiplicity adjusted statistical significance of 0.10 or less. These tables are also repeated in Tables A.3.1-A.3.4 in Appendix 3.

. Note that when one adjusts for multiplicity these nominally significant comparisons may not be statistically significant. Tables A.3.5-A.3.8 in this appendix display all incidences and statistical test results for both genders in mice and rats.

In these tables, for each species by gender by organ combination, the number of animals supposedly microscopically analyzed is presented first. The entry for each tumor is preceded by the adjusted number of animals at risk for that endpoint. It seems clear that an animal that dies early without having displaying that endpoint reduces the size of the risk set for getting that particular endpoint. The poly-k test down weights such animals, and as discussed in Section 1.3.1.3, below, the sum of these poly-k weights seems to be a better estimate of the number of animals at risk of getting that tumor. This sum is given in the row labeled “Adjusted # at risk”. Tumor incidence is presented next, with the significance levels of the tests of trend, and the results of pairwise tests between the high and medium dose groups versus vehicle. The next row continues with the p-values of the pairwise test between the low and vehicle dose groups and the p-values between the vehicle dose group and high dose group with water, respectively. For these analyses, incidence in the water only group is used to assess background tumor incidence, and thus whether a tumor is considered to be rare (background incidence <1%) or common. Note that for this analysis a tumor is only classified as rare if the H2O group shows none of that particular tumor.

**Table 5. Statistically Significant Neoplasms in Female Mice and Rats**

Organ/ Tumor	Overall Results					Significance		
	H2O	Veh	Low	Med	High	p trend	p high vs Veh	p med vs Veh/
						p low vs Veh	p veh vs H2O	p high vs H2O
<b>Female Rats</b>								
<b>LUNGS</b>								
<b>MAMMARY AREAS</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	49.2	48.2	44.4	49.5	44.7			
ADENOCARCINOMA	19	11	14	22	17	.1470	.0791	.0188
						.2345	.9724	.5893
Adjusted # at risk	49.2	48.2	45.1	49.5	45.0			
Adenoma/Adenocarcinoma	19	11	17	24	19	.1329	.0382	.0066
						.0908	.9724	.4482
<b>PITUITARY</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	60.1	63.2	63.9	62.0	61.7			
Pars Dist. Adenoma/Carc.	59	52	61	58	56	.3370	.1014	.0515
						.0081	.9998	.9856
<b>Female Mice</b>								
<b>LUNGS</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	43.5	46.6	43.8	44.3	38.1			
BRONCHIOLO/ALVEOLAR ADENOMA	8	0	4	8	5	.1456	.0163	.0023
						.0505	1	.8336
<b>UTERUS W/ CERVIX</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.7	46.6	44.5	44.1	37.6			
Leiomyoma/Liomyosarcoma	2	0	2	7	2	.4390	.1957	.0051
						.2362	1	.6428



Again, no tumors in male rats or mice achieved the Haseman-Lin-Rahman (HLR) bounds so as to be described as statistically significant at the multiplicity adjusted approximate 0.10 (10%) level. Using the incidence in the H2O group to determine whether the tumor would be classified as rare or common, all of the tumors above would be classified as common. Adjusting for multiplicity and accepting the increase in type I error resulting from including pairwise comparisons other than that between the high dose and primary control, the pairwise test between the medium dose group and vehicle in pooled adenoma/adenocarcinoma in the lungs of female rats would be considered as statistically significant ( $p = 0.0066 < 0.01$ ). The test between the low dose and vehicle in terms of pituitary pars distalis adenoma/carcinoma would also be classified as statistically significant ( $p = 0.0081 < 0.01$ ). No other test in rats achieved the multiplicity adjusted levels of statistical significance. Similarly, the pairwise tests in female mice between the medium dose and vehicle in terms of bronchiole/alveolar adenoma of the lung and pooled leiomyoma and leiomyosarcoma of the uterus with cervix would be classified as more or less statistically significant ( $p = 0.0023 < 0.01$  and  $p = 0.0051 < 0.01$ , respectively).

## 1.2. Brief Overview of the Studies

This submission had a rat study:

**Study 09-2178: Carcinogenicity Study (gavage) of S-349572 sodium in Rats for 104 weeks,**

and the obviously very similar, mouse study:

**Study 09-2177: Carcinogenicity Study (gavage) of S-349572 sodium in Mice for 104 weeks,**

Both studies were conducted (b) (4)  
Fairly detailed descriptions of these studies are available in Sections 3.2.1 and 3.2.2, below.

## 1.3. Statistical Issues and Findings

### 1.3.1. Statistical Issues

In this section, several issues, typical of statistical analyses of these studies, are considered. These issues include details on the survival analyses, tests on tumorigenicity, multiplicity of tests on neoplasms, and the validity of the designs.

#### 1.3.1.1. Control Groups:

Note that the determination of whether or not a tumor is classified as rare or common has a considerable impact upon results. A good case can be made to use historical control data for this determination. But it would seem to this reviewer that to make this determination in this group of animals, under this treatment regimen, the gavage with water only group is the most appropriate, and is used here. For testing the effect of S-349572 sodium at and beyond that of the vehicle, the treated groups 2-5 would seem to be the most appropriate dose groups.

**1.3.1.2. Survival Analysis:**

The survival analyses presented here are based on both the log rank test and the Wilcoxon test comparing survival curves. The log rank tests tend to put higher weight on later events, while the Wilcoxon test tends to weight events more equally, and thus is more sensitive to earlier differences in survival. The logrank test is most powerful when the survival curves track each other, and thus the hazards, i.e., the conditional probability of the event in the next infinitesimal interval, would be roughly proportional. This is the test used by the Sponsor in both studies and seems to be the test usually recommended by statisticians. In the FDA analysis, both tests were used to test both homogeneity of survival among the treatment groups and the effect of dose on trend in survival. Appendix 1 reviews the specific animal survival analyses in more detail. The results of the Sponsor's analysis are summarized in Sections 3.2.1.1 and 3.2.2.1.

**1.3.1.3. Multiplicity of Tests on Survival:**

Using both the logrank and Wilcoxon tests, for each gender in rats and mice, there are 12 tests of survival differences. Assuming tests were performed at the usual 0.05 level, and the tests were stochastically independent, but there were actually absolutely no differences in survival across groups (so one would hope no tests would be statistically significant), the probability of at least one statistically significant result in each species by gender was about 0.46. These bounds assume the tests are independent, which they clearly are not, but these values can give some idea of the possible price paid for the multiplicity of hypothesis tests in the statistical frequentist paradigm.

**1.3.1.4. Tests on Neoplasms:**

The data sets requested for the analysis of rodent carcinogenicity studies are supposed to include a record for each animal organ combination that was not evaluated. It is possible that for several organs in this study, this may have not been completely done. If a number of the animals are not examined, but the proportions of animals showing the tumor under study in each treatment group is roughly the same as in the subset of animals actually reported the calculated p-values will generally be too large, i.e., results will be less statistically significant than they should be, possibly much less. If we can assume the process that determines whether or not a tumor is analyzed in each specific tumor is random, it is perhaps appropriate to consider such endpoints to be both analyzed AND have the tumor.

Ignoring these possible problems, the Sponsor's analyses of tumorigenicity are Peto tests (Peto *et al*, 1980) for trend for those tumors with an incidence of at least two in the three treated groups. These require accurate determination of whether a tumor is fatal or incidental.

The FDA analysis is based on a modification of the Cochran-Armitage test of trend in mortality (please see Bailer & Portier, 1988, Bieler & Williams, 1993). Inspecting a large number of studies, Bailer and Portier noted that survival time seemed to fit a Weibull distribution, generally with a shape parameter of between 1 and 5, with 3 a typical value. With  $t_{\max}$  denoting the maximal time to terminal sacrifice and  $t_{\text{obs}}$  the time to death of the animal, they

proposed weighting the animal by  $(t_{\text{obs}}/t_{\text{max}})^k$ , so that an animal that survives for say 52 weeks in 104 week study without the tumor being analyzed is counted as  $(1/2)^k$  of an animal. For  $k = 3$ , that means that particular animal would count as 1/8 of an animal in the analysis of that tumor. Further, the  $k = 3$  specification seems to represent tumor incidence where some animals are perhaps more sensitive and respond earlier to the insult than the remaining animals. Under this structure time to incidence would tend to follow a cubic expression. Thus an animal with the specific tumor being studied or who survives to terminal sacrifice without the tumor will be given a weight of 1 when counting the number of animals at risk. However, animals that die early without the tumor are down weighted when counting the number of animals in the risk set for that specific tumor. With differential mortality, this can mean a substantial reduction in the size of that risk set. Note this seems to be an appropriate adjustment for dose groups that are terminated early as in the rats study. The report of the Society of Toxicological Pathology “town hall” meeting in June 2001 recommended the use of this poly-k modification of the so-called Cochran-Armitage tests of trend over the corresponding Peto tests used by the Sponsor.

The computed significance levels are based on small sample exact permutation tests of tumor incidence. In the tumor incidence tables the effective size of the risk set for each tumor is listed in the row labeled “Adjusted # at risk”, and seems to be a more appropriate denominator when comparing incidence rates than the simple unadjusted number evaluated.

#### **1.3.1.5. Multiplicity of Tests on Neoplasms:**

Frequentist hypothesis testing involves accepting or rejecting hypotheses about the parameters of interest on the basis of the values of some statistic. If one does not provide some sort of multiplicity adjustment to the significance level, the chances of rejecting one or more true null hypothesis increases as the number of such tests increases. To avoid this, it is common to adjust for multiplicity in hypothesis testing resulting in an adjustment in experiment-wise Type I error (i.e., the probability of rejecting a true null hypothesis and thus concluding there is an effect when in fact there is none). Based on his extensive experience with such carcinogenicity analyses in standard laboratory rodents, for pairwise tests between the highest dose group and controls in two species, Haseman (1983) claimed that for a roughly 0.10 (10%) overall false positive error rate, rare tumors should be tested at a 0.05 (5%) level, and common tumors (with a historical control incidence greater than 1%) at a 0.01 level. Similarly, simulations by Lin and Rahman (1998) indicated that tests of trend over all dose groups should be tested at about a 0.025 level for rare tumors and 0.005 for common tumors. This approach is intended to balance both Type I error and Type II error (i.e., the error of concluding there is no evidence of a relation to tumorigenicity when there actually is such a relation). Because of the possibility of genetic drift, or differences in treatment, in this study the vehicle group is used to determine if the tumor is classified as rare or common. These Haseman-Lin-Rahman rules are denoted by “HLR” at several points in this review.

Note that significance levels of the pairwise tests between the Vehicle group and the Water and Low and Medium dose groups, plus a comparison of the Water and High dose group, are also provided. Even following the HLR rules, adding these comparisons can be expected to

increase the overall type I error rate to some level above the usual rough 10% level, possibly considerably larger.

#### 1.3.1.6. Validity of the Designs:

When determining the validity of designs there are two key points:

- 1) adequate drug exposure,
- 2) tumor challenge to the tested animals.

1) is related to whether or not sufficient animals survived long enough to be at risk of forming late-developing tumors and 2) is related to the Maximum Tolerated Dose (MTD), designed to achieve the greatest likelihood of tumorigenicity.

Lin and Ali (2006), quoting work by Haseman, have suggested that in standard laboratory rodent species, a survival rate of about 25 animals, out of 50 or more animals (i.e. 50%), between weeks 80-90 of a two-year study may be considered a sufficient number of survivors as well as one measure of adequate exposure. As a percentage of the High dose group animals that survived to week 91, this criterion does seem to be exceeded slightly in male rats (High dose 47.7% < 50%) and more decisively in female rats (High dose 27.7%). Moreover, this criterion was exceeded in all dose groups in female rats (i.e., for all groups survival < 50%). The survival proportions were satisfied in male mice in all treatment groups (e.g., High dose 64.6%), while the criterion is exceeded in the High dose in females (43.1%), and, interestingly, only slightly in the water only group (47.7%). Please see Tables 15 and 16 on page 17 and Tables 21 and 22 on page 23 and 24, respectively. Like the other comments in this section this requires the expertise of the toxicologist, but it is possible that this suggests that the MTD may have been exceeded in female rats, and possibly in male rats.

The mean weight values used to derive differences and ratios in the following tables were taken directly from the Sponsor's reports (in both studies Table 3, Summary of Body Weight Values, pages 360-367 in rats, and pages 315-318 in mice). The change from baseline in the table below is the simple difference between the means at the specified dates, and thus animals that die early are only counted at the study initiation, not at the end of the study.

**Table 6. Mean Weights and Changes (in g) in Male Rats**

Dose Group	Dose mg/kg/day	Week		Change from Baseline	% change relative to vehicle
		1	104		
1. Water	0	228.8	819.8	565.5	93.5
2. Vehicle	0	229.1	856.3	604.8	
3. Low	2	230.0	803.0	554.2	91.6
4. Medium	10	231.7	824.2	568.1	93.9
5. High	50	230.8	831.7	571.6	85.6

**Table 7. Mean Weights and Changes (in g) in Female Rats**

Dose Group	Dose mg/kg/day	Week		Change from Baseline	% change relative to vehicle
		1	96		
1. Water	0	163.9	573.4	396.3	85.7
2. Vehicle	0	162.7	640.8	462.6	
3. Low	2	161.5	576.4	403.7	87.3
4. Medium	10	162.7	576.7	400.6	86.6
5. High	50	163.1	702.6	519.7	112.3

**Table 8. Mean Weights and Changes (in g) in Male Mice**

Dose Group	Dose mg/kg/day	Week		Change from Baseline	% change relative to vehicle
		1	104		
1. Water	0	30.0	44.7	14.5	96.7
2. Vehicle	0	29.6	44.2	15.0	
3. Low	2.5	29.6	44.9	15.2	101.3
4. Medium	25	29.7	45.0	15.7	104.7
5. High	500	29.9	42.1	12.0	80.0

**Table 9. Mean Weights and Changes (in g) in Female Mice**

Dose Group	Dose mg/kg/day	Week		Change from Baseline	% change relative to vehicle
		1	104		
1. Water	0	23.6	40.9	17.0	137.1
2. Vehicle	0	23.1	35.8	12.4	
3. Low	2.5	23.2	37.4	14.4	116.1
4. Medium	25	23.4	38.8	15.3	123.4
5. High	500	23.2	35.5	12.5	100.8

Chu, Ceuto, and Ward (1981), citing earlier work by Sontag *et al* (1976) recommend that the MTD “is taken as ‘the highest dose that causes no more than a 10% weight decrement as compared to the appropriate control groups, and does not produce mortality, clinical signs of toxicity, or pathologic lesions (other than those that may be related to a neoplastic response) that would be predicted to shorten the animal’s natural life span’ ” From Tables 6-9 above, the weight decrement criterion is clearly exceeded in the high dose in both male rats and mice. Again, although this requires the expertise of the toxicologist, this may be evidence that the MTD was exceeded in males of both species.

For both rats and mice the Sponsor states that “[t]here were no test article-related effects on food consumption. “Statistically significant differences that were observed were considered within the range of normal variability.” (page 50 of rat report, 48 of mouse report) This may be further evidence that the MTD was not exceeded in the high dose group in both genders in mice.

Again from 2) above, excess mortality not associated with any tumor or sacrifice in the higher dose groups might suggest that the MTD was exceeded. This suggests that a useful way to assess whether or not the MTD was achieved is to measure early mortality not associated with any identified tumor. If this is high in the higher dose groups it suggests that animals tend to die before having time to develop tumors. Tables 11 and 12, below, display the number of animals in each dose group that died of a natural death or moribund sacrifice, but did not show any tumors (i.e., the “Event”):

**Table 10. Natural Death with No Identified Tumor in Rats (Male/Female)**

	1. Water	2. Vehicle	3. Low	4. Medium	5. High
Males Event	6	14	10	13	12
No event	59	51	55	52	53
Females Event	1	0	1	2	3
No event	63	65	64	63	62

It is apparent that there is no evidence of heterogeneity in dying without tumor in female rats. This is confirmed in using a Fisher exact test of a lack of homogeneity ( $p = .6563$ ). Although differences in males seem to be more apparent, but these differences are not statistically significant (chi square  $p = .3574$ , Fisher exact  $p = 0.3401$ ). So neither gender seems to show dose related treatment differences in excess mortality unrelated to tumorigenicity.

**Table 11. Natural Death with No Identified Tumor in Mice (Male/Female)**

	1. Water	2. Vehicle	3. Low	4. Medium	5. High
Males Event	10	15	19	15	16
No event	55	50	46	50	49
Females Event	10	13	10	13	14
No event	55	52	55	52	51

Results in mice are similar. There is no strong evidence of such excess mortality in either gender (Males: chi-square  $p = 0.8388$ , Fisher exact  $p = .8460$ , Females: chi-square  $p = 0.4569$ , Fisher exact  $p = .4527$ ).

Thus, there is no evidence of excess mortality unrelated to tumorigenicity in either gender in either rodent species. Like the other observations above, this requires the expertise of the toxicologist, but these tests may provide evidence that the MTD was not exceeded in either gender in either rats or mice.

Combining these perhaps somewhat inconsistent observations into a valid assessment of whether or not the MTD was exceeded requires the expertise of the toxicologist.

### 1.3.2. Statistical Findings

Please see Section 1.1 above.

## 2. INTRODUCTION

### 2.1. Overview

This submission summarizes the results of two year rat and mouse studies to assess the carcinogenic potential of the test article, S-349572 sodium with vehicle described as “Aqueous 0.5 w/w% hydroxypropyl methylcellulose (HPMC) solution with 0.1 w/w% Tween 80 (0.5% HPMC/0.1% Tween 80) [polysorbate]/solution” (page 12 of rat report) Both studies were conducted (b) (4)

### 2.2. Data Sources

The Sponsor provided two SAS transport files: “tumor rat.xpt” and “tumor mice.xpt”, each containing a SAS file labeled tumor. sas7bdat. Note these data sets contained sufficient survival and tumorigenicity data to conduct the primary analyses in this report. Certain tumors and organs were combined for analysis, following the document written by Drs. Parola and Jacobs (2010).

## 3. STATISTICAL EVALUATION

### 3.1. Evaluation of Efficacy

NA

### 3.2. Evaluation of Safety

#### 3.2.1. Study 09-2178: Carcinogenicity Study (gavage) of S-349572 sodium in Rats for 104 weeks.

STUDY DURATION: 104 Weeks

STARTING DOSING DATE: March 19, 2011.

FINAL DOSING DATES: Males	Group 5:	5 March 2012	Week 102
	Groups 1-4:	18 March 2012	Week 104
Females	Group 5:	24 November 2011	Week 88
	Group 4:	3 January 2012	Week 94
	Group 3:	7 December 2011	Week 90
	Groups 1&2:	10 January 2012	Week 95
TERMINAL SACRIFICE DATES: Males;		13-19 March 2012.	Week 104
	Females	6, 9-11 January 2012	Week 95
STUDY ENDING DATE (Final Report dated): 13 November 2012.			
RAT STRAIN: Sprague-Dawley CD® Rats.			
ROUTE: Daily Oral Gavage			

The study is further summarized in Table 12. below ( a repeat of Table 1):

**Table 12. Design of Rat Study** (dose volume 5 mL/kg)

Treatment Group	# Main study animals (# TK animals)/gender	Dose (mg/kg/day)	Dosing Concentration (mL/kg)
1. Water <sup>b</sup>	65 (4)	0	0
2. Vehicle	65 (4)	0	0
3. Low	65 (12)	2	0.2
4. Medium	65 (12)	10	1
5. High	65 (12)	50	5

<sup>a</sup> Toxicokinetic phase animals began dosing during Week 1 of the carcinogenicity phase and terminated during Week 52

<sup>b</sup> Sterile water.

The Sponsor's report summarizes study conduct as follows: "Sprague-Dawley CD® rats (65/sex/group) were orally gavaged once daily with 0 (water) or 0 (0.5% HPMC/0.1% Tween 80), 2, 10, or 50 mg/kg/day S-349572 for up to 24 consecutive months. The dose volume was 10 mL/kg/day for all dose groups. Surviving males were euthanized and necropsied during Weeks 104 and 105, at the end of the 24 month dosing period. Dosing was discontinued for Groups 3 (2 mg/kg/day) and 5 (50 mg/kg/day) females in Weeks 90 and 88, respectively, due to declining survivorship ( $\leq 20$  animals/group) and these animals were held until terminal sacrifice for all females during Week 95 when the control (water) survival reached 20 animals. Satellite animals (4/sex/Groups 1 and 2; 12/sex/Groups 3 to 5) were similarly dosed and bled at the end of Weeks 4 and 28 for toxicokinetic analysis.." (page 11 of rat report)

The Sponsor reports that animals were dosed daily, and were after initiation of dosing were housed individually with food and water was available *ad libitum* throughout the study. Animals were assigned to doses, based on a randomization procedure stratifying on group mean weight.

Study dose levels were justified as follows: "Dosages of S-349572 sodium at 50, 150 and 500 mg/kg/day in rats (S-349572-TB-012-L) by oral gavage were well tolerated for up to fourteen days with no adverse effects reported and no significant clinical pathology or histopathological changes observed. Hemorrhage in the stomach was also observed at 1000 mg/kg/day in a 1-month study in rats (S-349572-TB-043-L) at dosages of 2, 10, 100 and 1000 mg/kg/day S-349572 sodium. In a 6-month study in rats with a 4-month interim analysis (S-349572-TF-068-L:SBL055-082:SNBL) at dosages of 5, 50 and 500 mg/kg/day S-349572 sodium, hemorrhage in the stomach was seen microscopically at 500 mg/kg/day. In the 6-month study in rats, the difference in exposure levels between the 500 mg/kg/day dose group and the 50 mg/kg/day dose group was as little as 2 fold. Based on dosing period of 104 weeks for this study, a high-dosage of 50 mg/kg/day was chosen as the maximally tolerated dose and lower dosages of 10 and 2 mg/kg/day were chosen to evaluate a potential dose-response relationship." (page 22 of rat report)



**3.2.1.1. Sponsor's Results and Conclusions**

This section will present a summary of the Sponsor's analysis on survivability and tumorigenicity in rats.

**Survival analysis:**

From the Sponsor: "The percentage of animals surviving at termination is shown in the following table:"

**Table 13. (Sponsor Text Table 8.3-1): Percentage of animals surviving at terminal sacrifice.<sup>a</sup>**

<b>Dose (mg/kg/day)</b>	0	0	2	10	50
<b>Treatment</b>	<b>Water</b>	<b>Vehicle</b>	<b>S-349572</b>	<b>S-349572</b>	<b>S-349572</b>
<b>Males</b>	38.5	33.8	33.8	38.5	26.2
<b>Females</b>	30.8	41.5	23.1	30.8	26.2

<sup>a</sup>Initial on-test number of animals = 65/sex/group; terminal sacrifice commenced Week 104 for males; females were euthanized Week 95.

"Mortality was slightly higher in females dosed at 2 and 50 mg/kg/day but was not dose-related and considered unrelated to test article administration.

"Reduced survival in females resulted in cessation of dosing on Weeks 88 at 50 mg/kg/day, Week 90 at 2 mg/kg/day and Week 94 at 10 mg/kg/day. All surviving females in Groups 1 through 5 were euthanized on Week 95 of the study. All males were euthanized beginning Week 104.

"Among the animals whose cause of death was determined, there were no major differences between the different groups. Overall, the most common causes of death were pituitary tumor (males and females) and mammary gland tumors (females)." (page 49 of rat report)

These comments were expanded upon as follows: "There was no test article-related mortality. Mortality was minimally increased in some dose groups given the test article when compared to control groups. However, this increase was independent of dose, inconsistent between sexes, and considered unrelated to the test article. The most common causes of death in males were pituitary gland neoplasms. The most common causes of death in females were pituitary gland or mammary gland neoplasms. Similar to overall mortality, pituitary gland neoplasms as the probable cause of death were slightly increased in some male dose groups given the test article. However, this increase was independent of dose, inconsistent between sexes, and considered unrelated to the test article." (page 51 of rat report)

**Table 14. (Sponsor Text Table 8.9.1-1): Major Causes of Death in Rats Administered Control Article or S-349572**

	Male					Female				
<b>S-349572 (mg/kg)</b>	0	0	2	10	50	0	0	2	10	50
<b>No. unscheduled decedents</b>	40	43	43	40	48	45	38	50	45	48
<b>Pituitary Gland Neoplasms</b>	11	11	16	14	17	30	33	37	30	39
<b>Mammary Gland Neoplasms</b>	0	0	0	0	0	5	3	7	7	3

**Tumorigenicity analysis:**

The Sponsor's report describes a Peto analyses of tumorigenicity where the logrank results on fatal, and mortality independent tumors were pooled with a life table analysis of incidental tumors. "For incidental tumours, the following fixed time intervals were used to adjust for differential mortality between the treatment groups: 1-52, 53-78, 79-92, 93-103 weeks and terminal sacrifice for males and 1-52, 53-78, 79-94 weeks and terminal sacrifice for females." (page 6 of statistical report on tumorigenicity, page 3688 of overall rat report)

The Sponsor summarizes carcinogenicity (i.e., neoplastic) results as follows: "There was no test article-related increase in the incidence of neoplasms in S-349572-treated animals. Neoplasms occurred at similar incidences in control and test article treated groups or they occurred sporadically with no dose relationship. There were no neoplasms that showed a statistically significant increase by Peto analysis." (page 51 of rat report) The Sponsor's Statistical Analysis of Tumors provides more details, but basically concludes that in both genders, "None of the comparisons were statistically significant." (page 7 of statistical report, page 3689 of rat report)

**3.2.1.2. FDA Reviewer's Results**

This section will present the Agency findings on survival and tumorigenicity in male and female rats.

**Survival analysis:**

The following tables (Table 15 for male rats, Table 16 for females) summarize the mortality results for the study groups. The data were grouped for the specified time period, and present the number of deaths during the time interval over the number at risk at the beginning of the interval. The percentage cited is the percent that survived at the end of the interval. In these tables the terminal period only includes those animals were sacrificed. Rats that died of other causes during the terminal period are included in the preceding, overlapping time period. The Kaplan-Meier survival plots in Appendix 1 provide a more detailed picture of the profile of mortality losses.

**Table 15. Summary of Male Rats Survival (dose label/dose<sup>1</sup>/weeks dosing)**

Period (Weeks)	Water 0/1-105	Vehicle 0/ 1-105	Low 2/ 1-105	Medium 10/1- 105	High 50/1-105
1-52	3/65 <sup>2</sup> 95.4% <sup>3</sup>	4/65 93.8%	2/65 96.9%	4/65 93.8%	2/65 96.9%
53-78	8/62 83.1%	7/61 83.1%	9/63 83.1%	10/61 78.5%	17/63 70.8%
79-91	18/54 55.4%	13/54 63.1%	18/54 55.4%	12/51 60.0%	15/46 47.7%
92-104	11/36 38.5%	19/41 33.8%	14/36 33.8%	14/39 38.5%	14/31 26.2%
Terminal <sup>4</sup> 105	25	22	22	25	17

<sup>1</sup> dose in mg/kg/day<sup>2</sup> number of deaths / number at risk<sup>3</sup> overall per cent survival to end of period.<sup>4</sup> number of animals that survived to terminal sacrifice weeks**Table 16. Summary of Female Rats Survival (dose label/dose<sup>1</sup>/weeks dosing)**

Period (Weeks)	Water 0/ 1-103	Vehicle 0/ 1-103	Low 2/ 1- 103	Medium 10/ 1- 103	High 50/1- 103
1-52	3/65 <sup>2</sup> 95.4% <sup>3</sup>	2/65 96.9%	5/65 92.3%	3/65 95.4%	7/65 89.2%
53-78	26/62 55.4%	24/63 60.0%	25/60 53.8%	19/62 66.2%	25/58 50.8%
79-91	9/36 41.5%	11/39 43.1%	17/35 27.2%	22/43 32.2%	15/33 27.7%
92-102	7/27 30.8%	1/28 41.5%	3/18 23.1%	1/21 30.8%	1/18 26.2%
Terminal <sup>4</sup> 102,103	20	27	15	20	17

<sup>1</sup> dose in mg/kg/day<sup>2</sup> number of deaths / number at risk<sup>3</sup> overall per cent survival to end of period.<sup>4</sup> number of animals that survived to terminal sacrifice

Table 17 below provides the significance levels of the tests of homogeneity and trend over dose groups as proposed in Section 1.3.1.1 above (and is a repeat of Table 3 above and Table A.1.1 in Appendix 1).

**Table 17. Statistical Significances of Tests of Homogeneity and Trend in Survival in the Rat Study**

Hypothesis Tested	Males		Females	
	Log rank	Wilcoxon	Log rank	Wilcoxon
Homogeneity over groups 1-5	0.5260	0.4717	0.2222	0.2543
Homogeneity over groups 2-5	0.4290	0.3610	0.1269	0.1408
No Trend over dose groups 2-5	0.1285	0.0943	0.1419	0.0865
No difference between groups 1 & 5	0.1478	0.1551	0.4183	0.4111
No difference between groups 2 & 5	0.1635	0.0953	0.0427	0.0390
No difference between groups 1 & 2	0.9786	0.7620	0.2142	0.2183

From the Kaplan-Meier plots in Figures A.1.1 and A.1.2 in Appendix 1, it seems that in both genders the high dose group tends to have the highest mortality and the vehicle group generally the lowest mortality with the other dose groups generally intertwined between these boundaries. The difference between the high dose and vehicle dose survival curves was sufficient to result in statistically significant test of differences between the vehicle and high dose in females (Logrank  $p = 0.0427$ , Wilcoxon  $p = 0.0390$ ), but not quite in males (Logrank  $p = 0.1635$ , Wilcoxon  $p = 0.0953$ ). The test of trend over treated groups 2-5 was somewhat close to statistical significance (Male: Wilcoxon  $p = 0.0943$ , Female: Wilcoxon  $p = 0.0865$ ), possibly suggestive of early, but small differences in trend in survival. No other test achieved even a 0.10 level of statistical significance, let alone the usual 0.05 level (all remaining  $p \geq 0.1269$ ).

#### **Tumorigenicity analysis:**

As discussed in Section 1.3.1.5, the Haseman-Lin-Rahman rules for adjusting for multiplicity in a single species study specify that for a very rough 0.10 (10%) overall false positive error rate, both overall trend and the comparison between control and the high dose should be tested at a 0.05 (5%) level in rare tumors (background incidence 1% or less) and at 0.01 (1%) level in common tumors. In this analysis we use the incidence in the sterile water vehicle control group to specify whether a tumor is treated as common or rare. Note that the period ‘.’ in the table denotes the p-values of tests of dose groups with none of the particular tumors the specified groups.

Table 18 below in rats show the tumors that had at least one mortality adjusted test whose nominal statistical significance was at least no more than 0.010. Note that when one adjusts for multiplicity these nominally significant comparisons most of these comparisons would not be statistically significant. Tables A.3.3-A.3.4 in Appendix 3 display all incidences and statistical test results for both genders in mice and rats.

**Table 18. Potentially Statistically Significant Neoplasms in Rats**

Organ/ Tumor	Overall Results					Significance				
	H2O	Veh	Low	Med	High	p trend	p high	p med		
						vs Veh				
						p low	p veh	p high		
vs Veh						vs H2O	vs H2O			
MALE RATS										
PANCREAS										
# Evaluated	65	65	65	65	65					
Adjusted # at risk	46.5	48.6	46.2	46.3	43.1					
ISLET CELL CARCINOMA	2	3	1	3	5	.0700	.2967	.6408		
						.9362	.5204	.1900		
PITUITARY										
# Evaluated	65	65	65	65	65					
Adjusted # at risk	52.0	54.5	55.6	52.9	52.7					
PARS DISTALIS-ADENOMA	28	22	29	25	29	.1321	.0878	.2863		
						.1441	.9505	.5436		
Adjusted # at risk	52.7	54.5	55.6	52.9	53.3					
Pars Dist. Adenoma/Carc.	29	22	29	25	30	.1099	.0736	.2863		
						.1441	.9595	.5439		
THYROID										
# Evaluated	65	65	65	65	65					
Adjusted # at risk	47.0	48.0	46.3	46.0	42.9					
FOLLICULAR CELL ADENOMA	2	0	4	1	2	.3751	.2199	.4946		
						.0559	1	.6480		
Adjusted # at risk	47.8	48.0	46.8	46.0	42.9					
Foll.cell Adenoma/Carc.	4	0	5	1	2	.4825	.2199	.4946		
						.0264	1	.8707		
FEMALE RATS										
LUNGS										
MAMMARY AREAS										
# Evaluated	65	65	65	65	65					
Adjusted # at risk	49.2	48.2	44.4	49.5	44.7					
ADENOCARCINOMA	19	11	14	22	17	.1470	.0791	.0188		
						.2345	.9724	.5893		
Adjusted # at risk	49.2	48.2	45.1	49.5	45.0					
Adenoma/Adenocarcinoma	19	11	17	24	19	.1329	.0382	.0066		
						.0908	.9724	.4482		
PITUITARY										
# Evaluated	65	65	65	65	65					
Adjusted # at risk	59.6	63.0	63.6	61.2	61.5					
PARS DISTALIS-ADENOMA	58	51	59	55	55	.3332	.1566	.1566		
						.0449	.9998	.9927		
Adjusted # at risk	60.1	63.2	63.9	62.0	61.7					
Pars Dist. Adenoma/Carc.	59	52	61	58	56	.3370	.1014	.0515		
						.0081	.9998	.9856		

Although all the organ tumor combinations in male rats listed above had at least one test that was statistically significant at a 0.10 level, after adjusting for multiplicity using the HLR rules, none were statistically significant. For example, using the incidence in the H2O group to determine whether the tumor would be classified as rare or common, the significance test between the low dose and vehicle in pooled follicular cell adenoma/carcinoma of the thyroid would not be statistically significant ( $p = 0.0264 > 0.01$ ). Note that if we used the vehicle group to determine the classification of whether or not the tumor is rare, it would be classified as statistically significant ( $p = 0.0264 < 0.05$ ). In either case, no other organ tumor combination in male rats achieved either multiplicity adjusted significance level. Using either the vehicle group

or the water group, all of the tumors in male rats above would be classified as common. In female rats, adjusting for multiplicity, and accepting the increase in type I error for including pairwise comparisons other than that between the high dose and primary control, the pairwise test between the medium dose group and vehicle in pooled adenoma/adenocarcinoma would be considered as statistically significant ( $p = 0.0066 < 0.01$ ). The test between the low dose and vehicle would also be classified as statistically significant ( $p = 0.0081 < 0.01$ ). However, again, no other test in female rats achieved the multiplicity adjusted levels of statistical significance.

Complete tumor incidence tables, including the adjusted number at risk, are provided in tables A.3.5 and A.3.6 of Appendix 2.

### **3.2.2. Study 09-2177: Carcinogenicity Study (gavage) of S-349572 sodium in Mice for 104 weeks**

STUDY DURATION: 104 Weeks

STARTING DOSING DATE: March 24, 2010

FINAL DOSING DATE: Males Groups 1-5: 21, 22, & 25 March 2012. Week 104

Females Group 5: 24 February 2012. Week 101

Females Groups 1-4: 6, 8, 11 March 2012. Weeks 101-102

TERMINAL SACRIFICE DATES: Males Groups 1-5: 22, 23, & 26 March 2012. Week 104

Females Groups 1-5: 7, 9, 12 March 2012. Weeks 101-102

STUDY ENDING DATE (Final Report dated): 17 October 2012.

MOUSE STRAIN: Charles River CD-1 [CrI:CD-1(ICR)BR] Mice

ROUTE: Daily Oral Gavage

The Sponsor described study conduct as follows: “CD-1 mice (65/sex/group) were administered via oral gavage once daily with 0 (water), 0 (0.5% HPMC/0.1% Tween 80), 7.5, 25, or 500 mg/kg/day S-349572 sodium for up to 24 consecutive months. The dose volume was 10 mL/kg/day for all dose groups. All surviving males were euthanized and necropsied at the end of the 24 month dosing period (Week 105). Dosing was discontinued for the 500 mg/kg/day females at Week 101 due to declining survivorship ( $\leq 20$  animals/group) and these animals were held until terminal sacrifice of all surviving females during Weeks 102 and 103 when the water control group survival reached 20 animals. Toxicokinetic animals (20/sex/Groups 1 and 2; 45/sex/Groups 3-5) were similarly dosed and bled during Weeks 4 (Day 26) and 26 (Day 182) for toxicokinetic analysis. Parameters evaluated during the study were: viability, clinical observations, body weights, food consumption, hematology (termination), macroscopic observations and microscopic pathology.” (page 11 of mice report) This is summarized in Table 19 below:

**Table 19. Design of Mouse Study** (dose volume 5 mL/kg)

Treatment Group	# Main study animals (# TK <sup>a</sup> animals)/gender	Dose (mg/kg/day)	Dosing Concentration (mL/kg)
1. Water <sup>b</sup>	65 (20)	0	0
2. Vehicle	65 (20)	0	0
3. Low	65 (45)	7.5	0.75
4. Medium	65 (45)	25	2.5
5. High	65 (45)	500	50

<sup>a</sup> Toxicokinetic phase animals began dosing during Week 1 of the carcinogenicity phase and terminated during Week 52

<sup>b</sup> Sterile water.

Animals were randomized to treatment balancing on mean weight. After randomization, animals were housed individually with food and water available *ad libitum*.

The Sponsor justified dosing as follows: “In the preliminary carcinogenicity study of S-349572 sodium in mice by oral gavage for 13 weeks (HLS Study No. 09 2119/Sponsor Study No. S-349572-TF-068-L), dosages up to 1500 mg/kg/day were not associated with any toxicologically significant findings. The exposure level (AUC) at 1500 mg/kg/day was approximately 25-fold and 18-fold above the anticipated human exposure for a 50 mg QD or BID dose, respectively. In this 104-week study, 500 mg/kg/day was chosen as the high dose based on saturation of absorption between 500 mg/kg/day and 1500 mg/kg/day, and concern for gastrointestinal intolerance (observed in rats and monkeys) which may manifest over time. Lower dosages of 25 and 7.5 mg/kg/day were chosen to evaluate a potential dose response-relationship.” (pages 21-22 of mice report)

### 3.2.1.1. Sponsor’s Results and Conclusions

This section will present a summary of the Sponsor’s analysis on survivability and tumorigenicity in mice.

#### Survival Analysis:

The Sponsor provided the results of logrank tests of trend for Groups 2-5, pairwise tests of Group 2 versus Groups 3-5, the pairwise test between the two control groups, and Groups 1 and 2. The Sponsor summarizes mortality results as follows:

#### “Males

The trend test was not statistically significant when all groups were included in the analysis (p=0.413). None of the pairwise comparisons were statistically significant.

#### “Females

The trend test was not statistically significant when all groups were included in the analysis (p=0.114). None of the pairwise comparisons were statistically significant.” (page 5 of mice statistical analysis of mortality, page 3790 of main report).

**Table 20. (Text Table 8.3-1): Percentage of animals surviving at terminal sacrifice.<sup>a</sup>**

<b>Dose (mg/kg/day)</b>	0	0	7.5	25	500
<b>Treatment</b>	<b>Water</b>	<b>Vehicle</b>	<b>S-349572</b>	<b>S-349572</b>	<b>S-349572</b>
<b>Males</b>	46.2	44.6	56.9	40.05	40.0
<b>Females</b>	30.8	41.5	35.4	35.4	29.2

<sup>a</sup>Initial on-test number of animals = 65/sex/group; terminal sacrifice commenced Week 105 for males and Weeks 102-103 for females.

The Sponsor reports that: “By both trend and pairwise comparison, there were no statistically significant differences in survival in males and females dosed at 7.5, 25 and 500 mg/kg/day in comparison with water or vehicle control group.

“Reduced survival (20) of females at 500 mg/kg/day resulted in cessation of dosing at Week 101. Reduce survival (20) of Group 1 females at water control resulted in earlier euthanization of all surviving females on Weeks 102-103 of the study. All surviving males were euthanized at the end of the study (Week 105). Among the animals whose cause of death was determined, there were no major differences between the different groups. Overall, the most common causes of death were lymphoreticular/hematopoietic neoplasm (males and females).” (page 47 of mice report)

#### **Tumorigenicity analysis:**

The Sponsor’s report describes a Peto analyses of tumorigenicity where the logrank results on fatal, and mortality independent tumors were pooled with a life table analysis of incidental tumors using the same categorization as in rats (page 6 of statistical report on tumorigenicity, page 3688 of overall rat report)

The Sponsor’s report indicated the following tests were conducted:

“1) a one-tailed test for a trend using nominal dose levels, for Groups 3, 4 and 5 with the vehicle control group (Group 2)

2) a one-tailed pairwise comparison test of each treatment group against the vehicle control group and of the vehicle control group against the water control group.”

The analyses were conducted using the SAS system.

The Sponsor summarizes tumor analysis results as follows: “

#### **“Males**

“None of the comparisons were statistically significant.

#### **“Females**

##### **“Lungs**

For benign bronchiolo/alveolar adenoma, the trend test was not statistically significant when groups 2 to 5 were included in the analysis (p=0.211). The pairwise comparison of Group 2 with Group 4 was statistically significant (p=0.006).



“Uterus w/cervix

For benign leiomyoma and malignant leiomyosarcoma combined, the trend test was not statistically significant when groups 2 to 5 were included in the analysis (p=0.521). The pairwise comparison between Groups 2 and 4 was statistically significant (p=0.010).” (page 7 of statistical report on tumorigenicity, page 3805 of overall rat report)

**3.2.1.2. FDA Reviewer's Results**

This section will present the Agency findings on survival and tumorigenicity in male and female rats.

**Survival analysis:**

The following tables (Table 21 for male mice, Table 22 for females) summarize the mortality results for the study groups. The data were grouped for the specified time period, and present the number of deaths during the time interval over the number at risk at the beginning of the interval. The percentage cited is the percent that survived at the end of the interval. In these tables the terminal period only includes those animals were sacrificed. Animals that died of other causes during the terminal period are included in the preceding, but overlapping time period. The Kaplan-Meier survival plots in Appendix 1 provide a more detailed picture of the profile of mortality losses.

**Table 21. Summary of Male Mice Survival by (dose<sup>1</sup>/weeks dosing)**

Period (Weeks)	Water 0/ 1-105	Vehicle 0/ 1-105	Low 2.5/1- 105	Medium 25/ 1- 105	High 500/1-104
1-52	4/65 <sup>2</sup> 93.8% <sup>3</sup>	8/65 87.7% <sup>3</sup>	3/65 95.4%	4/65 93.8%	5/65 92.3%
53-78	6/61 84.6%	9/57 73.8%	5/62 87.7%	9/61 80.0%	11/60 75.4%
79-91	11/55 67.7%	9/48 60.0%	7/57 76.9%	9/52 66.2%	7/49 64.6%
92-104	14/44 46.2%	10/39 44.6%	13/50 56.9%	17/43 40.0%	16/42 40.0%
Terminal <sup>4</sup> 104,105	30	29	37	26	26

<sup>1</sup> dose in mg/kg/day

<sup>2</sup> number of deaths / number at risk

<sup>3</sup> overall per cent survival to end of period.

<sup>4</sup> number of animals that survive ed to terminal sacrifice

**Table 22. Summary of Female Mice Survival (dose<sup>1</sup>/weeks dosing)**

Period (Weeks)	Water 0/ 1- 95	Vehicle 0/ 1- 95	Low 2.5/1- 95	Medium 25/1- 95	High 500/ 1- 95
1-52	6/65 <sup>2</sup> 90.8% <sup>3</sup>	6/65 90.8%	8/65 87.7%	3/65 95.4%	12/65 81.5%
53-78	11/59 73.8%	8/59 78.5%	10/57 72.3%	22/62 61.5%	14/53 60.0%
79-91	17/48 47.7%	11/51 61.5%	12/47 53.8%	7/40 50.8%	11/39 43.1%
92-95	11/31 30.8%	14/40 40.0%	12/35 35.4%	10/33 35.4%	9/28 29.2%
Terminal 95	20	26	23	23	19

<sup>1</sup> dose in mg/kg/day<sup>2</sup> number of deaths / number at risk<sup>3</sup> overall per cent survival to end of period.<sup>4</sup> number of animals that survived to terminal sacrifice

The following table, Table 23 (a repeat of Table 4 and Table A.1.2 in Appendix 1), summarizes the results from tests comparing survival profiles across study groups in the tumorigenicity data sets:

**Table 23. Statistical Significances of Tests of Homogeneity and Trend in Survival in the Mouse Study**

Hypothesis Tested	Males		Females	
	Log rank	Wilcoxon	Log rank	Wilcoxon
Homogeneity over groups 1-5	0.2818	0.2243	0.3814	0.1883
Homogeneity over groups 2-5	0.1772	0.1423	0.2779	0.1223
No Trend over dose groups 2-5	0.3183	0.3469	0.0733	0.0321
No difference between groups 1 & 5	0.4638	0.4233	0.4407	0.1911
No difference between groups 2 & 5	0.8313	0.9633	0.0577	0.0209
No difference between groups 1 & 2	0.5953	0.3892	0.1855	0.1854

Figures A.1.3 and A.1.4, in Appendix 1, display the gender specific survival curves over all five study groups in mice. From Figure A.1.3 in male mice there seems to be a slight tendency for the low dose group to have the lowest mortality and the vehicle group to have the highest mortality, but no particular evidence of a dose related trend. This is consistent with the results of tests. None of the tests comparing survival curves in males are statistically significant (all 12  $p \geq 0.1423$ ). From Figure A.1.4, as with rats, in female mice the high dose group tends to have the highest mortality and the vehicle group generally the lowest mortality with the other dose groups generally intertwined between these boundaries. The difference between the high dose and vehicle dose group survival curves was strong enough to result in statistically significant Wilcoxon test of differences between the vehicle and high dose in females (Logrank  $p = 0.0577$ , Wilcoxon  $p = 0.0209$ ), and a test of trend over groups 2-5 (Logrank  $p = 0.0733$ ,

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Wilcoxon  $p = 0.0321$ ). No other test was statistically significant in females (all 8 remaining  $p \geq 0.1223$ ).

### Tumorigenicity analysis:

The table below displays the organ-tumor combinations that are statistically significant using the Haseman-Lin-Rahman (HLR) rules for adjusting for multiplicity. A more complete table displaying those organ-tumor combinations that had at least one result statistically significant at the usual 0.05 level are given in Table A.3.2 in Appendix 2. Complete tables of all results are given in Tables A.3.5 and A.3.6 in that appendix.

**Table 24. Potentially Statistically Significant Neoplasms in Mice**

Organ/ Tumor	Overall Results					Significance		
	H2O	Veh	Low	Med	High	p trend	p high vs Veh	p med vs Veh/ p high vs H2O
<b>MALE MICE</b>								
<b>GALLBLADDER</b>								
# Evaluated	55	58	60	53	59			
Adjusted # at risk	43.4	41.3	50.9	40.8	43.6			
PAPILLOMA	0	0	0	0	2	.0600	.2590	.2471
<b>LUNGS</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	52.2	45.1	55.2	49.9	48.3			
BRONCHIOLO/ALVEOLAR CARCINOMA	10	3	8	9	11	.0436	.0269	.0810
						.1766	.9850	.4177
Adjusted # at risk	53.3	46.8	55.7	50.4	49.1			
Bronch. Alv. Adenoma/Carc.	21	10	20	12	16	.2696	.1681	.4927
						.0827	.9842	.8257
<b>FEMALE MICE</b>								
<b>HARDERIAN GL</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	43.4	49.1	44.9	43.2	39.2			
ADENOMA	4	10	5	7	9	.1799	.4812	.7810
						.9301	.1166	.0800
<b>LIVER</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.2	46.6	43.7	41.8	37.3			
Hepato. Adenoma/Carcinoma	0	0	0	0	2	.0480	.1957	.2162
						.	.	.
<b>LUNGS</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	43.5	46.6	43.8	44.3	38.1			
BRONCHIOLO/ALVEOLAR ADENOMA	8	0	4	8	5	.1456	.0163	.0023
						.0505	1	.8336
Adjusted # at risk	43.8	48.4	44.9	46.1	38.9			
Bronch. Alv. Adenoma/Carc.	9	4	9	12	7	.3837	.1434	.0210
						.0854	.9789	.7118
<b>LYMPHORETIC SYSTEM</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	54.3	53.0	46.2	46.6	46.1			
MALIGNANT LYMPHOMA	27	16	9	14	19	.0356	.1908	.6000
						.9343	.9869	.8579

**Table 24. (cont.) Potentially Statistically Significant Neoplasms in Mice**

Organ/ Tumor	Overall Results					Significance		
	H2O	Veh	Low	Med	High	p trend	p high vs Veh	p med vs Veh/ vs H2
FEMALE MICE (cont.)								
UTERUS W/ CERVIX								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.2	46.6	44.5	42.1	36.9			
LEIOMYOMA	1	0	2	4	1	.4748	.4390	.0480
						.2362	1	.7133
Adjusted # at risk	42.7	46.6	44.5	44.1	37.6			
Leiomyoma/Leiomyosarcoma	2	0	2	7	2	.4390	.1957	.0051
						.2362	1	.6428

In male mice none of the tests of the organ-tumor combinations above achieved the mortality adjusted significance levels determined by the HLR rles. Using the incidence in the water group to determine whether a tumor is common or rare, only the pairwise tests between the mediumn dose and vehicle in terms of bronchiole/alveolar adenoma of the lung and pooled leiomyoma and leiomyosarcoma of the uterus with cervix would be classified as statistically significant (  $p = 0.0023 < 0.01$  and  $p = 0.0051 < 0.01$ , respectively).

Tables A.3.7 and A.3.8 in Appendix 3 display tumor incidences and results of statistical test results for male and female mice, respectively.

#### 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

NA

#### 5. SUMMARY AND CONCLUSIONS

##### 5.1. Statistical Issues and Collective Evidence

Please see Section 1.3 above.

##### 5.2. Conclusions and Recommendation

Please see Section 1.1 above.

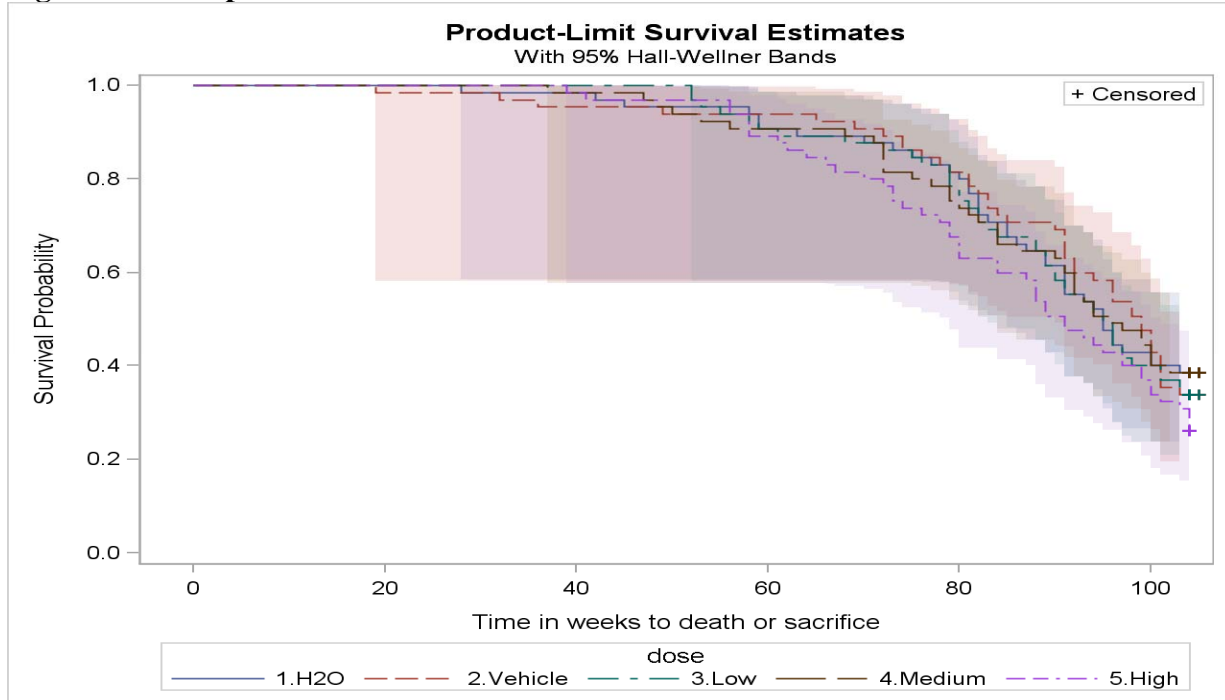
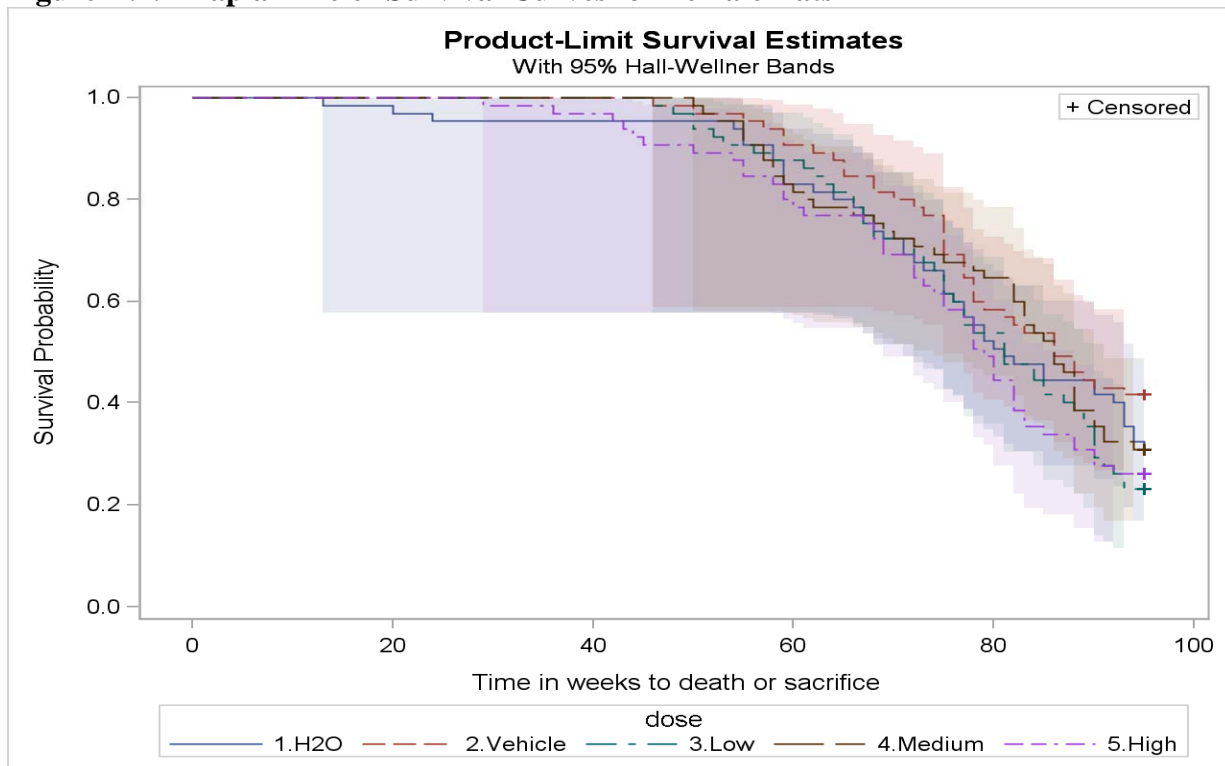
**APPENDICES****Appendix 1. FDA Survival Analysis**

Simple summary life tables in mortality are presented in the report (Tables 15, 16, 21, and 22 above). Kaplan-Meier estimated survival curves across study groups for each gender are displayed below in Figures A.1.1 and A.1.2 for rats and Figures A.1.3 and A.1.4 for mice. The plots include 95% confidence intervals around each survival curve (colored area around each curve). These plots are also supported by tests of homogeneity in survival over all the treatment groups, tests of homogeneity and trend over all groups 2-5, and the results of pairwise comparisons of the high dose to water and the vehicle, plus the comparison between vehicle and water. As discussed in Section 1.3.1.3 the appropriate test of trend is over groups 2-5. The statistical significance levels (i.e., p-values) are provided in Tables A.1.1. and A.1.2., below. One might note that the log rank tests places greater weight on later events, while the Wilcoxon test tends to weight them more equally, and thus places more weight on differences in earlier events than does the log rank test.

**Table A.1.1. Statistical Significances of Tests of Homogeneity and Trend in Survival in the Rat Study**

Hypothesis Tested	Males		Females	
	Log rank	Wilcoxon	Log rank	Wilcoxon
Homogeneity over groups 1-5	0.5260	0.4717	0.2222	0.2543
Homogeneity over groups 2-5	0.4290	0.3610	0.1269	0.1408
No Trend over dose groups 2-5	0.1285	0.0943	0.1419	0.0865
No difference between groups 1 & 5	0.1478	0.1551	0.4183	0.4111
No difference between groups 2 & 5	0.1635	0.0953	0.0427	0.0390
No difference between groups 1 & 2	0.9786	0.7620	0.2142	0.2183

From Figure A.1.1 and A.1.2, in both genders in rats the high dose groups tend to have the highest mortality and the vehicle groups generally the lowest mortality with the other dose groups generally intertwined between these boundaries. The difference between the high dose and vehicle dose survival curves was strong enough to result in statistically significant test of differences between the vehicle and high dose in females (Logrank  $p = 0.0427$ , Wilcoxon  $p = 0.0390$ ), but not quite in males (Logrank  $p = 0.1635$ , Wilcoxon  $p = 0.0953$ ). The test of trend over groups 2-5 was fairly close to statistical significance (Male: Wilcoxon  $p = 0.0943$ , Female: Wilcoxon  $p = 0.0865$ ), possibly suggestive of early, but small differences in trend in survival. Note that no other test was statistically significant in either males (all nine  $p \geq 0.1285$ ) or females (all nine  $p \geq 0.1269$ ).

**Figure A.1.1 Kaplan-Meier Survival Curves for Male Rats****Figure A.1.2 Kaplan-Meier Survival Curves for Female Rats**

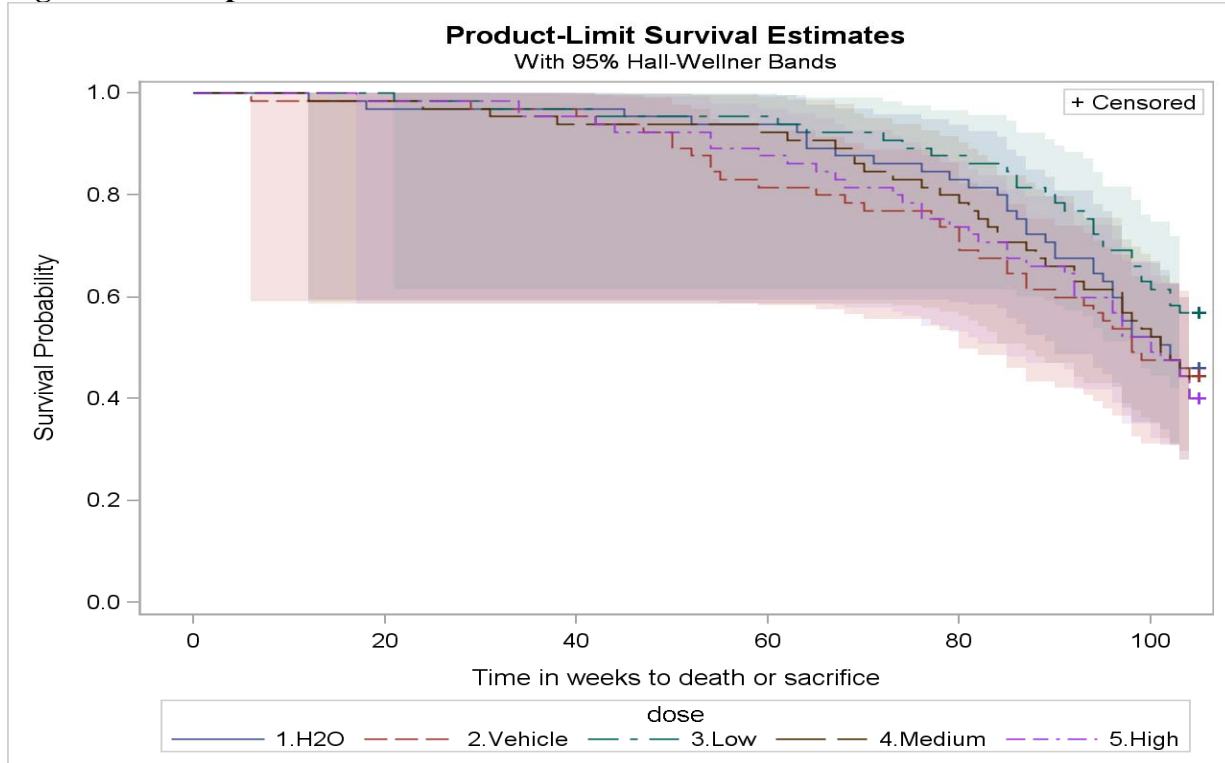
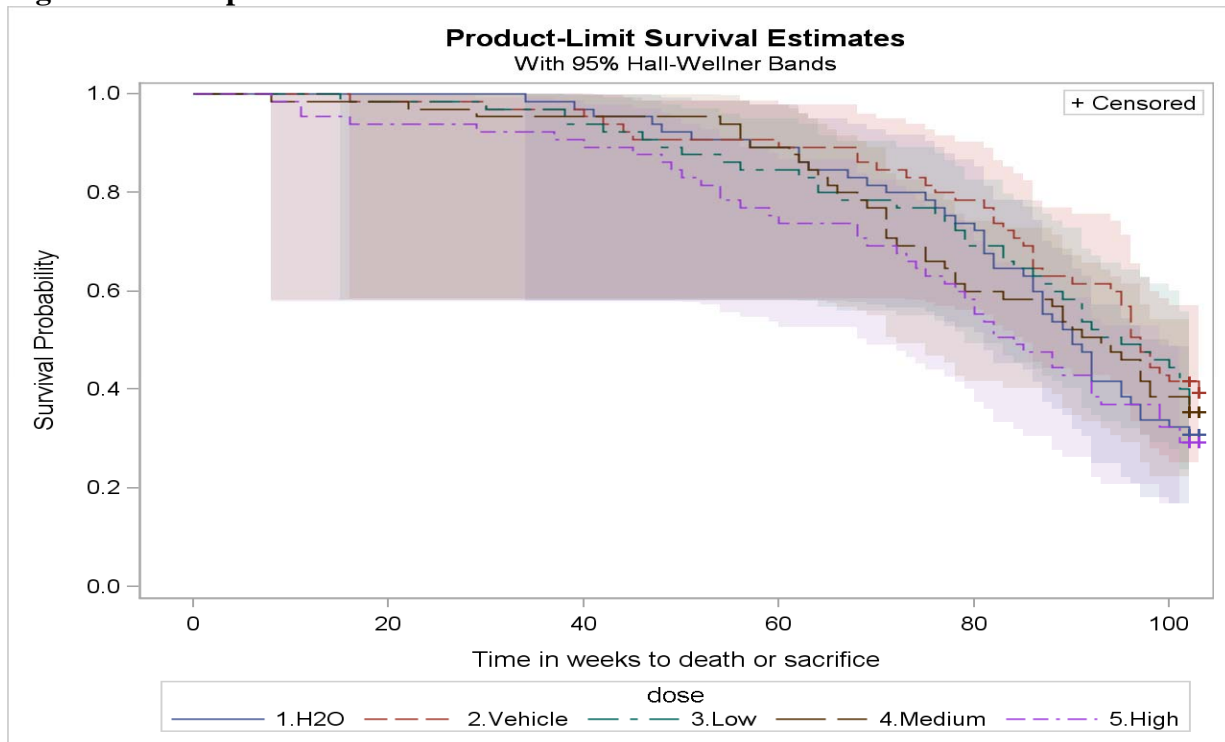
Results for statistical tests of differences in survival in mice are presented below:

**Table A.1.2. Statistical Significances of Tests of Homogeneity and Trend in Survival in the Mouse Study**

Hypothesis Tested	Males		Females	
	Log rank	Wilcoxon	Log rank	Wilcoxon
Homogeneity over groups 1-5	0.2818	0.2243	0.3814	0.1883
Homogeneity over groups 2-5	0.1772	0.1423	0.2779	0.1223
No Trend over dose groups 2-5	0.3183	0.3469	0.0733	0.0321
No difference between groups 1 & 5	0.4638	0.4233	0.4407	0.1911
No difference between groups 2 & 5	0.8313	0.9633	0.0577	0.0209
No difference between groups 1 & 2	0.5953	0.3892	0.1855	0.1854

Figures A.1.3 and A.1.4, below, display the gender specific survival curves over the five dose groups in mice. From Figure A.1.3 in male mice there seems to be a slight tendency for the low dose group to have the lowest mortality and the vehicle group to have the highest mortality, but no particular evidence of a dose related trend. This is consistent with the results of tests. None of the tests comparing survival curves in male mice are statistically significant (all 12  $p \geq 0.1423$ ).

From Figure A.1.4, as with rats, in female mice the high dose group tends to have the highest mortality and the vehicle group generally the lowest mortality with the other dose groups generally intertwined between these boundaries. The difference between the high dose and vehicle dose group survival curves was strong enough to result in statistically significant Wilcoxon test of differences between the vehicle and high dose in females (Logrank  $p = 0.0577$ , Wilcoxon  $p = 0.0209$ ), and a test of trend over groups 2-5 (Logrank  $p = 0.0733$ , Wilcoxon  $p = 0.0321$ ).

**Figure A.1.3 Kaplan-Meier Survival Curves for Male Mice****Figure A.1.4 Kaplan-Meier Survival Curves for Female Mice**



## Appendix 2. FDA Nonparametric Bayesian Survival Analysis

The probability of a subject surviving past time  $t$  is given by the survival function, i.e., for random survival time  $T$ ,  $S(t) = P(T > t)$ . Statistical inference on survival is based on proposing a probability model for  $S(t)$  or one of its derivations. The probability model is defined so that hypotheses to be investigated are specified as parameters in the model. A frequentist analysis takes parameters as fixed and assesses the likelihood of the observed data. A Bayesian analysis starts by noting that parameters are not known, and assumes that a so-called prior probability distribution is a natural measure of this lack of exact knowledge about the parameters. Then the Bayesian analysis assesses the impact of the actual observed data on this prior. In a nonparametric Bayesian analysis at least one of these parameters is the space of all probability distributions, or at least some large subset of this space. In other words, although some prior weight is placed on a particular parametric family of distributions, the results would be consistent for other distributions. The actual nonparametric analysis used here is based upon using a so-called Mixture of Dirichlet Processes (MDP) as the prior on the space of all probability distributions.

Specifically, let  $T_i$  denote a random variable representing the survival time of the  $i$ th animal. For time until natural death time  $t_i$  we write  $T_i = t_i$ , but if the animal is sacrificed at time  $a_i$ , all we know is that the time until natural death is greater than  $a_i$ , written as  $T_i \in (a_i, \infty)$ , i.e.  $T_i$  is in the time interval  $(a_i, \infty)$ . Note that animals whose death is in this interval are said to be censored. One useful probability model is to model the logarithm of  $T_i$  with a normal distribution, i.e., the  $T_i$  are modeled using a lognormal distribution. The mean of  $\log T_i$  can be expressed as a product of a linear effect  $X_i\beta$  times a usual lognormal term. Thus the linear effect accelerated (or decelerates) survival, justifying the Accelerated Failure Time (AFT) label for such a model. In this particular analysis we restrict attention to treated groups 2-5, assessing the effect of each of the three actual dose groups and the simple linear effect of dose over groups 3-5 where the baseline intercept is the vehicle effect. The distribution of  $\log(T_i)$  is expressed as a mixture of normal distributions weighted by a Dirichlet process on the baseline normal parameters. Mathematically, we can write:

$$T_i = \exp(-X_i\beta)V_i, i = 1, \dots, n$$

$$V_i | G \sim G$$

$$\beta | \beta_0, S_{\beta_0} \sim N(\beta_0, S_{\beta_0})$$

$$G | \alpha, G_0 \sim DP(\alpha G_0)$$

The distributions of the hyperparameters above are specified as follows:

$$G_0 \sim \text{Lognormal}(\cdot | \mu, \sigma)$$

$$\alpha | a_0, b_0 \sim \text{Gamma}(a_0, b_0)$$

$$\mu | m_0, s_0 \sim N(m_0, s_0)$$

$$\sigma^{-1} | \tau_1, \tau_2 \sim \text{Gamma}\left(\frac{\tau_1}{2}, \frac{\tau_2}{2}\right)$$

This analysis uses the DPsurvint function, for a Mixture of Dirichlet Processes in the DPpackage (Jara, 2007) of R (R Development Core Team, 2009). Currently, results should primarily be considered as supporting. The basic reference is de Iorio, et al (2009). The output for male rats follows:

**Table A.2.1 Output for Pairwise Differences From Vehicle in Male Rats**

Posterior Predictive Distributions (log):

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
-8.45600	-4.74600	-4.11900	-3.45800	-1.02500	-0.00348

Regression coefficients:

	Mean	Median	Std. Dev.	Naive Std.Err	95%HPD-Low	95%HPD-Upp
d2	1.133e-02	1.131e-02	6.965e-04	3.115e-06	9.992e-03	1.268e-02
d3	-1.119e-02	-1.116e-02	7.933e-04	3.548e-06	-1.276e-02	-9.748e-03
d4	5.222e-02	5.222e-02	9.020e-04	4.034e-06	5.055e-02	5.397e-02

Baseline distribution:

	Mean	Median	Std. Dev.	Naive Std.Error	95%HPD-Low	95%HPD-Upp
mu	4.5430797	4.5430973	0.0284311	0.0001271	4.4874274	4.5999188
sigma2	0.1414482	0.1385929	0.0260526	0.0001165	0.0940985	0.1925422

Precision parameter:

	Mean	Median	Std. Dev.	Naive Std.Error	95%HPD-Low	95%HPD-Upp
nclust	123.45306	123.	11.76337	0.05261	99.0	145.0
alpha	94.01344	90.87278	24.24951	0.10845	51.00767	142.24101

Acceptance Rate for Metropolis Step = 0.6134466

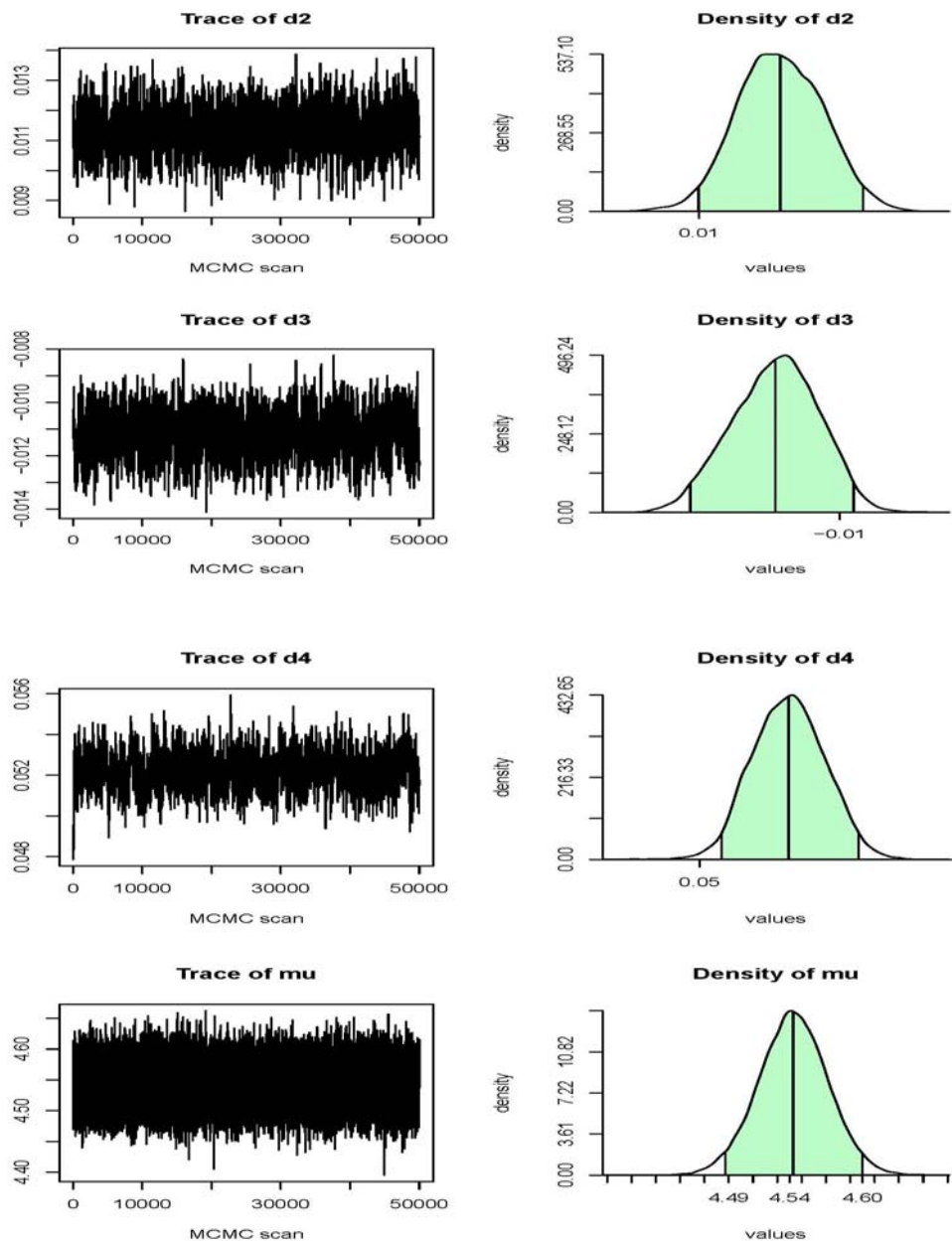
The effects for d2, d3, and d4 represent the differences between the low, medium, and high dose groups, respectively, and the vehicle, where the latter is confounded with the baseline. For male rats, the 95% credible intervals for the effect of the high dose over the simple effect of the vehicle is about (0.0505, 0.0540). Again, the posterior probability that the difference parameter is within those limits is about 0.95. Note that 0 is not in the interval, providing rather strong evidence the parameter is greater than 0, corresponding to an increase in deaths, i.e. a decrease in survival. On the other hand the corresponding credible interval for effect of the difference between the medium dose group and vehicle is (-0.0127,-0.00975), corresponding to a decrease in deaths. The credible interval for the difference between the low dose and vehicle is (0.00999, 0.0127), close to 0, suggesting a small increase in death rate for the low dose and vehicle.

Estimates are computed using Monte Carlo techniques on a Markov chain. The objective is to generate a rich pattern of feasible values for the parameters being analyzed. Proposed values are assessed if they fit the presumed model. If so, they are said to be accepted. The problem is that too high an acceptance rate is usually associated with small changes in the proposed parameter values and thus induces high autocorrelations and poor searching over the space of possible values. For multivariate normal models an acceptance rate of somewhere

between 0.2 to 0.25 is optimal, and, in general, the high acceptance rate above could be an indication that the estimated posterior distribution model may not be well estimated. However in this case, this does not seem to be true.

The trace is a plot of the posterior parameter estimate versus the iteration number. If the process is stationary, parameters can be estimates will be stable. In particular one looks for a flat, furry worm trace and a unimodal density for the posterior distribution of the parameter.

**Figure A.2.1 Assessing Output for Dose Group Differences in Male Rats**



Several other assessments of convergence are needed, but clearly here the MCMC seems to be doing a good job in searching over the possible values of the parameters, and thus results should be dependable.

The following analysis attempt to addresses the slope parameter over the treatment groups 2-5 (i.e. vehicle to high dose).

**Table A.2.2 Output for Dose Response Slope in Male Rats**

Posterior Predictive Distributions (log):

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
-8.355	-4.811	-4.249	-3.508	-0.993	-0.003375

Regression coefficients:

	Mean	Median	Std. Dev.	Naive Std.Error	95%HPD-Low	95%HPD-Upp
ndose	0.001215	0.001271	0.000096	3.506e-07	0.001041	0.00105

Baseline distribution:

	Mean	Median	Std. Dev.	Naive Std.Error	95%HPD-Low	95%HPD-Upp
mu	4.528	4.528	0.02759	0.0001007	4.472	4.581
sigma2	0.1395	0.1365	0.0252	9.201E-05	0.0479	0.1907

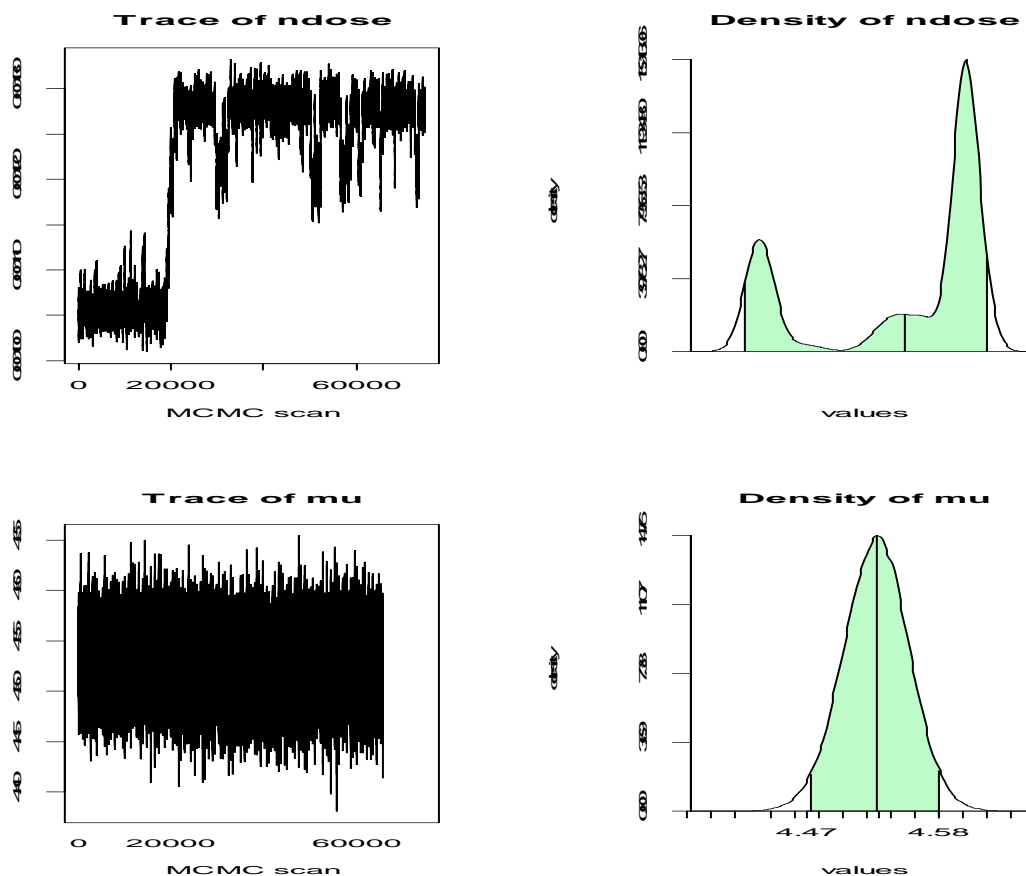
Precision parameter:

	Mean	Median	Std. Dev.	Naive Std.Error	95%HPD-Low	95%HPD-Upp
ncluster	128.58095	128.0	12.29070	0.04488	105.0	152.0
alpha	103.51031	99.64769	27.76788	0.10139	55.26032	159.03518

Acceptance Rate for Metropolis Step = 0.8002568

For male rats, the 95% credible intervals for the over all effect of dose in male rats in groups vehicle through the high dose group is about (0.001041,0.00105). Usually the posterior probability the dose slope parameter is within those limits is about 0.95. Note that 0 is not in the interval. Usually this would provide rather strong evidence the parameter is greater than 0, corresponding to a decrease in survival over increasing dose. If true, this seems to be largely due to the decrease in survival in the high dose group.

However, the trace plot of the posterior slope parameter estimate versus the iteration number, given below, indicates that iterations seem to be largely stuck in separate regions of the space of feasible parameter values. This is also reflected in the estimated posterior density. It may be due to small steps in the MCMC iterations, but this issue needs to be investigated.

**Figure A.2.2 Assessing Output for Dose Response Slope in Male Rats**

Note of course that the baseline mean,  $\mu$ , is well estimated, but is probably of little interest.

Results for female rats are summarized below:

**Table A.2.3 Output for Pairwise Differences From Vehicle in Female Rats**

Posterior Predictive Distributions (log):

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
-8.344	-4.665	-4.166	-3.586	-1.358	-1.138

Regression coefficients:

	Mean	Median	Std. Dev.	Naive Std. Error	95%HPD-Low	95%HPD-Upp
d2	-4.862e-05	-3.512e-05	5.353e-04	2.394e-06	-1.178e-03	1.047e-03
d3	-5.077e-05	-3.056e-05	5.376e-04	2.404e-06	-1.198e-03	1.049e-03
d4	6.964e-02	6.975e-02	1.333e-03	5.962e-06	6.668e-02	7.195e-02

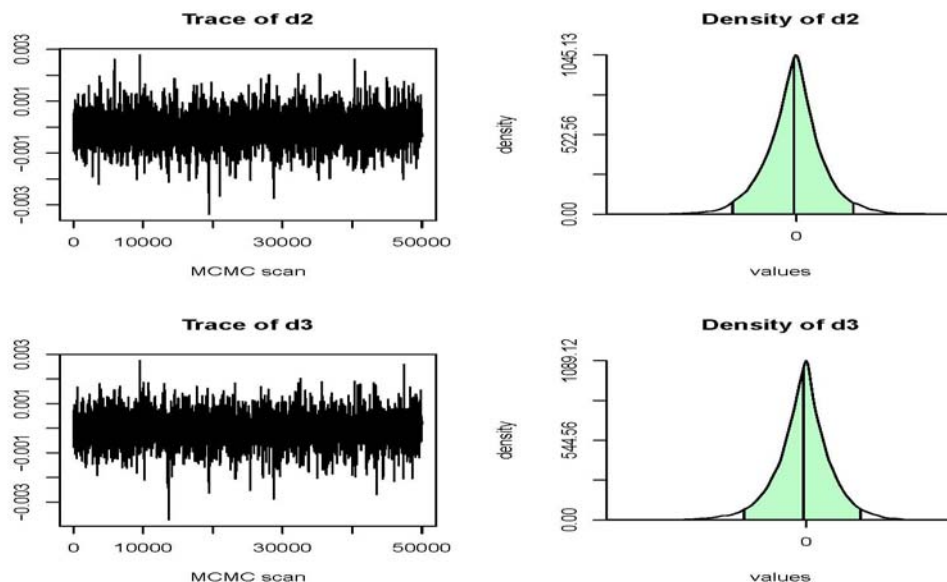
**Table A.2.3 (cont.) Output for Pairwise Differences From Vehicle in Female Rats**

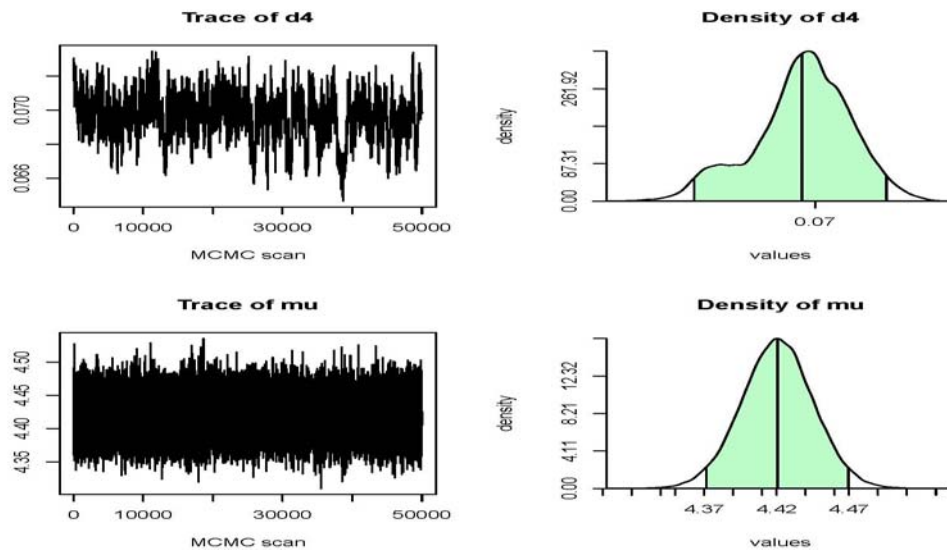
Baseline distribution:				Naive		
	Mean	Median	Std. Dev.	Std.Error	95%HPD-Low	95%HPD-Upp
mu	4.4205420	4.4206335	0.0248047	0.0001109	4.3715323	4.4694693
sigma2	0.1079811	0.1058287	0.0199898	0.0000894	0.0728534	0.1482682

Precision parameter:				Naive		
	Mean	Median	Std. Dev.	Std.Error	95%HPD-Low	95%HPD-Upp
ncluster	124.05270	124.0	11.28406	0.05046	103.00000	146.00000
alpha	94.95110	92.04517	23.87904	0.10679	53.04520	142.55696

Acceptance Rate for Metropolis Step = 0.677113

Again, the effects for d2, d3, and d4 represent the differences between the low, medium, and high dose groups and the vehicle. For female rats, the 95% credible intervals for the effect of the high dose over the simple effect of the vehicle is about (0.066, 0.072), strong evidence of an increase in deaths over vehicle. However 0 is in the intervals for the differences between the medium dose and low dose with vehicle, i.e. (-0.00119, 0.00105) and (-0.0017, 0.00105), respectively. These intervals suggest there is no strong evidence of differences in survival between either the medium dose or the low dose with vehicle.

**Figure A.2.3 Assessing Output for Dose Group Differences in Female Rats**

**Figure A.2.3 (cont.) Assessing Output for Dose Group Differences in Female Rats**

The only parameter that might somewhat challenged is the difference between the high dose and control, and it while mixing (i.e, searches over the parameter space) is something of a problem, 50,000 iterations seem likely to be sufficient.

For the linear effect of dose we get the following:

**Table A.2.4 Assessing Output for Dose Response Slope for Female Rats**

Posterior Predictive Distributions (log):

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
-8.225	-5.002	-4.285	-3.708	-1.396	-1.108

Regression coefficients:

	Mean	Median	Std. Dev.	Naive Std.Error	95%CI-Low	95%CI-Upp
ndose	0.001663	0.001.659	2.966e-05	1.083e-07	0.001621	0.001724

Baseline distribution:

	Mean	Median	Std. Dev.	Naive Std.Error	95%CI-Low	95%CI-Upp
mu	4.399	4.399	0.02231	8.147e-05	4.354	4.442
sigma2	0.1043	0.1023	0.01820	6.645e-05	0.07430	0.1452

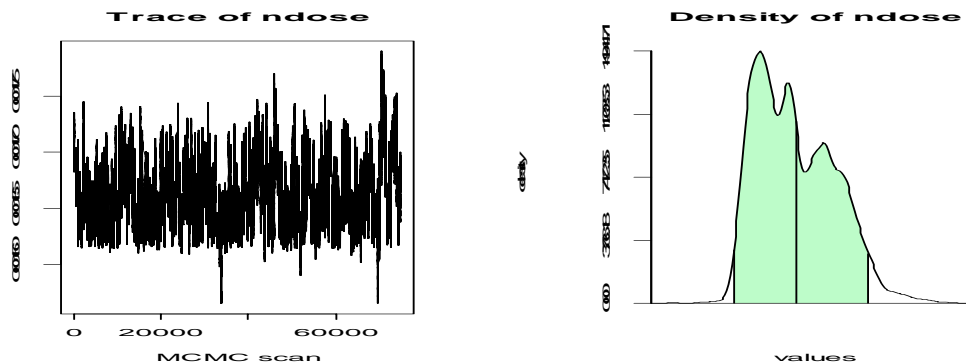
Precision parameter:

	Mean	Median	Std. Dev.	Naive Std.Error	95%CI-Low	95%CI-Upp
ncluster	138.55755	138.0	12.58893	0.04597	115.0	164.0
alpha	124.00676	119.09678	33.79208	0.12339	72.16651	202.73724

Acceptance Rate for Metropolis Step = 0.8191588

For female rats, the 95% credible interval (0.0016,0.0017), which, since it is some distance (in terms of standard deviation) from 0, strongly suggests an increasing effect of dose. From the previous analysis this is apparently largely due to the effect of the high dose.

**Figure A.2.4 Assessing Output for Dose Response Slope in Female Rats**



Note that mixing is a bit of a problem, and the density of the slope is multi-modal, possibly reflecting a mixture of distributions. Still 50,000 iterations seems likely to be sufficient for at least a rough estimate. As in the other analyses, the overall mean is well estimated, but for this analysis, of little interest.

Results for male mice are presented below:

**Table A.2.5 Output for Pairwise Differences From Vehicle in Male Mice**

Posterior Predictive Distributions (log):

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
-8.929000	-5.284000	-4.336000	-3.237000	-0.684000	-0.005413

Regression coefficients:

	Mean	Median	Std. Dev.	Naive Std.Error	95%CI-Low	95%CI-Upp
d2	-2.001e-01	-2.001e-01	2.099e-03	9.387e-06	-2.041e-01	-1.957e-01
d3	-1.295e-01	-1.300e-01	2.360e-03	1.055e-05	-1.329e-01	-1.243e-01
d4	-1.399e-01	-1.401e-01	2.150e-03	9.615e-06	-1.434e-01	-1.353e-01

Baseline distribution:

	Mean	Median	Std. Dev.	Naive Std.Error	95%CI-Low	95%CI-Upp
mu	4.5508662	4.5496761	0.0436665	0.0001953	4.4677216	4.6400173
sigma2	0.4040331	0.3964540	0.0701758	0.0003138	0.2880664	0.5634441

Precision parameter:

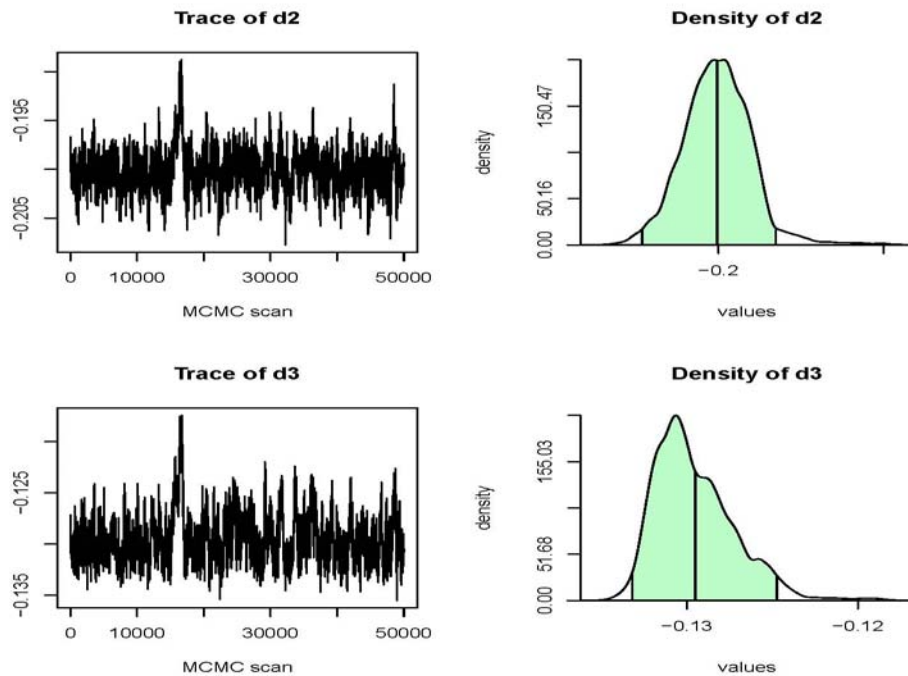
	Mean	Median	Std. Dev.	Naive Std.Error	95%CI-Low	95%CI-Upp
Nclust	158.27558	158.0	12.15454	0.05436	135.0	182.0
alpha	177.42870	170.32488	48.46455	0.21674	104.07175	292.39715

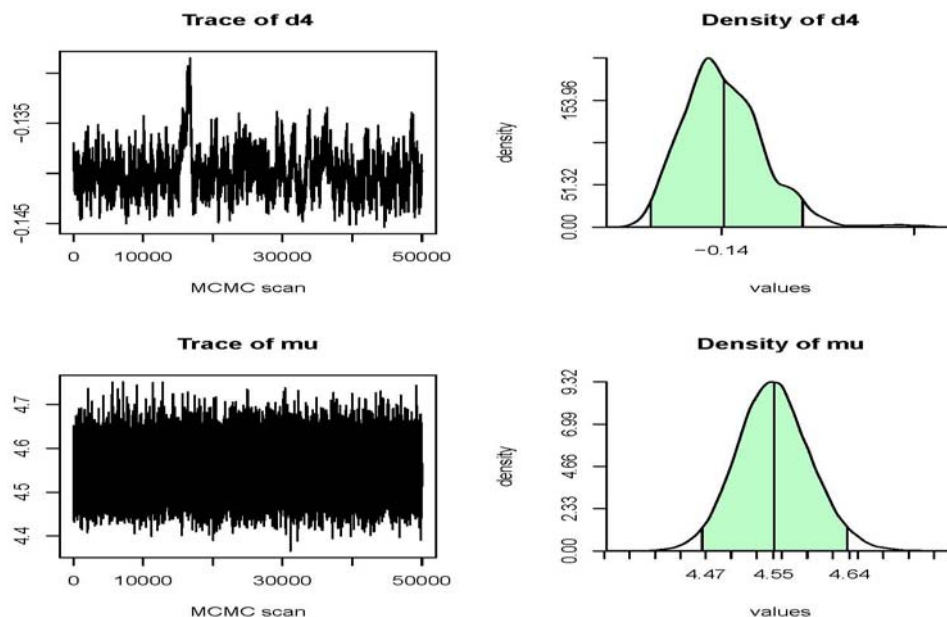
Acceptance Rate for Metropolis Step = 0.4683092



For male mice, the 95% credible intervals for the effect of each of the three actual treatment groups versus vehicle are completely negative, indicating that in general each has higher survival than the vehicle. In particular note that the approximate interval for the low dose versus vehicle is  $(-0.143, -0.135)$ , the medium dose versus vehicle is  $(-0.133, -0.124)$ , while the high dose group versus vehicle is  $(-0.204, -0.195)$ .

**Figure A.2.5 Assessing Output for Dose Group Differences in Male Mice**





Over all, the trace plots seem reasonably appropriate.

The analysis of the the linear effect of dose is as follows:

#### Figure A.2.6 Output for Dose Response Slope in Male Mice

Posterior Predictive Distributions (log):

	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
	-9.212000	-5.340000	-4.224000	-3.232000	-0.744500	-0.005605

Regression coefficients:

	Mean	Median	Std. Dev.	Naive Std.Error	95%CI-Low	95%CI-Upp
ndose	-0.001016	-0.001021	2.609e-06	9.526e-09	-1.063e-04	-9.636e-05

Baseline distribution:

	Mean	Median	Std. Dev.	Naive Std.Error	95%CI-Low	95%CI-Upp
mu	4.6935729	4.6919668	0.0483271	0.0001765	4.6028741	4.7930972
sigma2	0.4379450	0.4287341	0.0800021	0.0002921	0.3086252	0.6216108

Precision parameter:

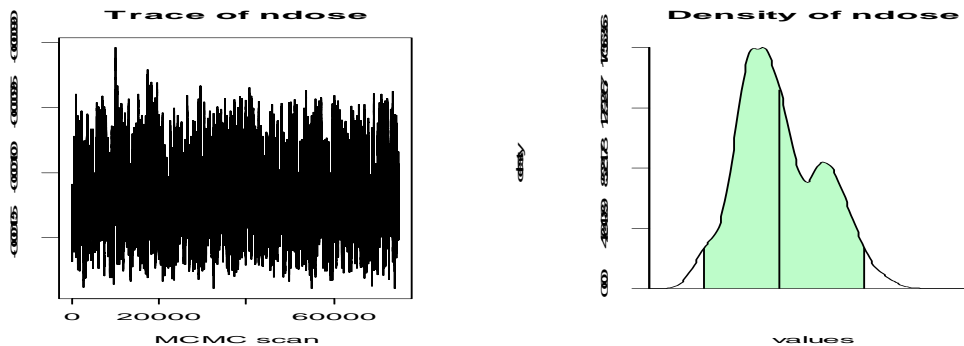
	Mean	Median	Std. Dev.	Naive Std.Error	95%CI-Low	95%CI-Upp
ncluster	155.81151	156.0	12.07390	0.04409	133.0	180.0
alpha	169.54526	163.14108	45.45311	0.16597	99.55746	276.11969

Acceptance Rate for Metropolis Step = 0.7208573

For male mice, (-0.0001063, -0.0000963) is the 95% credible interval for the linear effect of dose, corresponding to a small increase in survival over dose in male mice. This seems to be a

reflection of the fact that the vehicle tends to have the lowest survival and the low dose group the highest.

**Figure A.2.6 Assessing Output for Dose Response Slope in Male Mice**



Mixing seems reasonable, but the density seems to be a mixture.

Results for female mice are summarized below:

**Table A.2.7 Output for Pairwise Differences From Vehicle in Female Mice**

Posterior Predictive Distributions (log):

	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
	-8.78000	-5.41900	-4.74700	-3.70600	-0.99690	-0.00489

Regression coefficients:

	Mean	Median	Std. Dev.	Naive Std.Error	95%CI-Low	95%CI-Upp
d2	0.02190	2.184e-02	1.149e-03	5.139e-06	1.975e-02	2.404e-02
d3	0.07295	7.368e-02	3.067e-03	1.372e-05	6.333e-02	7.606e-02
d4	0.1193	1.170e-01	5.243e-03	2.345e-05	1.126e-01	1.292e-01

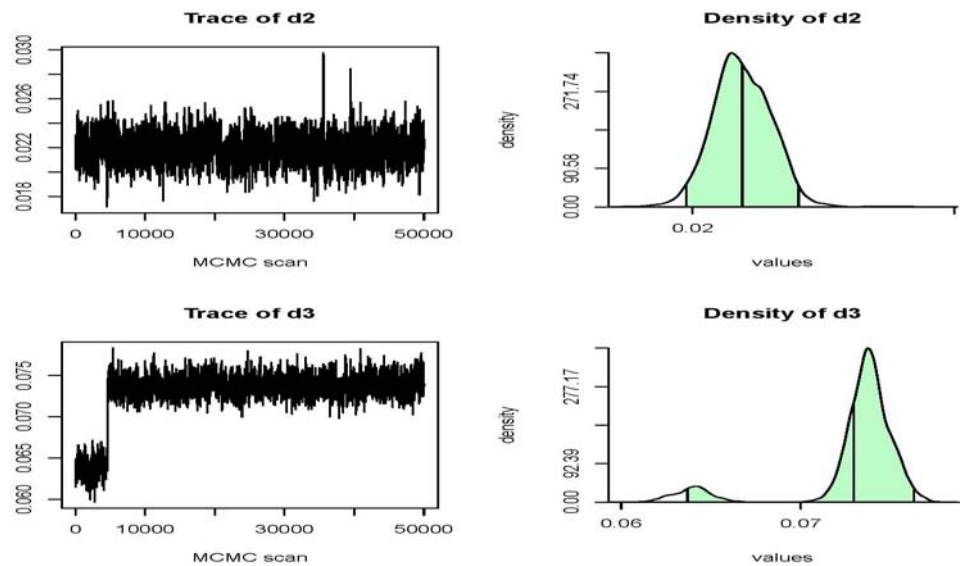
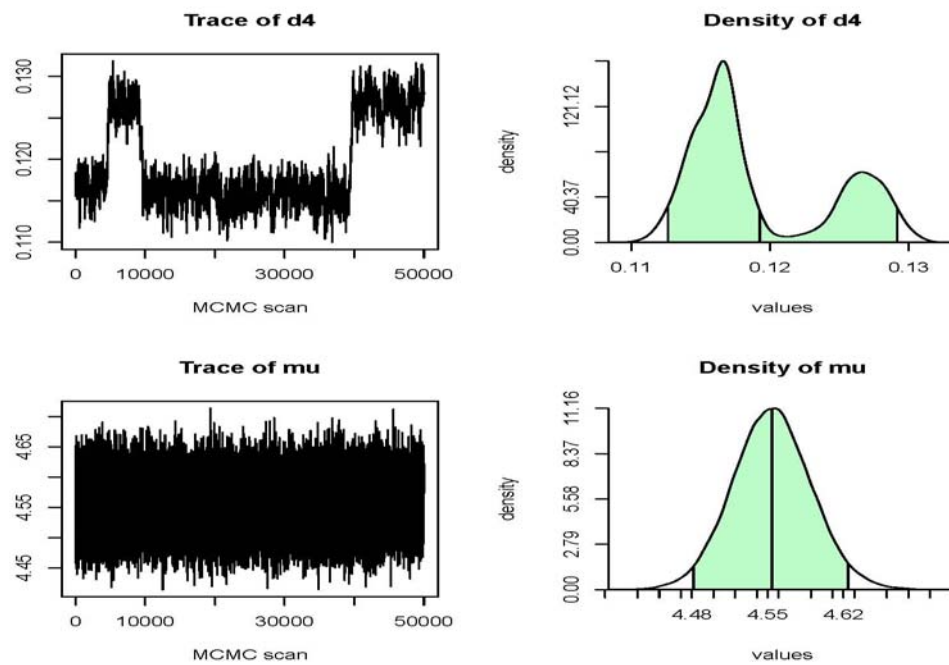
Baseline distribution:

	Mean	Median	Std. Dev.	Naive Std.Error	95%CI-Low	95%CI-Upp
mu	4.5541195	4.5538919	0.0362441	0.0001621	4.4837740	4.6267272
sigma2	0.3746225	0.3677425	0.0619013	0.0002768	0.2738578	0.5161572

Precision parameter:

	Mean	Median	Std. Dev.	Naive Std.Error	95%CI-Low	95%CI-Upp
ncluster	157.16544	157.0	11.34484	0.05074	136.0	180.0
alpha	172.97017	166.56496	44.70077	0.19991	104.11083	277.68203

One is tempted to state that for female mice, the 95% credible intervals for the effect of the high dose over the simple effect of the vehicle is about (0.112, 0.130), evidence of an increase in deaths over vehicle. The intervals for the differences between the medium dose and low dose with vehicle are , i.e. (0.063, 0.076) and (0.0197, 0.0241), respectively. However the trace plots below indicate a severe problem in the MCMC iterations for the first two comparisons.

**Figure A.2.7 Assessing Output for Dose Group Differences in Female Mice****Figure A.2.7 (cont.) Assessing Output for Dose Group Differences in Female Mice**

**Figure A.2.8 Output for Dose Response Slope in Female Mice**

Posterior Predictive Distributions (log):

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
-8.225	-5.002	-4.285	-3.708	-1.396	-1.108

Regression coefficients:

	Mean	Median	Std. Dev.	Naive Std.Error	95%CI-Low	95%CI-Upp
ndose	0.001663	0.001659	2.966e-05	1.083e-07	0.001621	0.001724

Baseline distribution:

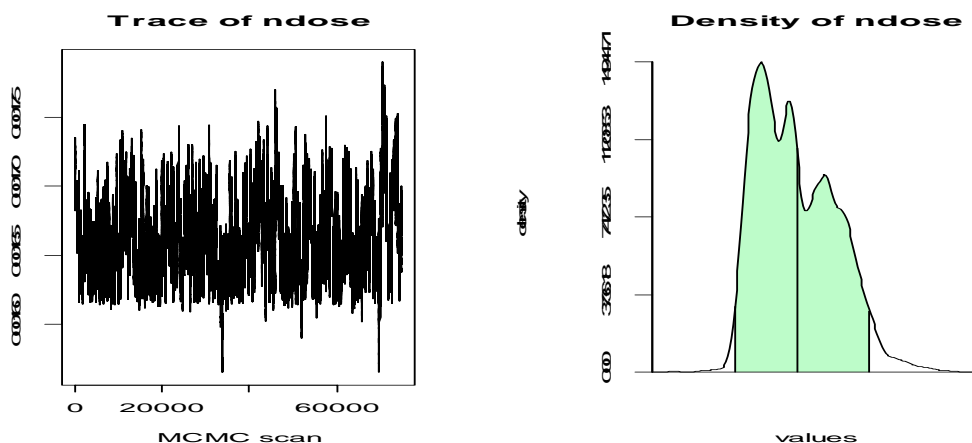
	Mean	Median	Std. Dev.	Naive Std.Error	95%CI-Low	95%CI-Upp
mu	4.399	4.399	0.02231	8.147e-05	4.354	4.442
sigma2	0.1043	0.1023	0.01820	6.645e-05	0.07430	0.1452

Precision parameter:

	Mean	Median	Std. Dev.	Naive Std.Error	95%CI-Low	95%CI-Upp
ncluster	138.55755	138.0	12.58893	0.04597	115.0	164.0
alpha	124.00676	119.09678	33.79208	0.12339	72.16651	202.73724

Acceptance Rate for Metropolis Step = 0.8191588

For female rats, the 95% credible interval for the effect of overall dose in female rats is (-0.001496,0.001295). Assuming the model fits, the posterior probability the dose slope parameter is within those limits is about 0.95. In particular, 0 is not in the interval, providing strong evidence the parameter is greater than 0, corresponding to a decrease in survival over dose, apparently due to the fact that the low dose has the highest survival. The trace suggests stationarity is not achieved until after 500-1000 further iterations.

**Figure A.2.8 Assessing Output for Dose Group Differences in Female Mice**

Note that the trace for dose seems to suggest slow mixing, which may indicate that many more iterations are needed, or that the linear effect in the AFT model may not fit the data very well.

### Appendix 3. FDA Poly-k Tumorigenicity Analysis

The poly-k test, here with  $k=3$ , modifies the original Cochran-Armitage test to adjust for differences in mortality (please see Bailer & Portier, 1988, Bieler & Williams, 1993). The tests used here are small sample exact permutation tests of tumor incidence. When there were no tumors of the specific type being analyzed in either column of the 2x2 table corresponding to a pairwise comparison an argument could be made that the p-value for this test should be 1.0. However, largely for readability, in the tables below these p-values are considered as missing (i.e., corresponding to a null test), denoted by a period “.”. Note that the StatXact program used for these analyses adjusts for the variance, which would be 0. Then the significance levels of the test statistics are based on the result of a division by 0, i.e., undefined, and hence StatXact codes these p-values as missing.

For each species by gender by organ the number of animals microscopically analyzed is presented first. Note that indicating an organ was not examined requires a specification in the data (please see section 2.2 above). This specification may be missing in some of this data. Thus, as discussed in Section 1.5 above, for some of these organs it is possibly more appropriate to define the actual endpoint used in the statistical analysis be the condition of being microscopically analyzed AND show the tumor. This does have problems unless treatment groups are not treated equally. The entry for each tumor is preceded by the adjusted number of animals at risk for that endpoint. It seems clear that an animal that dies early without having displaying that endpoint reduces the size of the risk set for that getting that particular endpoint. The poly-k test down weights such animals, and as discussed in Section 1.3.1.4, above, the sum of these poly-k weights seems to be a better estimate of the number of animals at risk of getting that tumor than the simple number of animals analyzed. This sum is given in the row labeled “Adjusted # at risk”. Tumor incidence is presented next, with the significance levels of the tests of trend, and the results of pairwise tests between the high and medium dose groups versus vehicle. The next row continues with the p-values of the pairwise test between the low and vehicle dose groups and the p-values between the vehicle dose group and high dose group with water, respectively. For these analyses, incidence in the water only group is used to assess background tumor incidence, and thus whether a tumor is considered to be rare (background incidence <1%) or common. Note that for this analysis a tumor is only classified as rare if the H2O group shows none of that particular tumor.

To adjust for the multiplicity of tests the so-called Haseman-Lin-Rahman (HLR) rules discussed in Section 1.3.1.5 are often applied. That is, when testing for trend over dose groups 2-5 and the difference between the highest dose group with a control group, to control the overall Type I error rate to roughly 10% for a standard two species, two sex study, one compares the unadjusted significance level of the trend test to 0.005 for common tumors and 0.025 for rare tumors, and the pairwise test to 0.01 for common tumors and 0.05 for rare tumors. Using these adjustments for other tests, like testing the comparisons between the low, medium, and water dose groups versus vehicle can be expected to increase the overall type I error rate to some value above the nominal rough 10% level, possibly considerably higher than the nominal 10% rate.

Tables A.3.1 and A.3.2 in rats and Tables A.3.3 and A.3.4 in mice show the tumors that had at least one mortality adjusted test whose nominal statistical significance was at least no more than 0.010. Note that when one adjusts for multiplicity these nominally significant comparisons may not be statistically significant.

**Table A.3.1. Potentially Statistically Significant Neoplasms in Male Rats**

Organ/ Tumor	Overall Results					Significance		
	H2O	Veh	Low	Med	High	p trend	p high	p med
						vs Veh		
						p low	p veh	p high
vs Veh								
vs H2O								
vs H2O								
PANCREAS								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	46.5	48.6	46.2	46.3	43.1			
ISLET CELL CARCINOMA	2	3	1	3	5	.0700	.2967	.6408
						.9362	.5204	.1900
PITUITARY								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	52.0	54.5	55.6	52.9	52.7			
PARS DISTALIS-ADENOMA	28	22	29	25	29	.1321	.0878	.2863
						.1441	.9505	.5436
Adjusted # at risk	52.7	54.5	55.6	52.9	53.3			
Pars Dist. Adenoma/Carc.	29	22	29	25	30	.1099	.0736	.2863
						.1441	.9595	.5439
THYROID								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	47.0	48.0	46.3	46.0	42.9			
FOLLICULAR CELL ADENOMA	2	0	4	1	2	.3751	.2199	.4946
						.0559	1	.6480
Adjusted # at risk	47.8	48.0	46.8	46.0	42.9			
Foll.cell Adenoma/Carc.	4	0	5	1	2	.4825	.2199	.4946
						.0264	1	.8707

Although all the organ tumor combinations in male rats listed above had at least one test that was statistically significant at a 0.10 level, adjusting for multiplicity, none were statistically significant. For example, using the incidence in the H2O group to determine whether the tumor would be classified as rare or common, the significance test between the low dose and vehicle in pooled follicular cell adenoma/carcinoma would not be statistically significant ( $p = 0.0264 > 0.1$ ). Note if we used the vehicle group to determine the classification of the tumor, following the HLR rules, it would be classified as statistically significant ( $p = 0.0264 < 0.05$ ). In either case, no other organ tumor combination achieved either multiplicity adjusted significance level.

**Table A.3.2. Potentially Statistically Significant Neoplasms in Female Rats**

Organ/ Tumor	Overall Results					Significance		
	H2O	Veh	Low	Med	High	p trend	p high vs Veh	p med vs Veh/ vs H2O
LUNGS								
MAMMARY AREAS								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	49.2	48.2	44.4	49.5	44.7			
ADENOCARCINOMA	19	11	14	22	17	.1470	.0791	.0188
						.2345	.9724	.5893
Adjusted # at risk	49.2	48.2	45.1	49.5	45.0			
Adenoma/Adenocarcinoma	19	11	17	24	19	.1329	.0382	.0066
						.0908	.9724	.4482
PITUITARY								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	59.6	63.0	63.6	61.2	61.5			
PARS DISTALIS-ADENOMA	58	51	59	55	55	.3332	.1566	.1566
						.0449	.9998	.9927
Adjusted # at risk	60.1	63.2	63.9	62.0	61.7			
Pars Dist. Adenoma/Carc.	59	52	61	58	56	.3370	.1014	.0515
						.0081	.9998	.9856

Using either the vehicle group or the water group, all of the tumors above would be classified as common. Adjusting for multiplicity and accepting the increase in type I error for including pairwise comparisons other than that between the high dose and primary control, the pairwise test between the medium dose group and vehicle in pooled adenoma/adenocarcinoma would be considered as statistically significant ( $p = 0.0066 < 0.1$ ). The test between the low dose and vehicle would also be classified as statistically significant ( $p = 0.0081 < 0.1$ ). Again, no other test achieved the multiplicity adjusted levels of statistical significance.

**Table A.3.3. Potentially Statistically Significant Neoplasms in Male Mice**

Organ/ Tumor	Overall Results					Significance		
	H2O	Veh	Low	Med	High	p trend	p high vs Veh	p med vs Veh/ vs H2O
GALLBLADDER								
# Evaluated	55	58	60	53	59			
Adjusted # at risk	43.4	41.3	50.9	40.8	43.6			
PAPILLOMA	0	0	0	0	2	.0600	.2590	.
						.	.	.2471
LUNGS								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	52.2	45.1	55.2	49.9	48.3			
BRONCHIOLO/ALVEOLAR CARCINOMA	10	3	8	9	11	.0436	.0269	.0810
						.1766	.9850	.4177
Adjusted # at risk	53.3	46.8	55.7	50.4	49.1			
Bronch. Alv. Adenoma/Carc.	21	10	20	12	16	.2696	.1681	.4927
						.0827	.9842	.8257

None of the tests of the organ-tumor combinations above achieved the mortality adjusted significance levels.



**Table A.3.4. Potentially Statistically Significant Neoplasms in Female Mice**

Organ/ Tumor	Female Mice					Significance		
	Overall Results					p trend vs Veh	p high vs Veh/ vs H2O	p med vs Veh/ vs H2O
	H2O	Veh	Low	Med	High			
<b>HARDERIAN GL</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	43.4	49.1	44.9	43.2	39.2			
ADENOMA	4	10	5	7	9	.1799	.4812	.7810
						.9301	.1166	.0800
<b>LIVER</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.2	46.6	43.7	41.8	37.3			
Hepato. Adenoma/Carcinoma	0	0	0	0	2	.0480	.1957	.
						.	.	.2162
<b>LUNGS</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	43.5	46.6	43.8	44.3	38.1			
BRONCHIOLO/ALVEOLAR ADENOMA	8	0	4	8	5	.1456	.0163	.0023
						.0505	1	.8336
Adjusted # at risk	43.8	48.4	44.9	46.1	38.9			
Bronch. Alv. Adenoma/Carc.	9	4	9	12	7	.3837	.1434	.0210
						.0854	.9789	.7118
<b>LYMPHORETIC SYSTEM</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	54.3	53.0	46.2	46.6	46.1			
MALIGNANT LYMPHOMA	27	16	9	14	19	.0356	.1908	.6000
						.9343	.9869	.8579
<b>UTERUS W/ CERVIX</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.2	46.6	44.5	42.1	36.9			
LEIOMYOMA	1	0	2	4	1	.4748	.4390	.0480
						.2362	1	.7133
Adjusted # at risk	42.7	46.6	44.5	44.1	37.6			
Leiomyoma/Leiomyosarcoma	2	0	2	7	2	.4390	.1957	.0051
						.2362	1	.6428

Again, using the incidence in the water group to determine whether a tumor is common or rare, only the pairwise tests between the medium dose and vehicle in terms of bronchiole/alveolar adenoma of the lung and pooled leiomyoma and leiomyosarcoma of the uterus with cervix would be classified as statistically significant ( $p = 0.0023 < 0.01$  and  $p = 0.0051 < 0.01$ , respectively).

Tables A.3.5 and A.3.6 display all incidences and statistical test results for male and female rats, respectively, while Tables A.3.7 and A.3.8 present similar results in male and female mice. Again, the p-values of the poly-k test are based on exact tests from StatXact as discussed above. As also noted above, the period ‘.’ denotes the p-values of tests of dose groups with no tumors in any group.

**Table A.3.5. Neoplasms in Male Rats**

Organ/ Tumor	Overall Results					Significance		
	H2O	Veh	Low	Med	High	p trend	p high vs Veh	p med vs Veh/
						p low vs Veh	p veh vs H2O	p high vs H2O
<b>ADIPOSE TISSUE</b>								
# Evaluated	3	2	1	1	3			
Adjusted # at risk	2.8	2.0	1.0	0.3	2.5			
LIPOMA	0	1	0	0	0	1	1	.
						1	.5000	.
Adjusted # at risk	2.8	1.9	1.0	1.0	2.5			
MALIGNANT HIBERNOMA	0	0	0	1	0	.6000	.	.5000
						.	.	.
<b>ADRENAL GLANDS</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	46.2	48.0	45.8	46.3	42.9			
CORTEX: ADENOMA	0	1	0	1	1	.3677	.7240	.7473
						1	.5054	.4773
Adjusted # at risk	46.9	48.5	46.2	46.4	42.9			
MEDULLA BENIGN PHEOCHROMOCYTOMA	4	5	3	4	4	.4281	.6860	.7353
						.8521	.5274	.5907
Adjusted # at risk	46.2	48.1	45.8	46.0	42.1			
MEDULLA: MALIGNANT PHEOCHROMOCYTOMA	0	1	0	0	0	1	1	1
						1	.5106	.
Adjusted # at risk	46.9	48.6	46.2	46.4	42.9			
Med.Pheochromocytoma [B&M]	4	6	3	4	4	.5054	.7820	.8239
						.9105	.3976	.5907
<b>BONE (OTHER)</b>								
# Evaluated	0	0	1	2	1			
Adjusted # at risk	0.0	0.0	0.7	1.1	1.0			
FIBROSARCOMA	0	0	0	0	1	.5000	.	.
						.	.	.
Adjusted # at risk	0.0	0.0	1.0	1.1	1.0			
HISTIOCYTOMA, FIBROUS	0	0	1	0	0	1	.	.
						.	.	.
<b>BRAIN</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	46.9	48.1	46.0	46.0	42.1			
ASTROCYTOMA	1	1	1	1	0	.8099	1	.7363
						.7419	.7632	1
Adjusted # at risk	46.2	48.9	45.8	46.0	42.1			
BENIGN MENINGIOMA	0	1	0	0	0	1	1	1
						1	.5106	.
Adjusted # at risk	46.2	48.4	45.8	46.0	42.4			
GRANULAR CELL TUMOR	0	1	0	0	1	.4132	.7184	1
						1	.5106	.4773
Adjusted # at risk	46.2	48.0	45.8	46.3	42.1			
OLIGODENDROGLIOMA	0	1	0	1	0	.7402	1	.7473
						1	.5054	.
<b>EAR(S)</b>								
# Evaluated	0	1	0	0	1			
Adjusted # at risk	0.0	0.9	0.0	0.0	1.0			
FIBROSARCOMA	0	0	0	0	1	1	.	.
						.	.	.

**Table A.3.5. (cont.) Neoplasms in Male Rats**

Organ/ Tumor	Overall Results					Significance		
	H2O	Veh	Low	Med	High	p trend	p high	p med
							vs Veh	vs Veh/
						p low	p veh	p high
vs Veh						vs H2O	vs H2O	
EXTREMITY								
# Evaluated	34	40	26	27	16			
Adjusted # at risk	27.6	30.7	17.7	20.5	13.1			
KERATOACANTHOMA	1	0	0	0	0	.	.	.
						.	1	1
JEJUNUM								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	46.2	48.0	45.8	46.0	42.1			
NEUROENDOCRINE NEOPLASM	0	0	0	1	0	.4860	.	.4891
						.	.	.
KIDNEYS								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	46.2	48.0	45.8	46.0	42.5			
CARCINOMA, TRANSITIONAL CELL	0	0	0	0	1	.2346	.4719	.
						.	.	.4773
Adjusted # at risk	46.2	48.0	45.8	46.0	42.1			
CARCINOMA, TUBULAR	0	0	0	1	0	.4860	.	.4891
						.	.	.
Adjusted # at risk	46.2	48.0	45.8	46.0	42.1			
LIPOSARCOMA	0	0	0	0	1	.2346	.4719	.
						.	.	.4773
LIVER								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	46.5	48.1	46.0	46.0	42.1			
HEPATOCELLULAR ADENOMA	3	2	2	2	1	.6918	.8528	.6668
						.6668	.8323	.9300
Adjusted # at risk	46.2	48.0	46.1	46.0	42.1			
HEPATOCELLULAR CARCINOMA	0	1	1	0	0	.9329	1	1
						.7473	.5054	.
Adjusted # at risk	46.5	48.1	46.2	46.0	42.1			
Hepato. Adenoma/Carcinoma	3	3	3	2	1	.8357	.9238	.7986
						.6408	.6816	.9300
LYMPH/RETIC SYS								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	46.8	48.0	45.8	46.0	42.1			
GRANULOCYTIC LEUKEMIA	1	0	0	0	0	.	.	.
						.	1	1
Adjusted # at risk	47.4	48.0	46.4	46.0	42.6			
HISTIOCYTIC SARCOMA	4	1	2	0	1	.5926	.7240	1
						.4918	.9721	.9630
Adjusted # at risk	48.5	48.0	45.8	46.0	42.1			
MALIGNANT LYMPHOMA	3	0	0	1	0	.4860	.	.4891
						.	1	1
MAMMARY AREAS								
# Evaluated	56	59	54	54	52			
Adjusted # at risk	41.5	42.9	37.8	38.5	33.7			
FIBROADENOMA	0	1	0	0	0	1	1	1
						1	.5060	.
MENINGES								
# Evaluated	0	1	0	0	0			
Adjusted # at risk	0.0	1.0	0.0	0.0	0.0			
MALIGNANT MENINGIOMA	0	1	0	0	0	1	.	.
						.	.	.

**Table A.3.5. (cont.) Neoplasms in Male Rats**

Organ/ Tumor	Overall Results					Significance		
	H2O	Veh	Low	Med	High	p trend	p high vs Veh	p med vs Veh/
							p low vs Veh	p high vs H2O
<b>MESENTERY/PERITO</b>								
# Evaluated	0	0	0	1	2			
Adjusted # at risk	0.0	0.0	0.0	1.0	2.0			
MALIGNANT MESOTHELIOMA	0	0	0	0	1	.5000	.	.
						.	.	.
<b>PANCREAS</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	46.2	48.0	45.8	46.1	43.0			
ACINAR CELL ADENOMA	1	0	0	1	1	.1734	.4719	.4946
						.	1	.7296
Adjusted # at risk	46.2	48.0	46.7	46.0	42.1			
HEMANGIOMA	0	0	1	0	0	.7389	.	.
						.4946	.	.
Adjusted # at risk	46.6	48.3	45.8	47.2	42.5			
ISLET CELL ADENOMA	2	3	1	7	4	.2410	.4249	.1497
						.9334	.5204	.2957
Adjusted # at risk	46.5	48.6	46.2	46.3	43.1			
ISLET CELL CARCINOMA	2	3	1	3	5	.0700	.2967	.6408
						.9362	.5204	.1900
Adjusted # at risk	46.8	49.0	46.2	47.6	43.5			
Islet Cell Adenoma/Carc.	4	6	2	10	7	.0574	.2121	.1928
						.9662	.3974	.0905
<b>PARATHYROID</b>								
# Evaluated	61	64	61	63	63			
Adjusted # at risk	44.5	47.5	44.1	45.0	41.7			
ADENOMA	0	1	0	0	0	1	1	1
						1	.5165	.
<b>PITUITARY</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	52.0	54.5	55.6	52.9	52.7			
PARS DISTALIS-ADENOMA	28	22	29	25	29	.1321	.0878	.2863
						.1441	.9505	.5436
Adjusted # at risk	46.9	48.0	45.8	46.0	42.7			
PARS DISTALIS: CARCINOMA	1	0	0	0	1	.2346	.4719	.
						.	1	.7296
Adjusted # at risk	46.2	48.0	45.8	46.0	42.1			
PARS INTERMEDIA: ADENOMA	0	0	0	0	1	.2346	.4719	.
						.	.	.4773
Adjusted # at risk	52.7	54.5	55.6	52.9	53.3			
Pars Dist. Adenoma/Carc.	29	22	29	25	30	.1099	.0736	.2863
						.1441	.9595	.5439
<b>SALIVARY GLAND</b>								
# Evaluated	65	64	65	65	65			
Adjusted # at risk	46.2	47.3	45.8	46.3	42.1			
LEIOMYOMA	0	0	0	1	0	.4889	.	.4946
						.	.	.

**Table A.3.5. (cont.) Neoplasms in Male Rats**

Organ/ Tumor	Overall Results					Significance		
	H2O	Veh	Low	Med	High	p trend	p high vs Veh	p med vs Veh/
						p low vs Veh	p veh vs H2O	p high vs H2O
<b>SKIN</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	46.2	48.3	45.8	46.0	42.9			
BENIGN BASAL CELL TUMOR	1	1	0	2	2	.1453 1	.4495 .7632	.4755 .4655
Adjusted # at risk	46.8	48.3	45.8	46.0	42.9			
Basal Cell Tumor [B&M]	2	1	0	2	2	.1453 1	.4495 .8868	.4755 .6566
Adjusted # at risk	46.2	48.1	46.6	46.0	42.1			
FIBROMA	0	1	2	1	0	.8575 .4839	1 .5106	.7363 .
Adjusted # at risk	47.2	48.7	46.2	46.5	42.1			
FIBROSARCOMA	2	3	1	2	0	.9238 .9362	1 .5101	.8057 1
Adjusted # at risk	46.2	48.3	46.4	46.0	42.5			
HISTIOCYTOMA, FIBROUS	0	1	1	0	1	.5006 .7419	.7184 .5106	1 .4773
Adjusted # at risk	46.5	48.8	46.9	47.7	43.6			
KERATOACANTHOMA	2	4	3	4	3	.5431 .7645	.7347 .3592	.6309 .4677
Adjusted # at risk	46.2	48.0	45.8	46.0	42.7			
LIPOMA	1	1	1	0	2	.2122 .7418	.4574 .7581	1 .4655
Adjusted # at risk	46.8	48.0	45.8	46.0	42.1			
MALIGNANT BASAL CELL TUMOR	1	0	0	0	0	. .	. 1	. 1
Adjusted # at risk	46.2	48.0	45.8	46.0	42.1			
MALIGNANT SCHWANNOMA	0	0	0	1	0	.4860 .	. .	.4891 .
Adjusted # at risk	46.2	48.0	46.2	46.0	42.1			
MYXOSARCOMA	1	0	1	0	0	.7389 .4946	. 1	. 1
Adjusted # at risk	46.2	48.3	45.9	46.0	42.1			
SQUAMOUS CELL CARCINOMA	0	1	1	0	0	.9300 .7363	1 .5106	1 .
Adjusted # at risk	46.2	48.0	45.8	46.3	42.8			
SQUAMOUS CELL PAPILLOMA	1	0	0	3	1	.2476 .	.4719 1	.1170 .7296
Adjusted # at risk	46.2	48.3	45.9	46.3	42.8			
Sq.Cell Pap./Carcinoma	1	1	1	3	1	.4843 .7363	.7184 .7632	.2924 .7296
<b>SPLEEN</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	46.2	48.0	45.8	46.0	42.1			
HEMANGIOMA	0	0	1	0	0	.7374 .4891	. .	. .
<b>STOMACH</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	46.2	48.0	45.8	46.0	42.1			
CARCINOMA, SQUAMOUS CELL	0	1	0	0	0	1 1	1 .5054	1 .

**Table A.3.5. (cont.) Neoplasms in Male Rats**

Organ/ Tumor	Overall Results					Significance			
	H2O	Veh	Low	Med	High	p trend	p high	p med	
							vs Veh	vs Veh/	
							p low vs Veh	p veh vs H2O	p high vs H2O
Systemic									
# Evaluated	65	65	65	65	65				
Adjusted # at risk	46.2	48.0	46.7	46.0	42.1				
HEMANGIOMA	0	0	2	0	0	.7987	.	.	
						.2419	.	.	
TAIL									
# Evaluated	17	16	18	17	12				
Adjusted # at risk	14.6	12.3	14.7	14.8	8.8				
BASAL CELL TUMOR	1	0	0	0	0	.	.	.	
						.	1	1	
TESTES									
# Evaluated	65	65	65	65	65				
Adjusted # at risk	46.2	48.3	45.8	46.5	42.4				
BENIGN INTERSTITIAL CELL TUMOR	0	1	0	2	1	.3386	.7184	.4839	
						1	.5106	.4773	
THYMUS									
# Evaluated	62	64	65	64	65				
Adjusted # at risk	44.1	47.1	45.8	45.6	42.1				
MALIGNANT THYMOMA	0	0	0	1	0	.4860	.	.4891	
						.	.	.	
THYROID									
# Evaluated	65	65	65	65	65				
Adjusted # at risk	47.0	49.6	45.8	46.4	42.5				
C-CELL ADENOMA	4	4	2	5	1	.8497	.9590	.4594	
						.8774	.6660	.9630	
Adjusted # at risk	46.2	48.0	46.3	46.9	42.3				
C-CELL CARCINOMA	2	0	1	1	2	.1022	.2199	.4946	
						.4946	1	.6566	
Adjusted # at risk	47.0	49.6	46.3	47.4	42.7				
C-cell Adenoma/Carcinoma	5	4	3	6	3	.5625	.7140	.3436	
						.7554	.7774	.8272	
Adjusted # at risk	47.0	48.0	46.4	46.0	42.1				
CARCINOMA, FOLLICULAR CELL	2	0	1	0	0	.7389	.	.	
						.4946	1	1	
Adjusted # at risk	47.0	48.0	46.3	46.0	42.9				
FOLLICULAR CELL ADENOMA	2	0	4	1	2	.3751	.2199	.4946	
						.0559	1	.6480	
Adjusted # at risk	47.8	48.0	46.8	46.0	42.9				
Foll.cell Adenoma/Carc.	4	0	5	1	2	.4825	.2199	.4946	
						.0264	1	.8707	
ZYMBAL'S GLAND									
# Evaluated	1	0	1	0	0				
Adjusted # at risk	0.2	0.0	1.0	0.0	0.0				
ADENOMA	0	0	1	0	0	1	.	.	
						.	.	.	
Adjusted # at risk	1.0	0.0	1.0	0.0	0.0				
Adenoma/Carcinoms	1	0	1	0	0	1	.	.	
						.	.	.	
Adjusted # at risk	1.0	0.0	1.0	0.0	0.0				
CARCINOMA	1	0	0	0	0	.	.	.	
						.	.	.	

**Table A.3.6. Neoplasms in Female Rats**

Organ/ Tumor	Overall Results					Significance		
	H2O	Veh	Low	Med	High	p trend	p high	p med
							vs Veh	vs Veh/
						p low	p veh	p high
						vs Veh	vs H2O	vs H2O
<b>ADRENAL GLANDS</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.7	46.2	41.1	43.7	38.8			
CORTEX: ADENOMA	3	1	0	0	1	.4023	.7031	1
						1	.9520	.9292
Adjusted # at risk	42.3	46.0	41.1	44.3	38.4			
CORTEX: CARCINOMA	2	1	0	2	0	.6576	1	.4831
						1	.8954	1
Adjusted # at risk	42.7	46.2	41.1	44.3	38.8			
Cortex: Carcinoma/Adenoma	5	2	0	2	1	.4831	.8407	.6747
						1	.9577	.9825
Adjusted # at risk	42.3	46.0	41.5	43.9	38.4			
MEDULLA BENIGN PHEOCHROMOCYTOMA	0	0	1	1	1	.2591	.4524	.4831
						.4713	.	.4750
<b>BRAIN</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.3	46.0	41.1	44.1	38.4			
OLIGODENDROGLIOMA	0	0	0	2	0	.4668	.	.2362
						.	.	.
<b>CECUM</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.3	46.0	41.1	43.7	38.4			
FIBROMA	1	0	0	0	0	.	.	.
						.	1	1
<b>ILEUM</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.3	46.0	41.1	43.7	38.4			
ADENOCARCINOMA	0	1	0	0	0	1	1	1
						1	.5227	.
<b>JEJUNUM</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.3	46.0	41.1	43.7	38.4			
LEIOMYOMA	0	0	0	1	0	.4821	.	.4831
						.	.	.
Adjusted # at risk	42.3	46.0	41.1	43.7	38.4			
LEIOMYOSARCOMA	0	1	0	0	0	1	1	1
						1	.5227	.
Adjusted # at risk	42.3	46.0	41.1	43.7	38.4			
Leiomyoma/Leiomyosarcoma	0	1	0	1	0	.7333	1	.7357
						1	.5227	.

**Table A.3.6. (cont.) Neoplasms in Female Rats**

Organ/ Tumor	Overall Results					Significance		
	H2O	Veh	Low	Med	High	p trend	p high vs Veh	p med vs Veh/
						p low vs Veh	p veh vs H2O	p high vs H2O
<b>LIVER</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.3	46.0	41.1	43.7	38.6			
HEMANGIOSARCOMA	0	0	0	0	1	.2262	.4524	.4750
Adjusted # at risk	42.3	46.0	41.4	43.7	39.6			
HEPATOCELLULAR ADENOMA	1	2	3	1	3	.2935	.4213	.8663
Adjusted # at risk	42.3	46.0	41.1	43.7	38.4			
HEPATOCELLULAR CARCINOMA	1	1	0	0	0	1	1	1
Adjusted # at risk	42.3	46.0	41.4	43.7	39.6			
Hepato. Adenoma/Carcinoma	2	3	3	1	3	.3843	.5799	.9332
						.6052	.5436	.4644
<b>LUNGS</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.3	46.0	41.1	43.7	38.6			
BRONCHIOLO/ALVEOLAR CARCINOMA	0	0	0	0	1	.2262	.4524	.4750
Adjusted # at risk	42.3	46.2	41.1	43.7	38.4			
CARCINOMA NOS	0	1	0	0	0	1	1	1
Adjusted # at risk	42.3	46.0	41.1	43.7	38.6			
HEMANGIOSARCOMA	0	0	0	0	1	.2262	.4524	.4750
						.	.	.
<b>LYMPH/RETIC SYS</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.8	46.0	41.1	43.7	38.4			
HISTIOCYTIC SARCOMA	1	0	0	0	0	.	.	.
Adjusted # at risk	44.0	46.8	41.6	43.7	38.8			
MALIGNANT LYMPHOMA	2	1	1	0	1	.4884	.7031	1
						.7233	.8913	.8554
<b>MAMMARY AREAS</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	49.2	48.2	44.4	49.5	44.7			
ADENOCARCINOMA	19	11	14	22	17	.1470	.0791	.0188
Adjusted # at risk	43.1	46.0	42.3	43.9	38.8			
ADENOMA	1	1	4	3	2	.4851	.4279	.2830
Adjusted # at risk	49.2	48.2	45.1	49.5	45.0			
Adenoma/Adenocarcinoma	19	11	17	24	19	.1329	.0382	.0066
Adjusted # at risk	47.0	51.7	46.0	50.4	42.8			
FIBROADENOMA	20	28	17	29	15	.9267	.9805	.4550
						.9761	.1540	.8095



**Table A.3.6. (cont.) Neoplasms in Female Rats**

Organ/ Tumor	Overall Results					Significance		
	H2O	Veh	Low	Med	High	p trend	p high	p med
							vs Veh	vs Veh/
						p low	p veh	p high
						vs Veh	vs H2O	vs H2O
<b>MESENTERY/PERITO</b>								
# Evaluated	1	1	1	1	0			
Adjusted # at risk	1.0	1.0	0.5	0.2	0.0			
LIPOMA	1	0	0	0	0	.	.	.
						.	1	.
Adjusted # at risk	1.0	1.0	1.0	0.2	0.0			
LIPOSARCOMA	0	0	1	0	0	.5000	.	.
						.5000	.	.
Adjusted # at risk	1.0	1.0	1.0	0.2	0.0			
Lipoma/Liposarcoma	1	0	1	0	0	.5000	.	.
						.5000	1	.
<b>MUSCLE (OTHER)</b>								
# Evaluated	0	0	2	0	0			
Adjusted # at risk	0.0	0.0	1.5	0.0	0.0			
CARCINOMA (NOS)	0	0	1	0	0	1	.	.
						.	.	.
<b>PANCREAS</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.4	46.0	41.2	44.0	38.4			
ISLET CELL ADENOMA	2	1	1	1	0	.8082	1	.7416
						.7233	.8954	1
Adjusted # at risk	42.3	46.6	41.1	43.7	38.4			
ISLET CELL CARCINOMA	1	2	0	2	2	.2426	.6165	.6658
						1	.5345	.4620
Adjusted # at risk	42.4	46.6	41.2	44.0	38.4			
Islet Cell Adenoma/Carc.	3	3	1	3	2	.4582	.7557	.6401
						.9267	.7043	.7877
<b>PITUITARY</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	59.6	63.0	63.6	61.2	61.5			
PARS DISTALIS-ADENOMA	58	51	59	55	55	.3332	.1566	.1566
						.0449	.9998	.9927
Adjusted # at risk	42.7	46.3	41.3	44.5	38.6			
PARS DISTALIS: CARCINOMA	1	1	2	3	1	.5622	.7031	.2916
						.4564	.7751	.7275
Adjusted # at risk	60.1	63.2	63.9	62.0	61.7			
Pars Dist. Adenoma/Carc.	59	52	61	58	56	.3370	.1014	.0515
						.0081	.9998	.9856
<b>RECTUM/LOW COLON</b>								
# Evaluated	1	0	0	0	0			
Adjusted # at risk	1.0	0.0	0.0	0.0	0.0			
FIBROMA	1	0	0	0	0	.	.	.
						.	.	.

**Table A.3.6. (cont.) Neoplasms in Female Rats**

Organ/ Tumor	Overall Results					Significance		
	H2O	Veh	Low	Med	High	p trend	p high vs Veh	p med vs Veh/
						p low vs Veh	p veh vs H2O	p high vs H2O
<b>SKIN</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.3	46.0	41.1	43.7	38.4			
BENIGN BASAL CELL TUMOR	0	0	0	1	0	.4821	.	.4831
						.	.	.
Adjusted # at risk	42.9	46.0	41.1	43.7	38.4			
FIBROMA	1	0	1	0	0	.7262	.	.
						.4713	1	1
Adjusted # at risk	42.3	46.0	41.1	43.7	39.0			
HISTIOCYTOMA, FIBROUS	0	0	0	0	1	.2308	.4588	.
						.	.	.4815
Adjusted # at risk	42.3	47.2	41.1	43.7	38.4			
KERATOACANTHOMA	1	2	0	0	0	1	1	1
						1	.5426	1
Adjusted # at risk	42.3	47.2	41.1	43.7	38.4			
Keratocanth./Sq.Cell Pap	1	4	1	0	0	.9986	1	1
						.9608	.2174	1
Adjusted # at risk	42.3	46.0	41.1	43.7	38.4			
SQUAMOUS CELL PAPILOMA	0	2	1	0	0	.9804	1	1
						.8568	.2704	.
<b>Systemic</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.3	46.0	41.1	43.7	38.6			
HEMANGIOSARCOMA	0	0	0	0	1	.2262	.4524	.
						.	.	.4750
<b>TAIL</b>								
# Evaluated	1	5	7	6	10			
Adjusted # at risk	1.0	2.7	5.7	4.6	6.2			
KERATOACANTHOMA	0	0	1	0	0	.8824	.	.
						.7143	.	.
<b>THYMUS</b>								
# Evaluated	64	65	63	62	65			
Adjusted # at risk	41.3	46.0	40.1	42.1	38.4			
MALIGNANT THYMOMA	0	0	0	1	0	.4819	.	.4773
						.	.	.

**Table A.3.6. (cont.) Neoplasms in Female Rats**

Organ/ Tumor	Overall Results					Significance		
	H2O	Veh	Low	Med	High	p trend	p high vs Veh	p med vs Veh/
						p low vs Veh	p veh vs H2O	p high vs H2O
<b>THYROID</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.4	46.0	41.1	44.7	38.9			
C-CELL ADENOMA	1	1	4	3	1	.7208	.7031	.2916
						.1464	.7751	.7275
Adjusted # at risk	42.3	46.6	41.1	44.1	39.0			
C-CELL CARCINOMA	0	2	0	1	1	.5199	.8407	.8708
						1	.2704	.4750
Adjusted # at risk	42.4	46.6	41.1	45.1	39.4			
C-cell Adenoma/Carcinoma	1	3	4	4	2	.7032	.7642	.4876
						.4351	.3434	.4719
Adjusted # at risk	42.3	46.0	41.8	44.0	38.4			
CARCINOMA, FOLLICULAR CELL	1	0	1	1	0	.5923	.	.4831
						.4713	1	1
Adjusted # at risk	42.9	46.0	41.1	43.7	38.4			
FOLLICULAR CELL ADENOMA	1	0	0	0	0	.	.	.
						.	1	1
Adjusted # at risk	42.9	46.0	41.8	44.0	38.4			
Foll.cell Adenoma/Carc.	2	0	1	1	0	.5923	.	.4831
						.4713	1	1
<b>UTERUS W/ CERVIX</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.3	46.0	41.1	43.7	39.2			
BENIGN SCHWANNOMA	0	0	0	0	1	.2308	.4588	.
						.	.	.4815
Adjusted # at risk	42.7	46.8	41.6	44.6	38.8			
ENDOMETRIAL STROMAL POLYP	2	3	1	2	2	.4568	.7547	.8054
						.9267	.5436	.6534
Adjusted # at risk	42.3	46.0	41.1	43.7	38.4			
LEIOMYOMA	0	1	0	0	0	1	1	1
						1	.5227	.
<b>VAGINA</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.3	46.0	41.1	44.4	38.4			
GRANULAR CELL TUMOR	0	0	0	1	0	.4852	.	.4889
						.	.	.

**Table A.3.7. Neoplasms in Male Mice**

Organ/ Tumor	Overall Results					Significance		
	H2O	Veh	Low	Med	High	p trend	p high	p med
						vs Veh		
						p low vs Veh	p veh vs H2O	p high vs H2O
ADRENALS								
# Evaluated	65	64	64	63	64			
Adjusted # at risk	49.8	44.0	52.9	46.8	46.3			
CORTEX: ADENOMA	0	1	1	1	1	.5124	.7694	.7694
						.7978	.4674	.4842
Adjusted # at risk	49.8	44.0	52.6	46.6	46.2			
MEDULLA BENIGN PHEOCHROMOCYTOMA	1	0	0	0	0	.	.	.
						.	1	1
BONE (OTHER)								
# Evaluated	7	3	6	4	2			
Adjusted # at risk	3.6	2.4	5.2	3.2	1.9			
OSTEOMA	1	1	0	0	0	1	1	1
						1	.7000	1
Adjusted # at risk	3.4	2.4	5.2	3.8	1.9			
SARCOMA, NOS	0	0	0	1	0	.3636	.	.6000
						.	.	.
FEMORAL MARROW								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	49.8	45.0	54.0	48.4	46.6			
HEMANGIOMA	0	0	1	0	0	.7708	.	.
						.5510	.	.
GALLBLADDER								
# Evaluated	55	58	60	53	59			
Adjusted # at risk	43.4	41.3	50.9	41.0	43.1			
CYSTADENOMA/ADENOMA	0	0	0	2	0	.4861	.	.2407
						.	.	.
Adjusted # at risk	43.4	41.3	50.9	40.8	43.6			
PAPILLOMA	0	0	0	0	2	.0600	.2590	.
						.	.	.2471
HARDERIAN GL								
# Evaluated	65	65	65	64	65			
Adjusted # at risk	51.8	46.5	54.7	47.6	46.6			
ADENOMA	11	11	14	9	4	.9904	.9892	.7912
						.5013	.4861	.9808
Adjusted # at risk	51.8	46.5	54.7	47.6	46.6			
Adenoma/Carcinoma	12	11	14	9	4	.9904	.9892	.7912
						.5013	.5762	.9890
Adjusted # at risk	49.8	45.0	53.6	47.4	46.6			
CARCINOMA	1	0	0	0	0	.	.	.
						.	1	1
LACRIMAL GLAND								
# Evaluated	65	65	65	64	65			
Adjusted # at risk	49.8	45.0	53.6	47.4	46.9			
ADENOMA	0	0	0	0	1	.2421	.5111	.
						.	.	.4842

**Table A.3.7. (cont.) Neoplasms in Male Mice**

Organ/ Tumor	Overall Results					Significance		
	H2O	Veh	Low	Med	High	p trend	p high	p med
							vs Veh	vs Veh/
						p low	p veh	p high
						vs Veh	vs H2O	vs H2O
<b>LIVER</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	49.8	45.0	53.6	48.4	46.6			
HEMANGIOMA	0	0	1	0	0	.7696	.	.
						.5464	.	.
Adjusted # at risk	50.1	45.4	53.8	50.3	46.9			
HEMANGIOSARCOMA	3	2	5	4	1	.8748	.8832	.3903
						.2912	.7846	.9307
Adjusted # at risk	49.9	46.1	54.4	50.4	49.2			
HEPATOCELLULAR ADENOMA	11	13	15	16	10	.8739	.8713	.4307
						.6099	.3389	.6884
Adjusted # at risk	50.2	45.2	54.5	49.4	48.6			
HEPATOCELLULAR CARCINOMA	7	7	11	10	6	.8217	.7651	.3673
						.3627	.5288	.6962
Adjusted # at risk	50.4	46.3	54.7	51.1	50.4			
Hepato. Adenoma/Carcinoma	17	19	23	22	15	.9364	.9148	.5095
						.5295	.2989	.7397
<b>LUNGS</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	50.9	46.6	54.7	49.1	47.4			
BRONCHIOLO/ALVEOLAR ADENOMA	12	8	15	5	6	.8726	.8193	.9065
						.1608	.8527	.9551
Adjusted # at risk	52.2	45.1	55.2	49.9	48.3			
BRONCHIOLO/ALVEOLAR CARCINOMA	10	3	8	9	11	.0436	.0269	.0810
						.1766	.9850	.4177
Adjusted # at risk	53.3	46.8	55.7	50.4	49.1			
Bronch. Alv. Adenoma/Carc.	21	10	20	12	16	.2696	.1681	.4927
						.0827	.9842	.8257
<b>LYMPH/RETIC SYS</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	50.6	45.2	54.6	49.7	46.7			
HISTIOCYTIC SARCOMA	3	1	2	3	1	.5971	.7582	.3414
						.5687	.9277	.9307
Adjusted # at risk	54.6	51.8	56.4	51.7	50.2			
MALIGNANT LYMPHOMA	14	17	8	6	10	.5479	.9595	.9981
						.9950	.2684	.8287
<b>MESENTERIC LN</b>								
# Evaluated	65	63	64	64	61			
Adjusted # at risk	49.8	43.5	52.6	48.3	43.8			
HEMANGIOSARCOMA	0	0	0	1	0	.4892	.	.5275
						.	.	.
<b>MUSCLE (OTHER)</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	50.0	45.0	53.6	48.4	46.6			
HEMANGIOSARCOMA	1	0	0	0	0	.	.	.
						.	1	1
Adjusted # at risk	49.8	45.0	53.6	48.4	46.6			
RHABDOMYOSARCOMA	0	0	0	1	0	.4921	.	.5217
						.	.	.

**Table A.3.7. (cont.) Neoplasms in Male Mice**

Organ/ Tumor	Overall Results					Significance		
	H2O	Veh	Low	Med	High	p trend	p high	p med
							vs Veh	vs Veh/
						p low	p veh	p high
						vs Veh	vs H2O	vs H2O
<b>MUSCLE PROTOCOL</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	50.0	45.0	53.6	48.4	46.6			
HEMANGIOSARCOMA	1	0	0	0	0	.	.	.
						.	1	1
<b>PANCREAS</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	49.8	45.0	53.6	48.6	46.6			
ISLET CELL ADENOMA	1	1	0	1	0	.7434	1	.7740
						1	.7251	1
<b>PROSTATE</b>								
# Evaluated	65	65	63	65	65			
Adjusted # at risk	49.8	45.0	51.6	48.6	46.6			
CARCINOMA	0	0	0	1	0	.4974	.	.5217
						.	.	.
<b>SKIN</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	50.0	45.0	54.0	48.4	46.6			
CARCINOMA	1	0	1	0	1	.3123	.5111	.
						.5510	1	.7366
Adjusted # at risk	49.8	45.0	53.6	48.4	46.6			
FIBROSARCOMA	0	0	1	0	0	.7696	.	.
						.5464	.	.
Adjusted # at risk	49.8	45.0	53.6	48.4	46.6			
HISTIOCYTOMA	0	0	0	1	0	.4921	.	.5217
						.	.	.
Adjusted # at risk	49.8	45.1	53.6	48.4	46.6			
SCHWANNOMA	0	1	0	0	1	.4227	.7582	1
						1	.4787	.4842
<b>SPLEEN</b>								
# Evaluated	64	65	64	65	65			
Adjusted # at risk	48.8	45.2	52.6	48.4	46.6			
HEMANGIOMA	0	1	0	0	0	1	1	1
						1	.4839	.
<b>STOMACH</b>								
# Evaluated	65	65	64	64	64			
Adjusted # at risk	50.2	45.0	52.9	48.2	46.6			
GLANDULAR MUCOSA: ADENOMA	1	0	0	0	0	.	.	.
						.	1	1
<b>Systemic</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	49.8	45.2	54.0	48.4	46.6			
HEMANGIOMA	0	1	2	0	0	.9427	1	1
						.5687	.4787	.
Adjusted # at risk	50.4	45.4	53.8	50.3	46.9			
HEMANGIOSARCOMA	4	2	5	4	1	.8748	.8832	.3903
						.2912	.8720	.9653
Adjusted # at risk	50.4	45.4	54.2	50.3	46.9			
Hemangioma/Hemangiosarcoma	4	2	7	4	1	.9265	.8832	.3903
						.1314	.8720	.9653

**Table A.3.7. (cont.) Neoplasms in Male Mice**

Organ/ Tumor	Overall Results					Significance		
	H2O	Veh	Low	Med	High	p trend	p high vs Veh	p med vs Veh/ p high vs H2O
<b>TESTES</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	50.0	45.0	53.6	48.4	46.7			
BENIGN INTERSTITIAL CELL TUMOR	1	1	0	2	1	.3536	.7638	.5330
						1	.7251	.7366
<b>THYROID</b>								
# Evaluated	65	65	64	65	61			
Adjusted # at risk	49.8	45.0	53.0	48.4	45.6			
FOLLICULAR CELL ADENOMA	0	0	1	0	1	.3083	.5056	.
						.5464	.	.4787
<b>ZYMBAL'S GLAND</b>								
# Evaluated	0	0	1	0	0			
Adjusted # at risk	0.0	0.0	1.0	0.0	0.0			
CARCINOMA	0	0	1	0	0	1	.	.
						.	.	.

**Table A.3.8. Neoplasms in Female Mice**

Organ/ Tumor	Overall Results					Significance		
	H2O	Veh	Low	Med	High	p trend	p high vs Veh	p med vs Veh/ p high vs H2O
<b>ADRENALS</b>								
# Evaluated	65	64	65	64	65			
Adjusted # at risk	42.2	46.1	43.7	41.6	36.8			
CORTEX: ADENOMA	0	2	0	1	0	.8483	1	.8568
						1	.2704	.
Adjusted # at risk	42.2	45.8	43.7	41.7	36.8			
CORTEX: CARCINOMA	0	0	0	1	0	.4667	.	.4767
						.	.	.
Adjusted # at risk	42.2	46.1	43.7	41.7	36.8			
Cortex:Adenoma/Carcinoma	0	2	0	2	0	.7673	1	.6471
						1	.2704	.
<b>BONE (OTHER)</b>								
# Evaluated	3	3	0	3	1			
Adjusted # at risk	2.0	3.0	0.0	0.6	1.0			
OSTEOMA	0	3	0	0	0	1	1	.
						.	.1000	.
<b>DISTAL FEMUR</b>								
# Evaluated	64	64	65	65	65			
Adjusted # at risk	41.6	45.7	43.7	41.8	36.8			
OSTEOMA	0	1	0	0	0	1	1	1
						1	.5233	.
<b>FEMORAL MARROW</b>								
# Evaluated	65	64	65	65	65			
Adjusted # at risk	42.4	45.7	43.7	41.8	36.8			
HEMANGIOMA	1	0	0	0	0	.	.	.
						.	1	1

**Table A.3.8. (cont.) Neoplasms in Female Mice**

Organ/ Tumor	Overall Results					Significance		
	H2O	Veh	Low	Med	High	p trend	p high vs Veh	p med vs Veh/ vs H2O
<b>GALLBLADDER</b>								
# Evaluated	57	58	60	60	58			
Adjusted # at risk	37.6	43.5	40.2	38.0	33.0			
CYSTADENOMA/ADENOMA	0	0	1	0	0	.7190	.	.
						.4819	.	.
Adjusted # at risk	37.6	43.5	40.1	38.0	33.0			
PAPILLOMA	0	1	0	0	0	1	1	1
						1	.5375	.
<b>HARDERIAN GL</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	43.4	49.1	44.9	43.2	39.2			
ADENOMA	4	10	5	7	9	.1799	.4812	.7810
						.9301	.1166	.0800
<b>HEART</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.6	46.6	43.7	41.8	36.8			
ENDOCARDIAL SCHWANNOMA	1	0	0	0	0	.	.	.
						.	1	1
Adjusted # at risk	42.2	46.6	43.7	41.8	36.8			
HEMANGIOSARCOMA	0	0	1	0	0	.7229	.	.
						.4831	.	.
<b>LIVER</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.9	46.6	43.8	41.8	36.8			
HEMANGIOSARCOMA	1	0	1	0	0	.7229	.	.
						.4831	1	1
Adjusted # at risk	42.2	46.6	43.7	41.8	37.3			
HEPATOCELLULAR ADENOMA	0	0	0	0	1	.2216	.4458	.
						.	.	.4684
Adjusted # at risk	42.2	46.6	43.7	41.8	36.8			
HEPATOCELLULAR CARCINOMA	0	0	0	0	1	.2169	.4390	.
						.	.	.4615
Adjusted # at risk	42.2	46.6	43.7	41.8	37.3			
Hepato. Adenoma/Carcinoma	0	0	0	0	2	.0480	.1957	.
						.	.	.2162
<b>LUNGS</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	43.5	46.6	43.8	44.3	38.1			
BRONCHIOLO/ALVEOLAR ADENOMA	8	0	4	8	5	.1456	.0163	.0023
						.0505	1	.8336
Adjusted # at risk	43.0	48.4	44.8	43.6	37.6			
BRONCHIOLO/ALVEOLAR CARCINOMA	2	4	5	5	2	.7792	.8271	.4295
						.4441	.3925	.6333
Adjusted # at risk	43.8	48.4	44.9	46.1	38.9			
Bronch. Alv. Adenoma/Carc.	9	4	9	12	7	.3837	.1434	.0210
						.0854	.9789	.7118



**Table A.3.8. (cont.) Neoplasms in Female Mice**

Organ/ Tumor	Overall Results					Significance		
	H2O	Veh	Low	Med	High	p trend	p high	p med
							vs Veh	vs Veh/
						p low	p veh	p high
						vs Veh	vs H2O	vs H2O
<b>LYMPH/RETIC SYS</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.9	47.5	45.1	44.5	38.4			
HISTIOCYTIC SARCOMA	2	3	3	6	4	.2781	.3813	.2104
						.6405	.5538	.2908
Adjusted # at risk	54.3	53.0	46.2	46.6	46.1			
MALIGNANT LYMPHOMA	27	16	9	14	19	.0356	.1908	.6000
						.9343	.9869	.8579
<b>MAMMARY AREAS</b>								
# Evaluated	65	64	65	65	64			
Adjusted # at risk	42.2	46.5	43.7	41.9	37.2			
ADENOCARCINOMA	0	0	0	1	1	.1575	.4458	.4713
						.	.	.4684
<b>MESENTERY/PERITO</b>								
# Evaluated	2	4	1	2	2			
Adjusted # at risk	0.5	2.6	1.0	1.6	1.5			
MALIGNANT MESOTHELIOMA	0	0	1	0	0	.6000	.	.
						.3333	.	.
<b>OVARIES</b>								
# Evaluated	64	65	65	65	64			
Adjusted # at risk	41.6	46.8	43.7	41.8	36.1			
ADENOCARCINOMA	0	1	0	0	0	1	1	1
						1	.5287	.
Adjusted # at risk	41.9	46.6	43.7	41.8	36.1			
BENIGN GRANULOSA CELL TUMOR	1	0	0	0	0	.	.	.
						.	1	1
Adjusted # at risk	41.6	46.6	43.7	41.8	36.1			
CYSTADENOMA	0	2	0	0	1	.5221	.8286	1
						1	.2767	.4675
Adjusted # at risk	41.9	46.6	43.8	41.8	36.1			
TUBULOSTROMAL ADENOMA	3	0	1	0	1	.2668	.4390	.
						.4831	1	.9252
<b>PANCREAS</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.2	46.6	43.7	41.8	36.8			
ISLET CELL ADENOMA	0	0	0	1	0	.4639	.	.4713
						.	.	.
<b>PITUITARY</b>								
# Evaluated	64	65	64	64	65			
Adjusted # at risk	41.7	46.6	43.6	41.6	36.8			
PARS DISTALIS-ADENOMA	0	0	2	0	1	.3773	.4390	.
						.2306	.	.4675

**Table A.3.8. (cont.) Neoplasms in Female Mice**

Organ/ Tumor	Overall Results					Significance		
	H2O	Veh	Low	Med	High	p trend	p high	p med
							vs Veh	vs Veh/ vs H2O
<b>SKIN</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.2	46.6	44.3	41.8	36.8			
CARCINOMA	0	1	1	0	0	.9253	1	1
						.7416	.5227	.
Adjusted # at risk	42.2	46.6	43.7	41.8	36.8			
FIBROSARCOMA	1	0	0	0	0	.	.	.
						.	1	1
Adjusted # at risk	42.2	46.6	43.7	41.8	37.2			
HEMANGIOSARCOMA	0	0	0	0	1	.2216	.4458	.
						.	.	.4684
Adjusted # at risk	42.3	46.7	43.7	41.8	36.8			
SARCOMA NOT OTHERWISE SPECIFIED	1	1	0	0	0	1	1	1
						1	.7751	1
Adjusted # at risk	42.2	46.6	43.7	42.0	36.8			
SCHWANNOMA	0	0	0	1	0	.4639	.	.4713
						.	.	.
Adjusted # at risk	42.6	46.6	43.7	41.8	36.8			
SEBACEOUS CELL ADENOMA	1	0	0	0	0	.	.	.
						.	1	1
<b>SPLEEN</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.4	46.8	43.7	42.1	37.3			
HEMANGIOSARCOMA	2	1	0	1	1	.3416	.6959	.7296
						1	.8954	.8548
<b>STERNUM</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.4	46.6	43.7	41.8	36.8			
OSTEOGENIC SARCOMA	1	0	0	0	0	.	.	.
						.	1	1
<b>STOMACH</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.2	46.6	43.7	42.1	36.8			
FORESTOMACH: SQUAMOUS CELL CARCI	0	0	0	1	0	.4671	.	.4773
						.	.	.
Adjusted # at risk	42.2	46.6	43.7	42.4	36.8			
GLANDULAR MUCOSA: ADENOMA	0	0	0	1	1	.1545	.4390	.4773
						.	.	.4615
<b>Systemic</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.4	46.8	44.4	41.8	37.3			
HEMANGIOMA	1	1	3	1	1	.6277	.6959	.7233
						.2916	.7751	.7205
Adjusted # at risk	43.1	46.8	43.8	42.1	37.7			
HEMANGIOSARCOMA	3	1	2	1	2	.2795	.4180	.7296
						.4744	.9495	.7700
Adjusted # at risk	43.1	46.9	44.4	42.1	38.1			
Hemangioma/Hemangiosarcoma	3	2	5	2	3	.4258	.4091	.6566
						.1990	.8400	.6012

**Table A.3.8. (cont.) Neoplasms in Female Mice**

Organ/ Tumor	Overall Results					Significance		
	H2O	Veh	Low	Med	High	p trend	p high	p med
							vs Veh	vs Veh/
						p low	p veh	p high
						vs Veh	vs H2O	vs H2O
<b>THYROID</b>								
# Evaluated	65	65	65	65	63			
Adjusted # at risk	42.2	46.6	43.7	41.8	36.3			
FOLLICULAR CELL ADENOMA	0	0	0	1	1	.1538	.4390	.4713
						.	.	.4615
<b>UTERUS W/ CERVIX</b>								
# Evaluated	65	65	65	65	65			
Adjusted # at risk	42.2	46.6	44.5	41.8	36.8			
BENIGN GRANULAR CELL TUMOR	0	0	1	0	0	.7246	.	.
						.4889	.	.
Adjusted # at risk	42.2	47.1	43.7	41.8	36.8			
ENDOMETRIAL CARCINOMA	0	1	0	1	0	.7111	1	.7176
						1	.5281	.
Adjusted # at risk	43.3	47.6	43.8	44.4	38.6			
ENDOMETRIAL STROMAL POLYP	2	5	4	9	7	.1617	.2379	.1572
						.7109	.2556	.0524
Adjusted # at risk	43.2	46.8	43.7	41.8	36.8			
ENDOMETRIAL STROMAL SARCOMA	2	1	0	0	0	1	1	1
						1	.8913	1
Adjusted # at risk	43.7	47.8	43.8	44.4	38.6			
Endo.Stromal Polyp/Sarcoma	3	6	4	9	7	.1997	.3366	.2405
						.8035	.2891	.1104
Adjusted # at risk	42.8	46.6	43.7	41.8	36.8			
GRANULAR CELL TUMOR	1	0	0	0	0	.	.	.
						.	1	1
Adjusted # at risk	42.2	46.8	44.4	41.8	37.3			
HEMANGIOMA	0	1	3	1	1	.6277	.6959	.7233
						.2916	.5227	.4684
Adjusted # at risk	42.2	46.6	43.7	42.1	36.8			
HEMANGIOSARCOMA	0	0	0	1	0	.4671	.	.4773
						.	.	.
Adjusted # at risk	42.2	46.6	44.5	42.1	36.9			
LEIOMYOMA	1	0	2	4	1	.4748	.4390	.0480
						.2362	1	.7133
Adjusted # at risk	42.7	46.6	43.7	43.9	37.5			
LEIOMYOSARCOMA	1	0	0	3	1	.2228	.4458	.1087
						.	1	.7205
Adjusted # at risk	42.7	46.6	44.5	44.1	37.6			
Leiomyoma/Leiomyosarcoma	2	0	2	7	2	.4390	.1957	.0051
						.2362	1	.6428

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STEVEN F THOMSON

03/18/2013

Statistical carcinogenicity Review

KARL K LIN

03/18/2013

Concur with review

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number: 204790**

**Applicant: ViiV Healthcare**

**Stamp Date: 12/17/2012**

**Drug Name: Dolutegravir**

**NDA/BLA Type: NDA**

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

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

**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.

<b>Content Parameter (possible review concerns for 74-day letter)</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	X			
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

File name: 5\_Statistics Filing Checklist for a New NDA\_BLA110207

**STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA**

Thomas Hammerstrom	1/24/13
Reviewing Statistician	Date
Greg Soon	
Supervisor/Team Leader	Date



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THOMAS S HAMMERSTROM  
01/24/2013

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01/31/2013