STATISTICAL REVIEW AND EVALUATION

NDA#:	204790 SDN 001
DRUG NAME:	Dolutegravir
INDICATION:	Treatment of HIV Infection
TYPE OF REVIEW:	Clinical
APPLICANT:	ViiV Healthcare
DATES:	Dec 11, 2012
REVIEW PRIORITY:	Priority
BIOMETRICS DIVISION:	Division of Biometrics IV
STATISTICAL REVIEWER:	Thomas Hammerstrom, (HFD-725)
TEAM LEADER:	Greg Soon, PhD, (HFD-725)
MEDICAL DIVISION:	DAVDP
CLINICAL TEAM:	Charu Mullick, MD (HFD-530), Wendy Carter, M.D. (HFD-530)
PROJECT MANAGER:	Sohail Mosaddegh, (HFD-530)

STATISTICAL REVIEW AND EVALUATION

NDA#: 71582

4.1.2 Two Class Resistant INI Naïve Trial
4.1.3 Two Class Resistant, INI Resistant Trials
4.2 Baseline HIV, CD4, CDC Class
4.2.1 Treatment Naïve Trials
4.2.2 Two Class Resistant INI Naïve Trials
4.2.3 Two Class Resistant, INI Resistant Trials
4.3 Demographic Covariates
4.3.1 Treatment Naïve Trials
4.3.2 Two Class Resistant INI Naïve Trial
4.1.3 Two Class Resistant, INI Resistant Trials
4.4 Prior ART Exposure Covariates
4.4.1 Two Class Resistant INI Naïve Trials
4.4.2 Two Class Resistant INI Resistant Trials
4.5 Baseline Resistance Covariates
4.5.1 Two Class Resistant INI Naïve Trial: Baseline Sensitivity Scores
4.5.2 Two Class Resistant, INI Resistant Trial: Small Trial
4.5.2.1 Baseline Mutations
4.5.2.2 Baseline Fold Change in Resistance
4.5.2.3 Baseline Sensitivity Scores
4.5.3 Two Class Resistant, INI Resistant Trial: Pivotal Trial
4.5.3.1 Baseline INI Exposure
4.5.3.2 Baseline Mutations
4.5.3.3 Baseline Fold Change in Resistance
4.5.3.4 Baseline Sensitivity Scores
4.5.3.5 Miscellaneous
4.4 Exploratory Looks for Treatment-Covariate Interactions
4.4.1 Treatment Naïve Trials
4.4.2 Two Class Resistant INI Naïve Trial
4.4.3 Two Class Resistant, INI Resistant Trials
5. Summary and Conclusions:

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 12 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 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	% IN CDC CLASS C	MEDIAN BASELINE HIV-1 RNA	MEDIAN BASELINE 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 Ultrasensitve 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	50mg bid
Day Analyzed	11	11	8
% Success	21/27=78%	23/24=96%	.
95% Limits	58%-91%	79%-99%	
Mean Change	-1.45	-1.76	-1.43
95% Limits	-2.96,-.06	-2.82,-.70	-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	50mg bid
Week_24	11/27=41%	19/23=79%	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%
		FDA	124/196=63.3%	109/201=54.2%
Viking	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%
		Summary Data	17/24=70.8%	9/27=33.3%
		FDA	16/24=66.7%	9/27=33.3%
Viking 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 DIFF	95% LIMITS LOWER	UPPER	DTG_50mg	CONTROL
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 Kozyrev)

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 Kozyrev)

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.

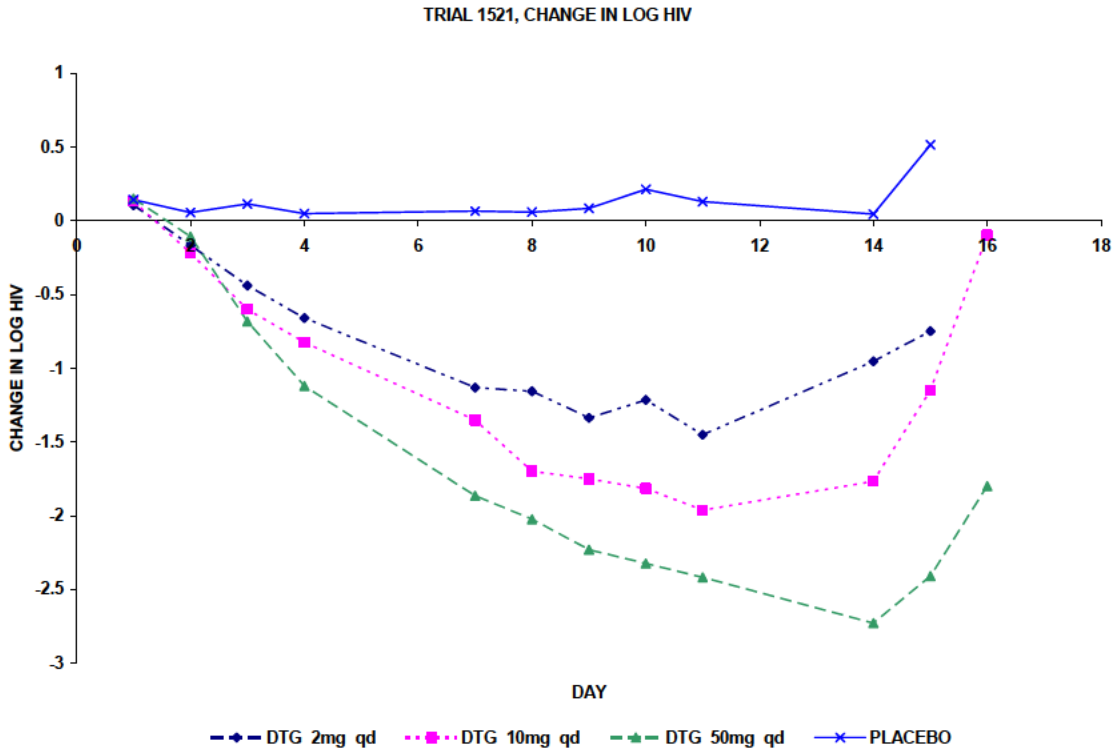
In trial Sailing in two class resistant subjects, the DTG 50mg QD arm was intermittently statistically significantly superior to the RAL arm with respect to both change in log HIV and percent BLQ. With respect to percent BLQ where there is an agreed margin of clinical non-inferiority, DTG 50mg QD was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

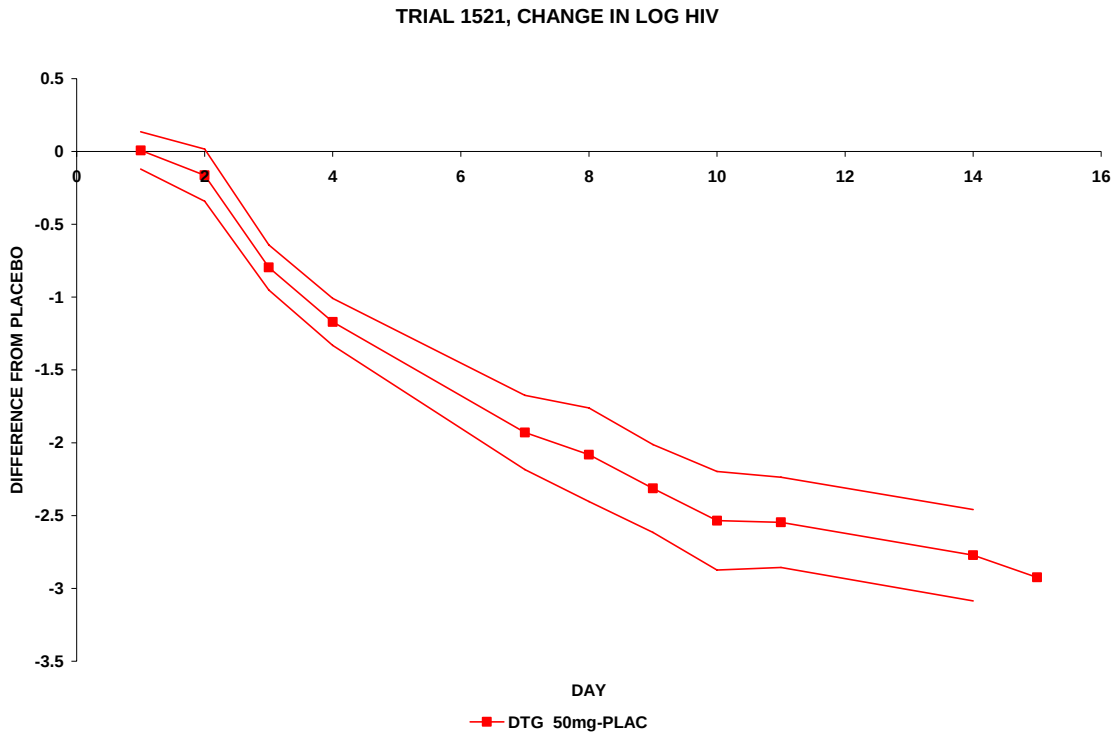
In the Viking 3 trial, where there a one sample comparison to a constant response of zero, statistically significant superiority was achieved with respect to both log change and percent BLQ throughout the period of observation. In fact, the magnitude of the improvement is comparable to what one expects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

3.2.1 Treatment Naïve Trials

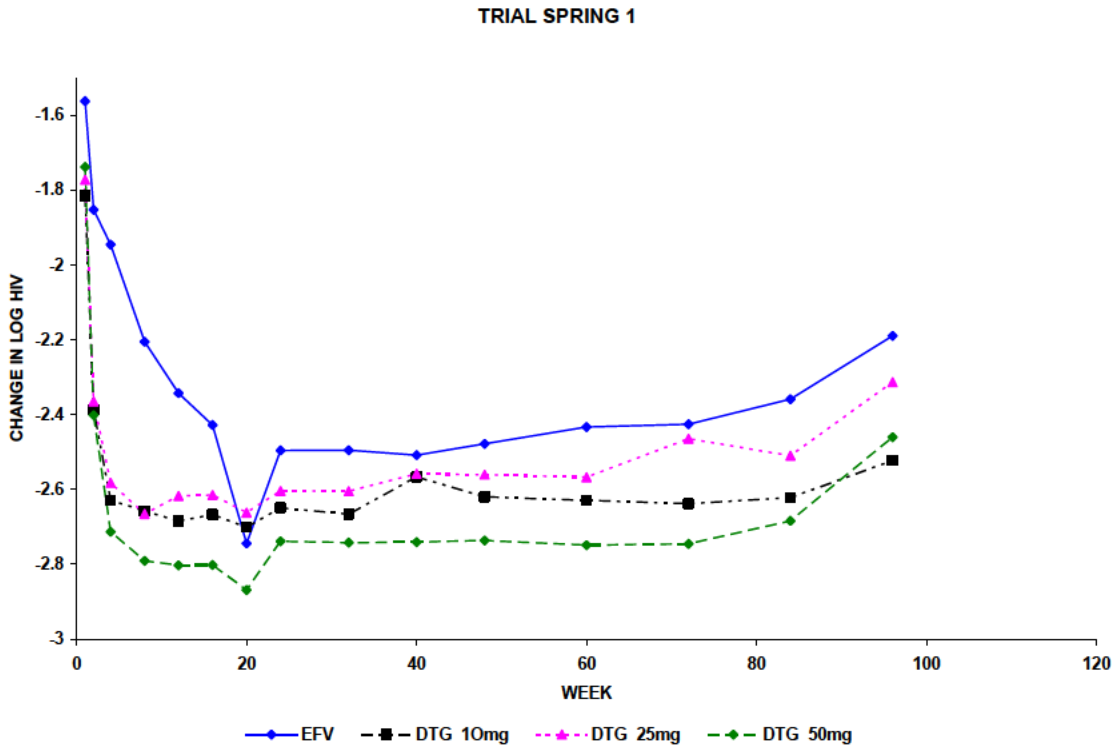
The first graph shows the change in log HIV for the four arms of trial 1521 with the superiority of all four doses over placebo readily apparent.



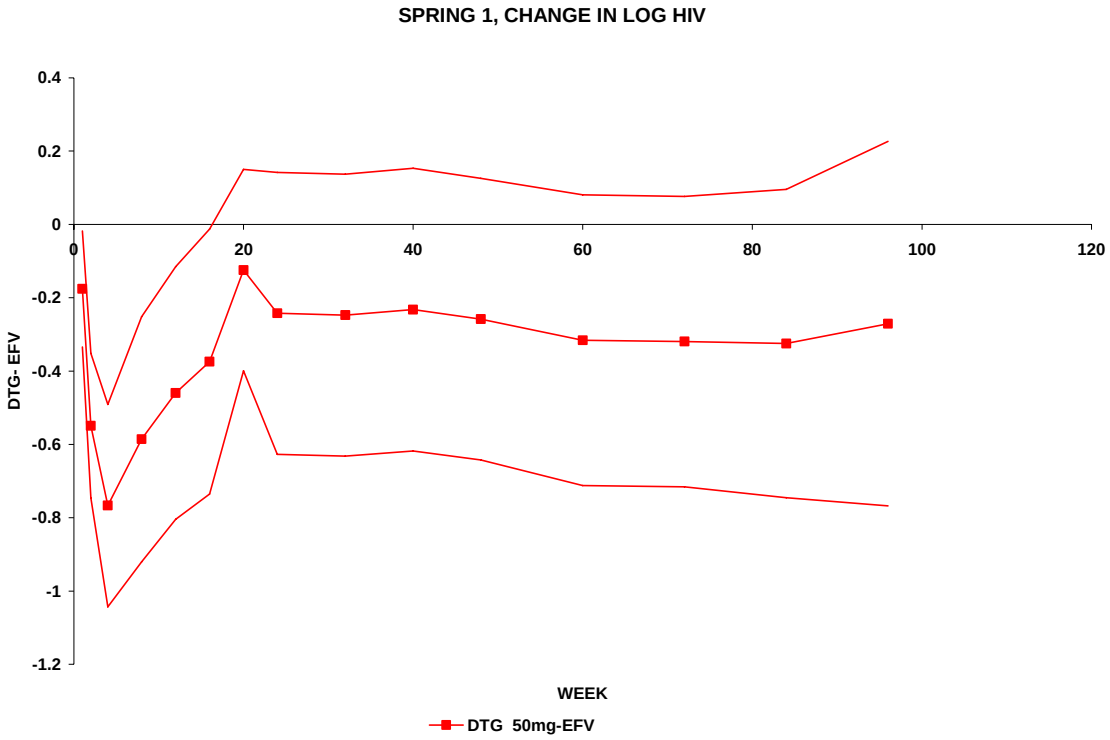
The second graph shows the point estimates and 95% confidence limits for the difference between DTG_50mg and placebo. Negative values correspond to larger decreases so the statistical superiority of DTG to placebo is again readily apparent.



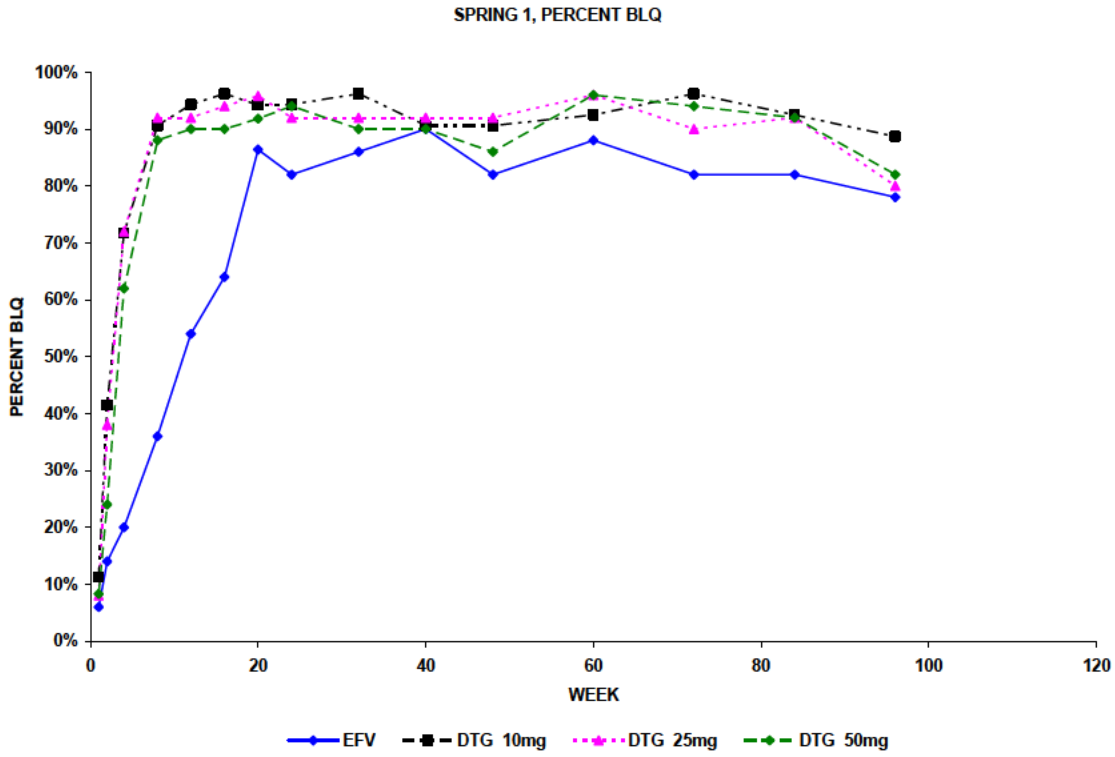
The next graph shows the time course of change in log HIV for the Spring 1 trial. The EFV control does most poorly of the four arms although it does clearly reduce viral load. The 50 mg dose of DTG is the best of the four arms.



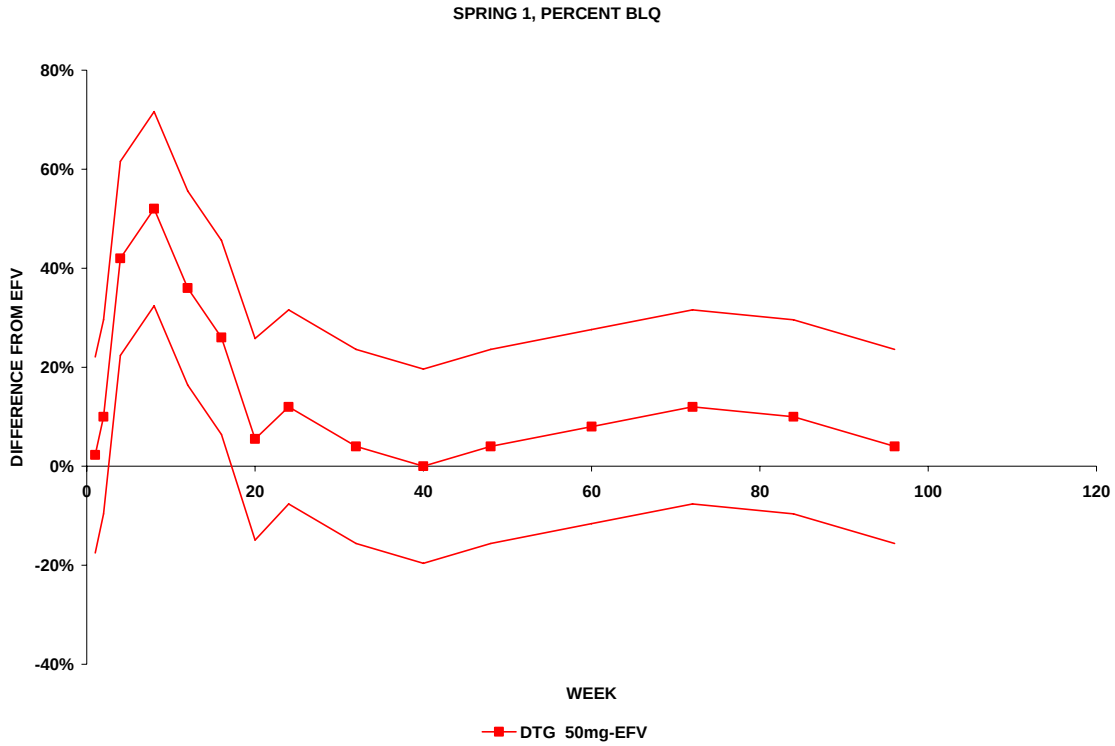
The next graph shows the point estimates and 95% confidence limits for the difference in log change between 50mg DTG and EFV. One can see that the DTG superiority is not quite statistically significant but is maintained in the long term.



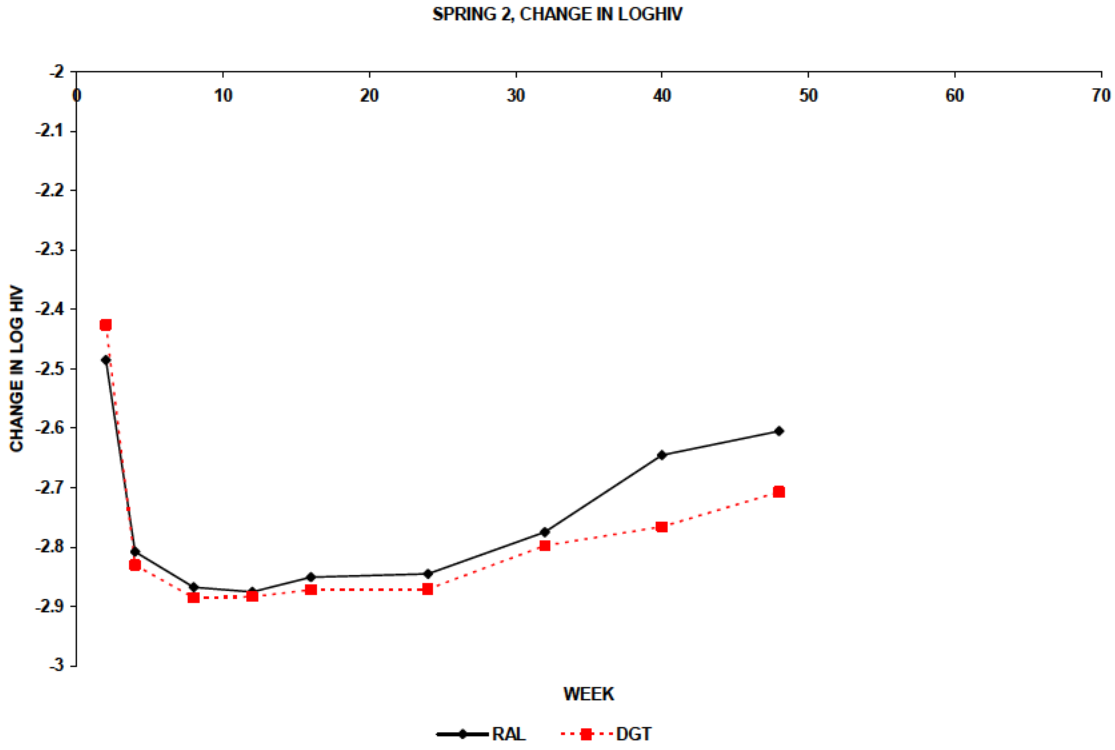
The next graph shows the percent BLQ over time in Spring 1. Interestingly, all three DTG doses seem to do equally well and slightly, but not statistically significantly, better than EFV.

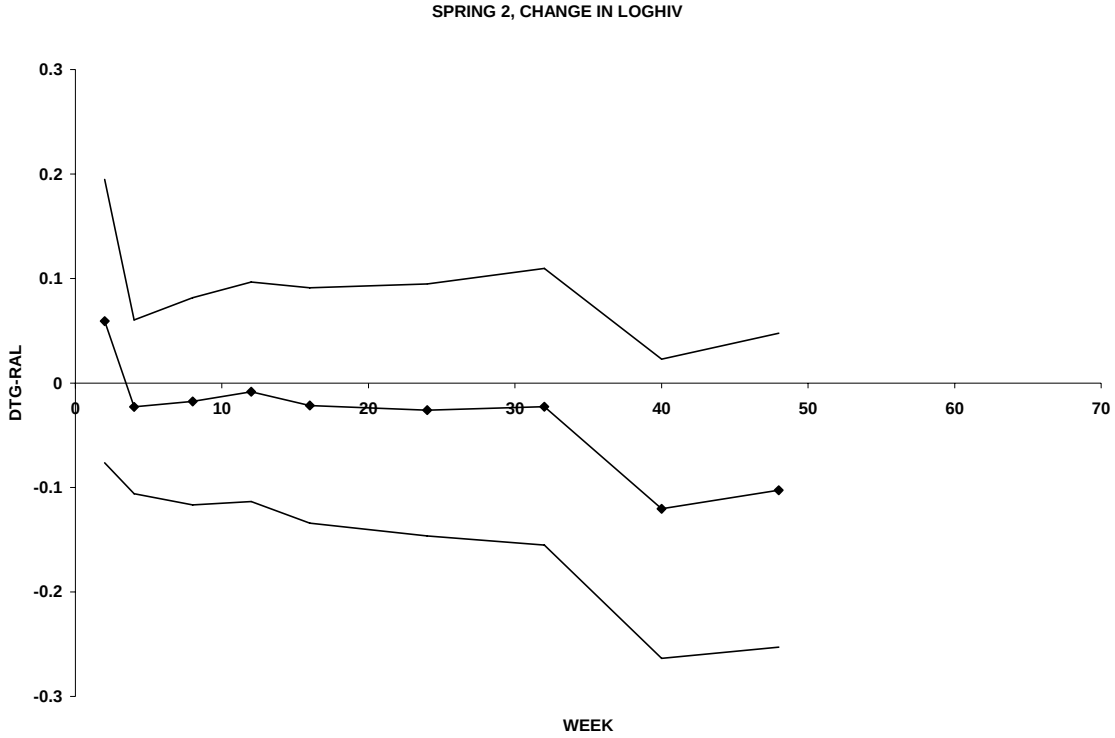


This graph gives the point estimates and 95% confidence limits for the difference between 50mg DTG and EFV in %BLQ. The lower bound is not quite >-10% and thus not quite high enough for statistical non-inferiority.

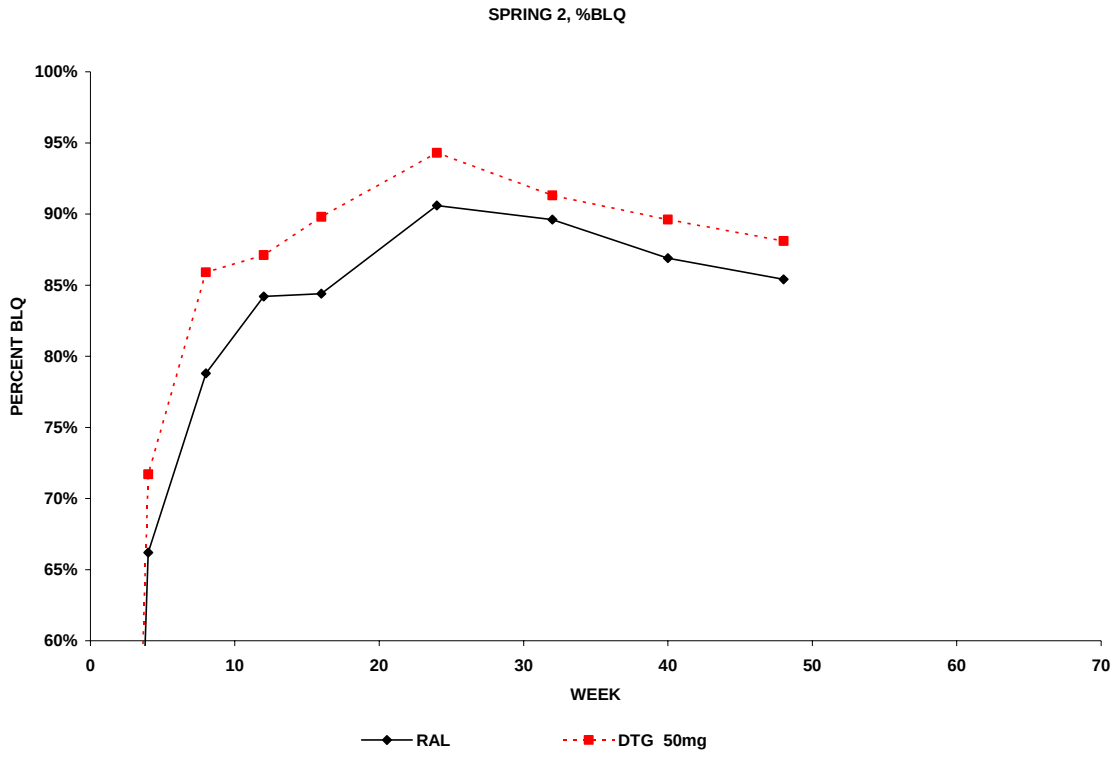


The next two graphs show the change in log HIV in the DTG and RAL arms of Spring 2 and the point estimates and 95% confidence intervals for the DTG-RAL difference in change in log HIV.

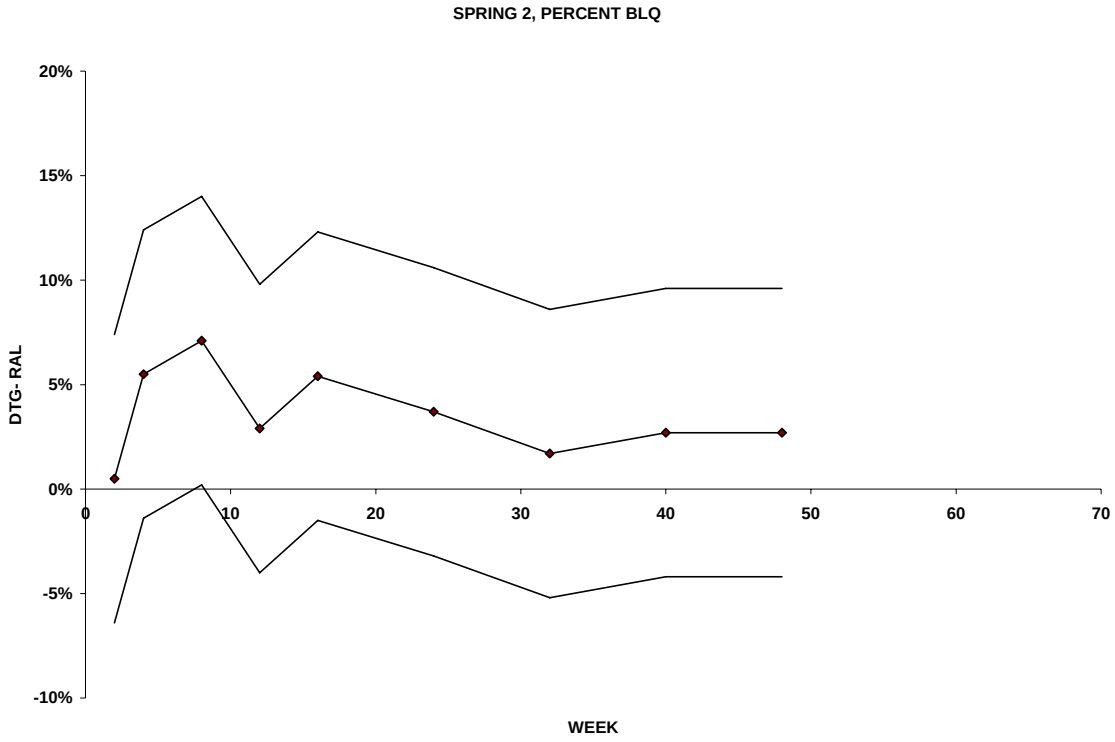



SPRING 2, CHANGE IN LOGHIV
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
DTG-RAL
0
10
20
30
40
50
60
70
WEEK

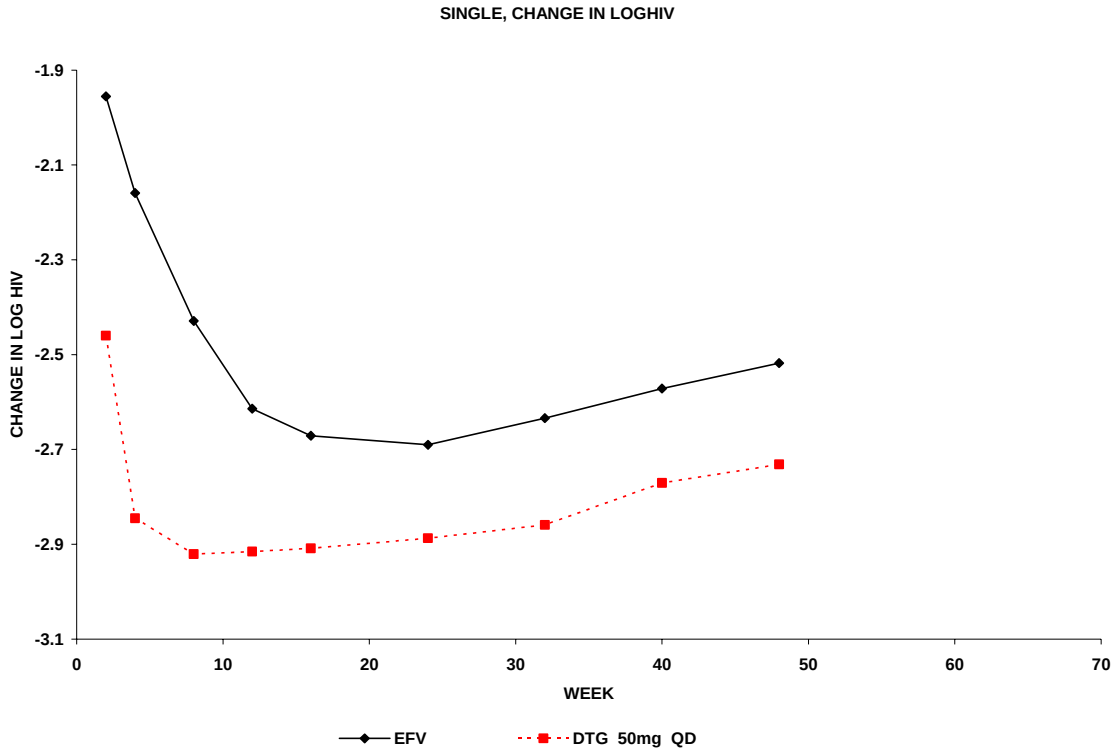
The next two graphs will show the %BLQ for the DTG and RAL arms in trial Spring 2 and the point estimates and 95% confidence limits for their difference.



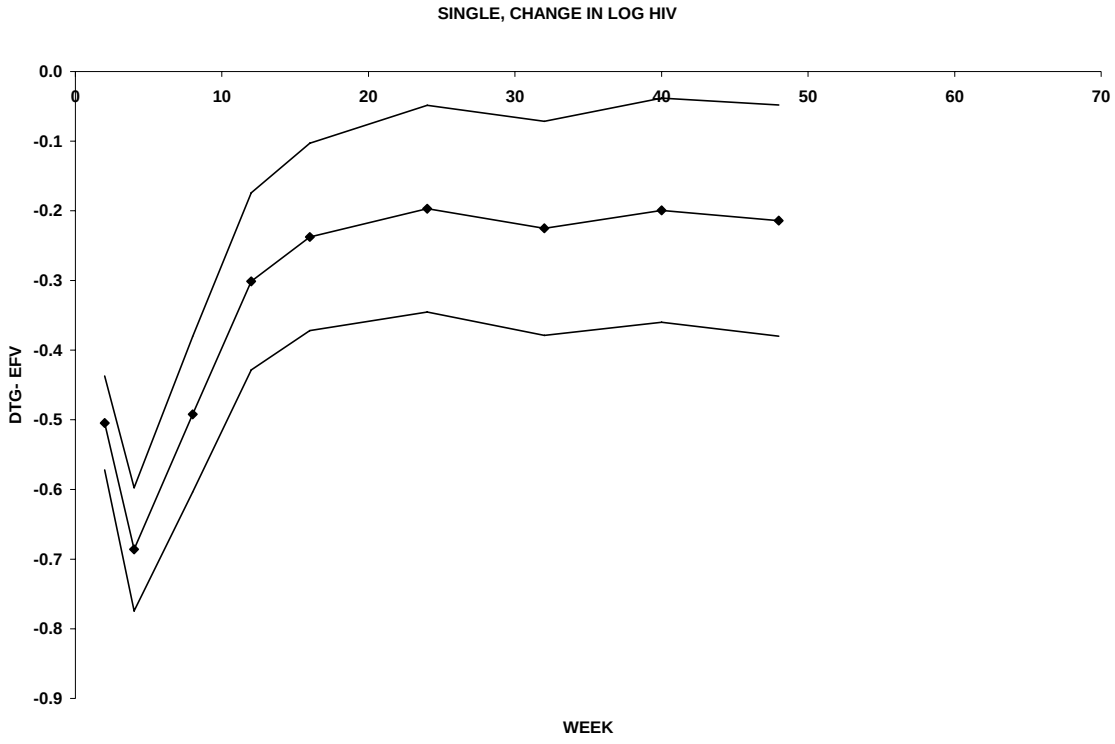
In this graph of the 95% confidence limits around the DTG-RAL difference, one does see that the lower bound exceeds -10%, providing statistically convincing evidence of non-inferiority throughout the first 48 weeks.

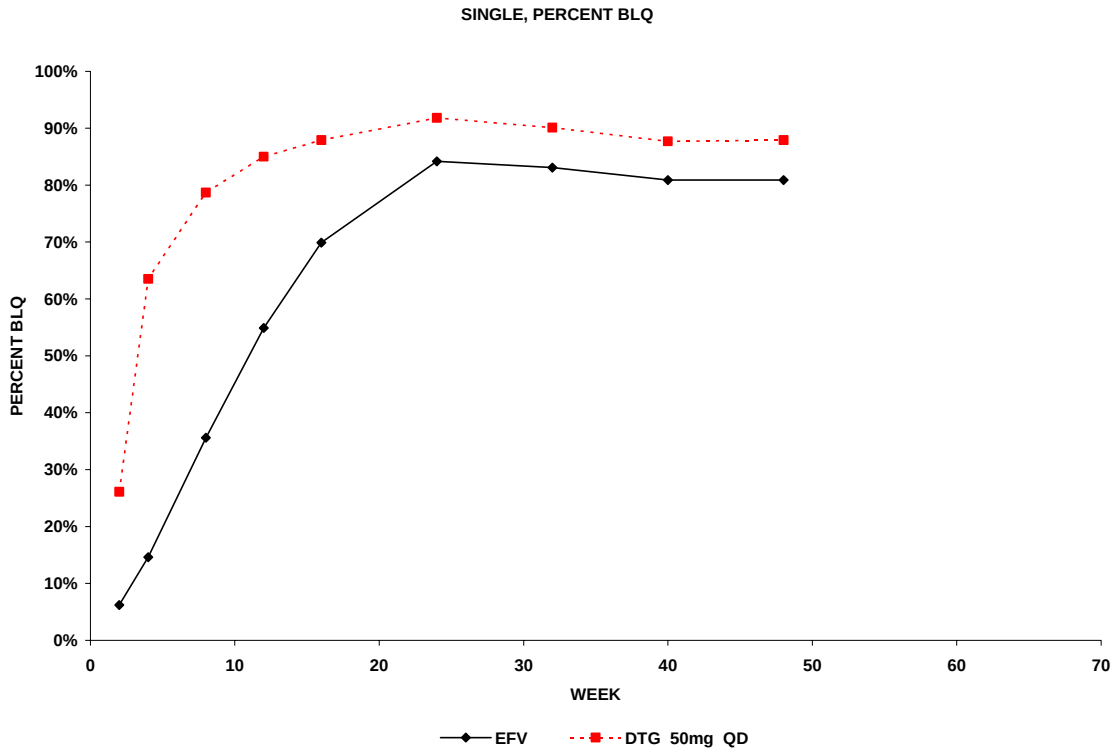


The next four graphs will repeat the previous four graphs for the other pivotal trial in treatment naïve subjects, Single. Change in log HIV and the 95% limits for change in log HIV are given first.

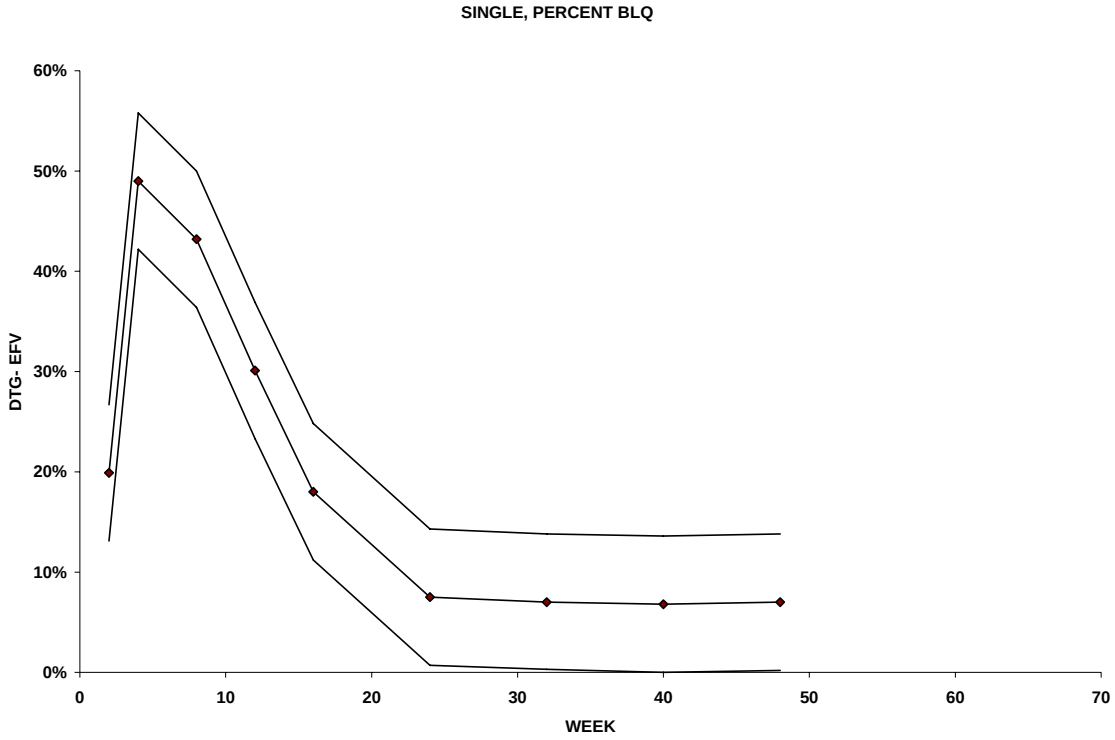


It is important to notice that the DTG 50mg QD arm was statistically significantly superior to the EFV arm throughout the first 48 weeks. Recall negative values in the difference correspond to larger decrease in viral load with DTG.



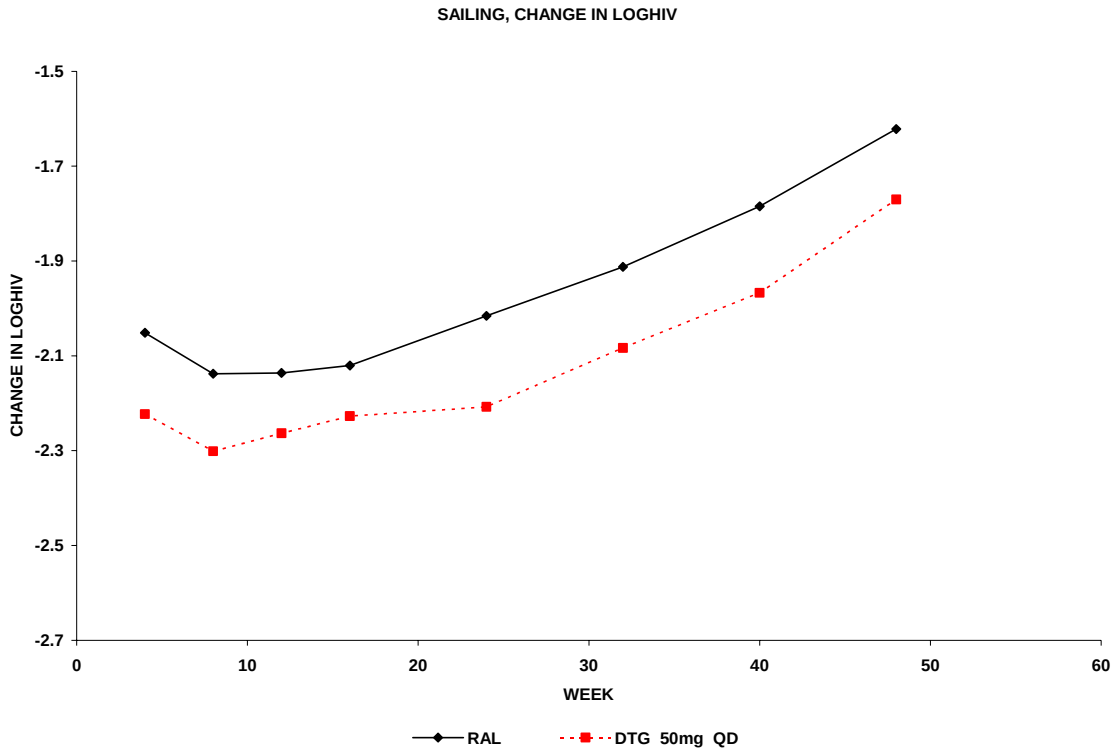

SINGLE, PERCENT BLQ
PERCENT BLQ
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
10
20
30
40
50
60
70
WEEK
EFV
DTG 50mg QD

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

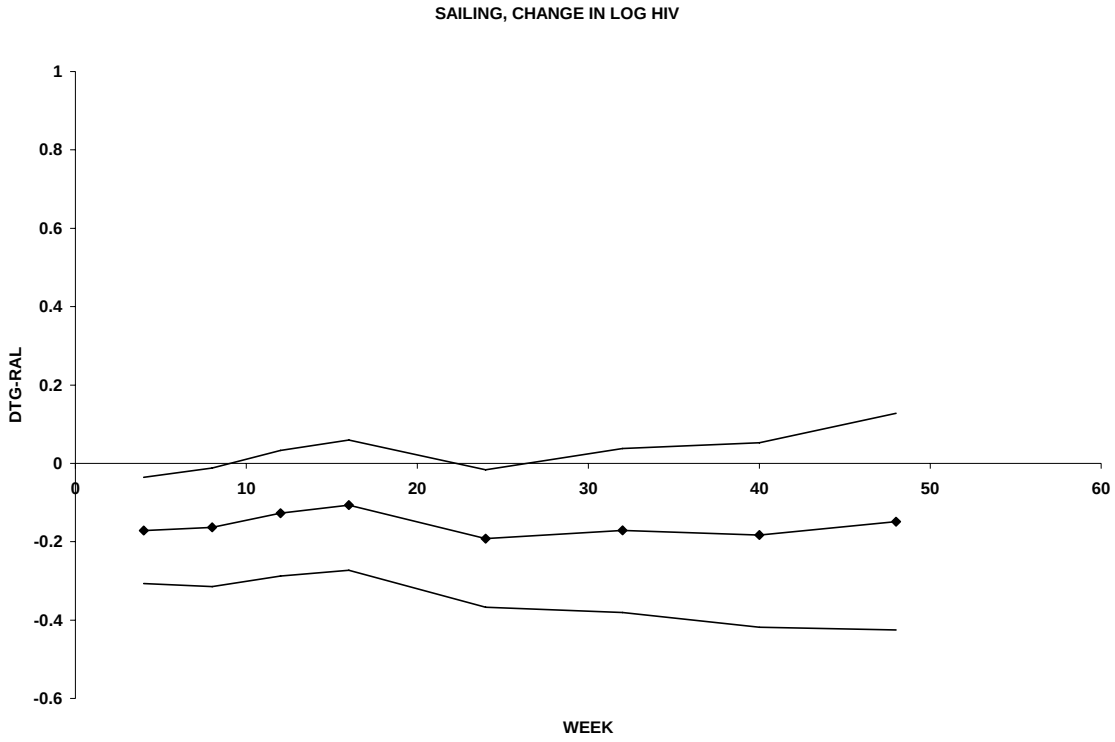


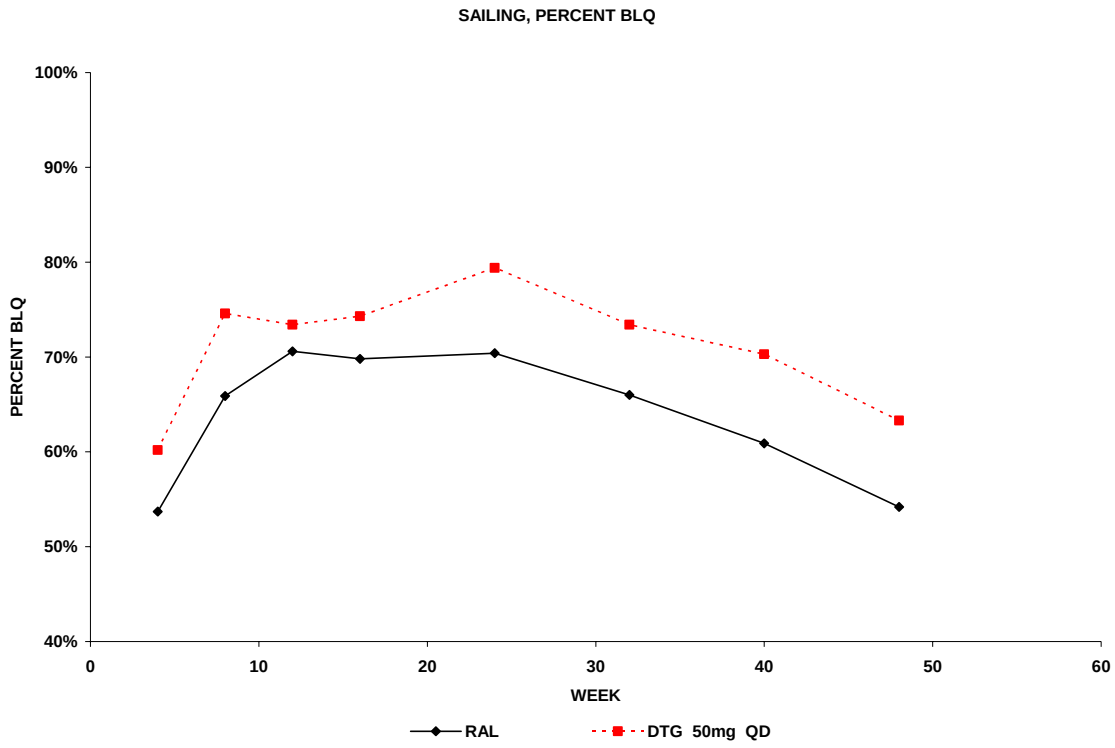
3.2.2 Two Class Resistant INI Naïve Trials

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.

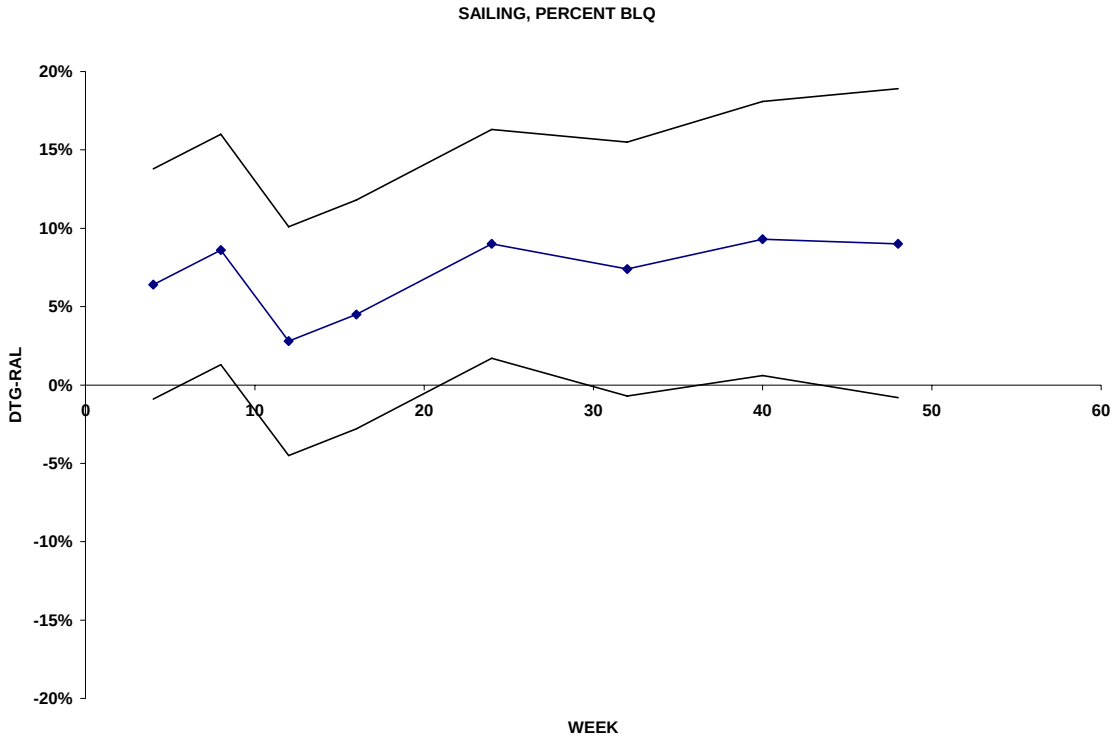


It is worth noting in this graph of the 95% confidence limits on the difference in the change in log HIV that the DTG 50mg QD arm is intermittently statistically significantly superior to the RAL arm.



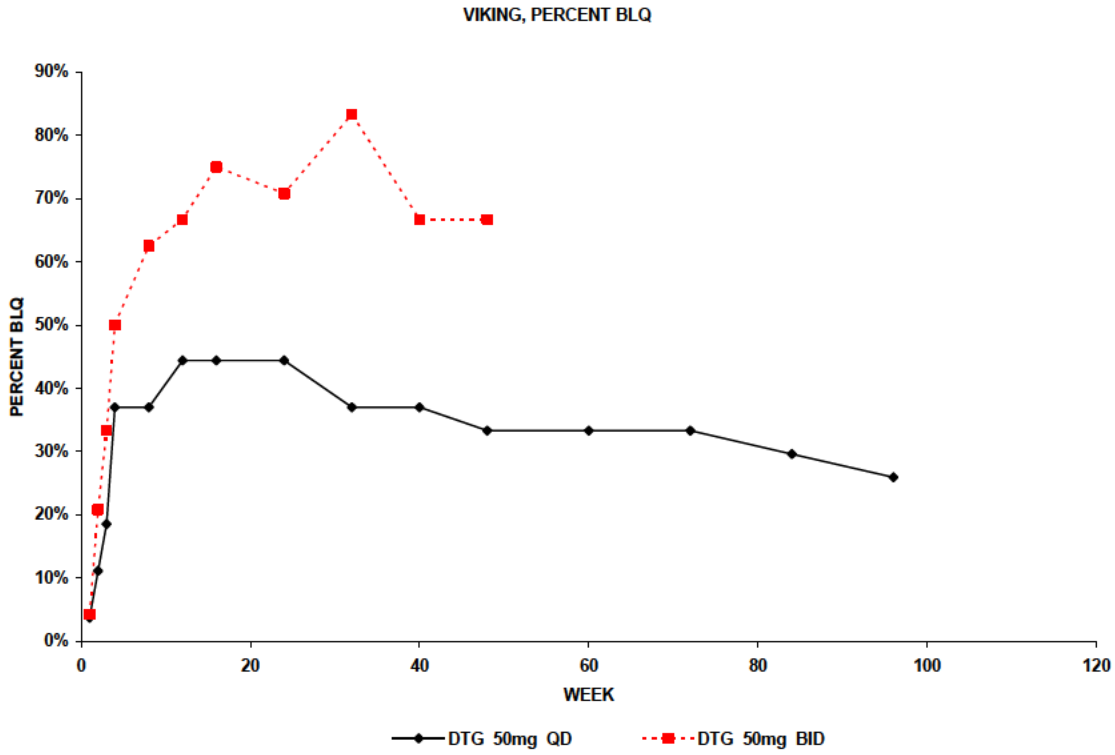

SAILING, PERCENT BLQ
100%
90%
80%
70%
60%
50%
40%
PERCENT BLQ
0
10
20
30
40
50
60
WEEK
RAL
DTG 50mg QD

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%.

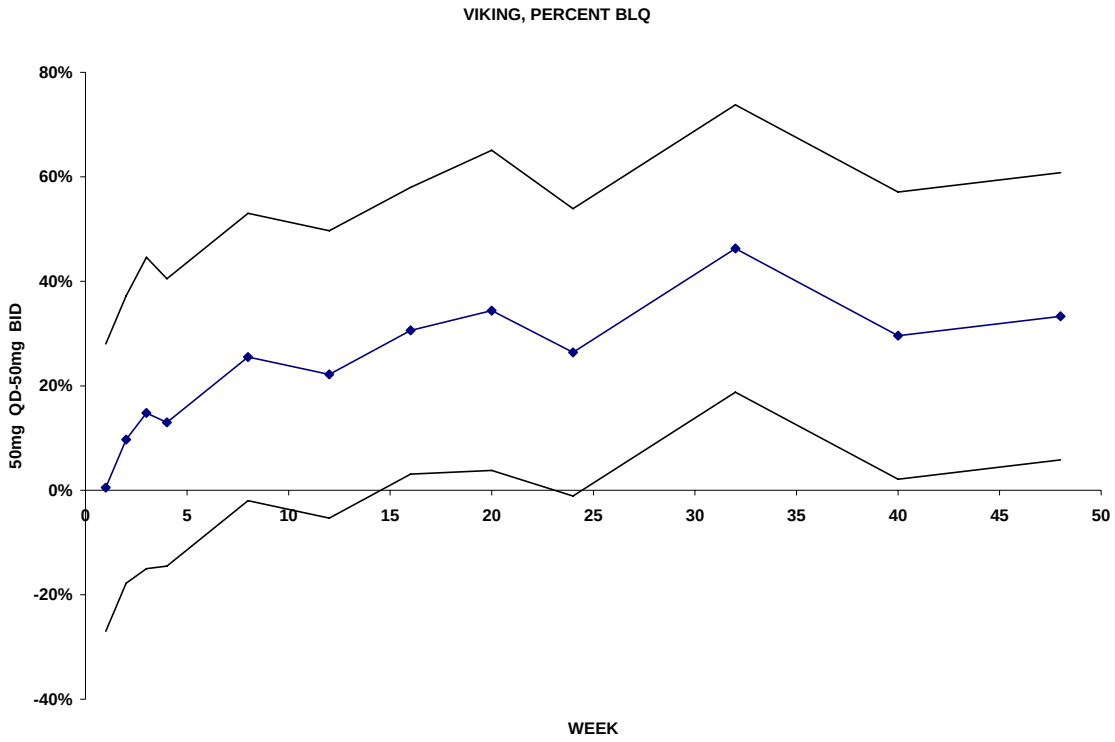


3.2.3 Two Class Resistant, INI Resistant Trials

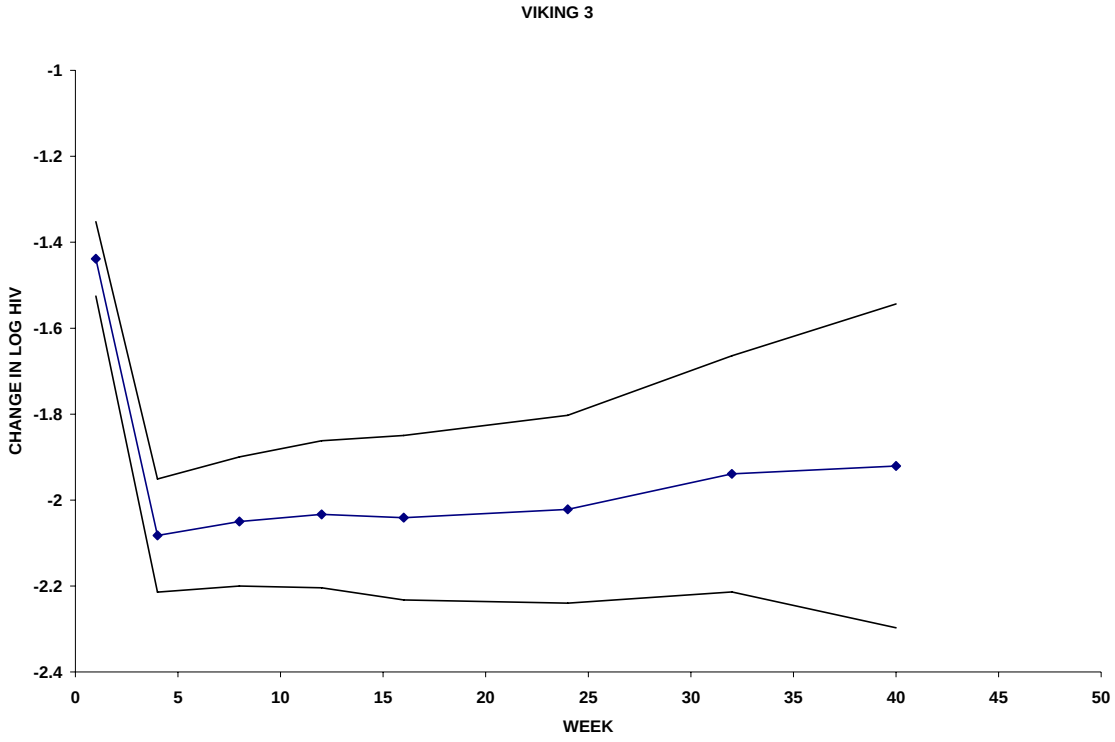
The first two graphs give the %BLQ in the two cohorts of the Viking trial, DTG 50mg QD and BID. Remember that these are enrolled sequentially and are not randomized. This accounts for the shorter duration of the observation of the BID cohort. Nonetheless, one will notice a much higher response rate in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



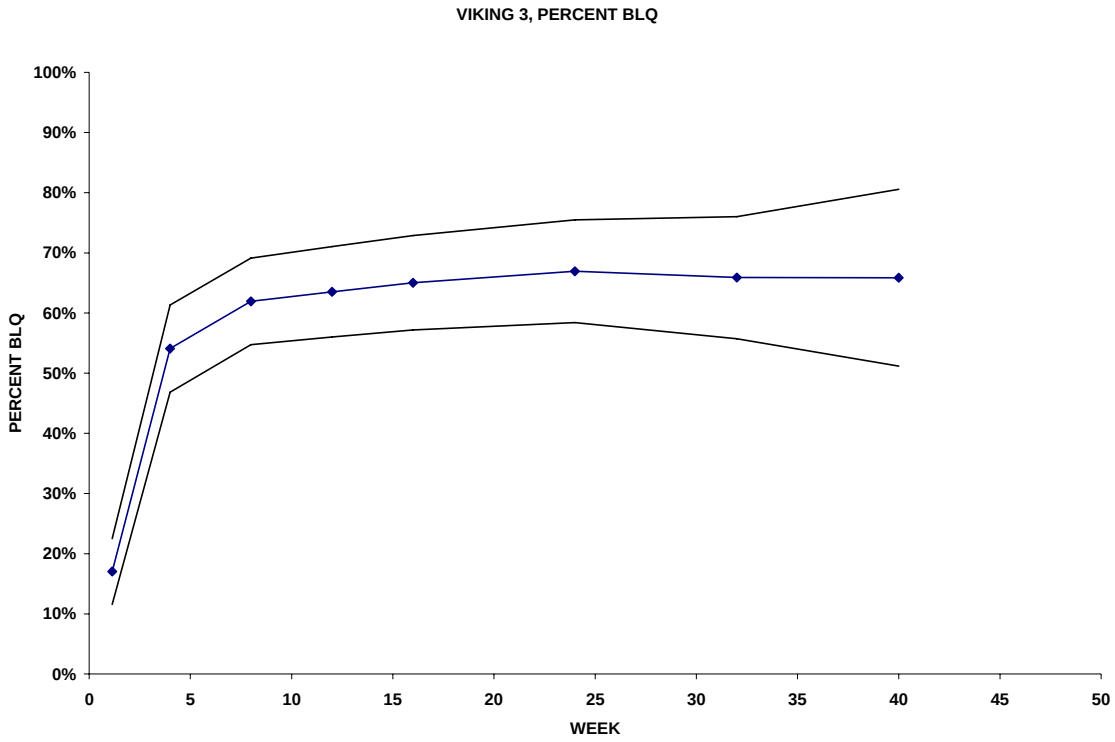
One will notice that the BID cohort (in a non-randomized but still statistically reasonable comparison) is very close to statistically significant superiority over the QD cohort. Given the non-randomized nature of the comparison, some checking for any differences in baseline covariates between the cohorts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

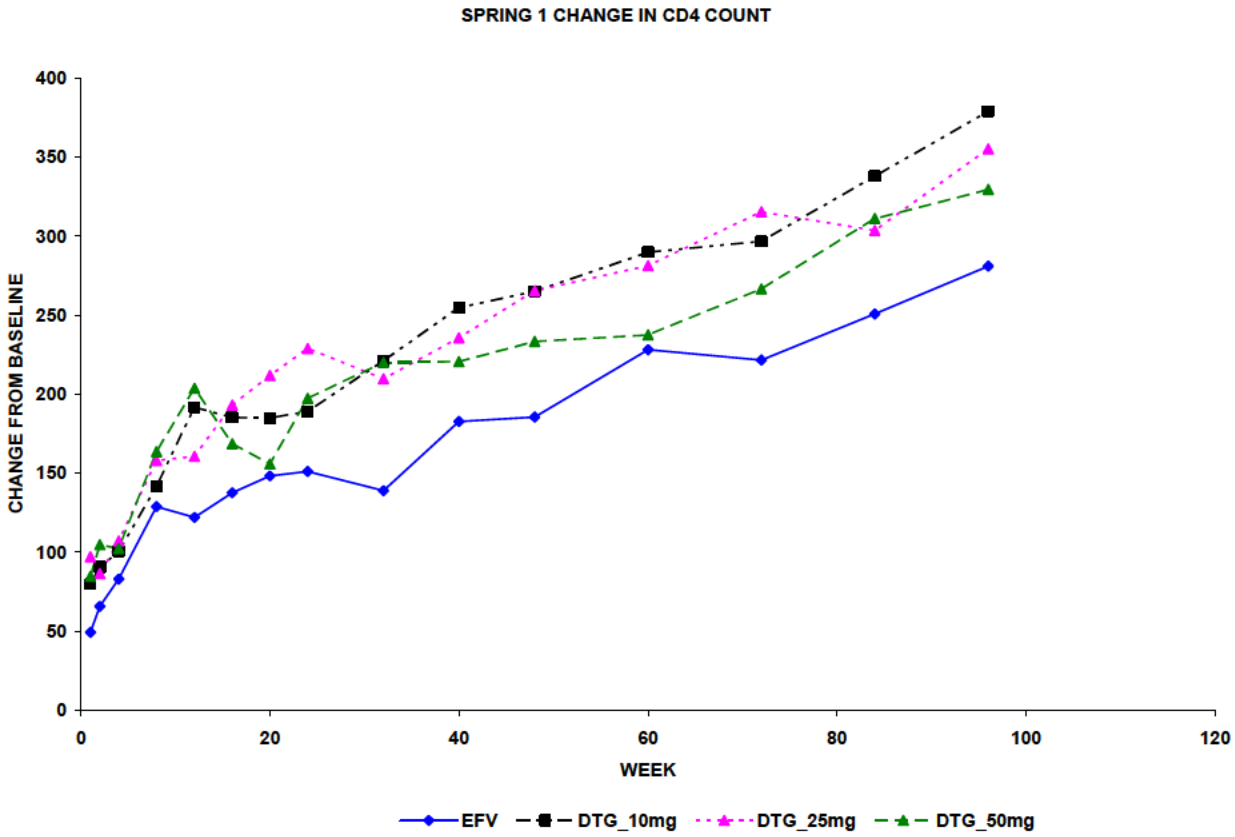
In the Sailing trial in two class resistant subjects, the DTG and RAL CD4 responses are nearly identical, as was the case with the same drugs in naïve subjects (Spring 2 trial). One can be confident that the DTG regimen is no more than 20 cells/ml worse than the RAL regimen among the resistant subjects.

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.

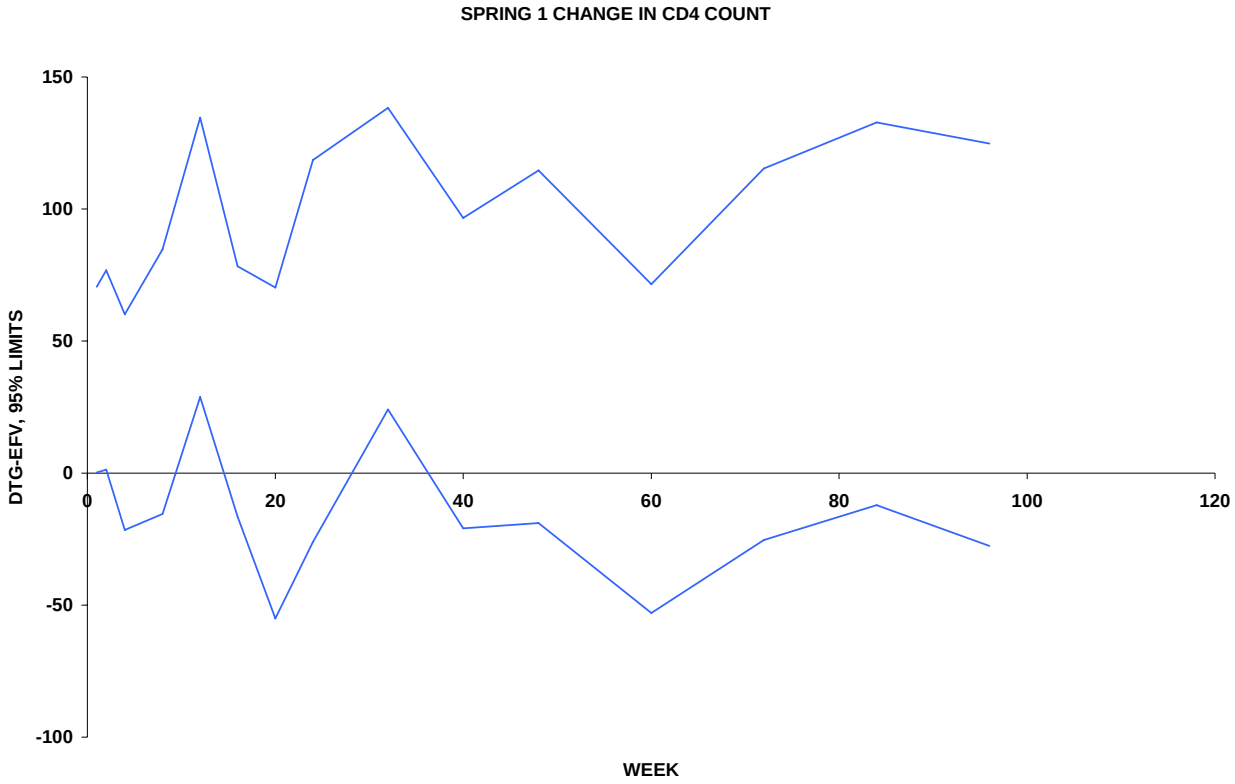
In the one arm Viking 3 trial, one can be confident that this highly resistant population will experience a gain of at least 50-60 cells/ml in CD4 count with DTG at 50mg BID.

3.4.1 Treatment Naïve Trials

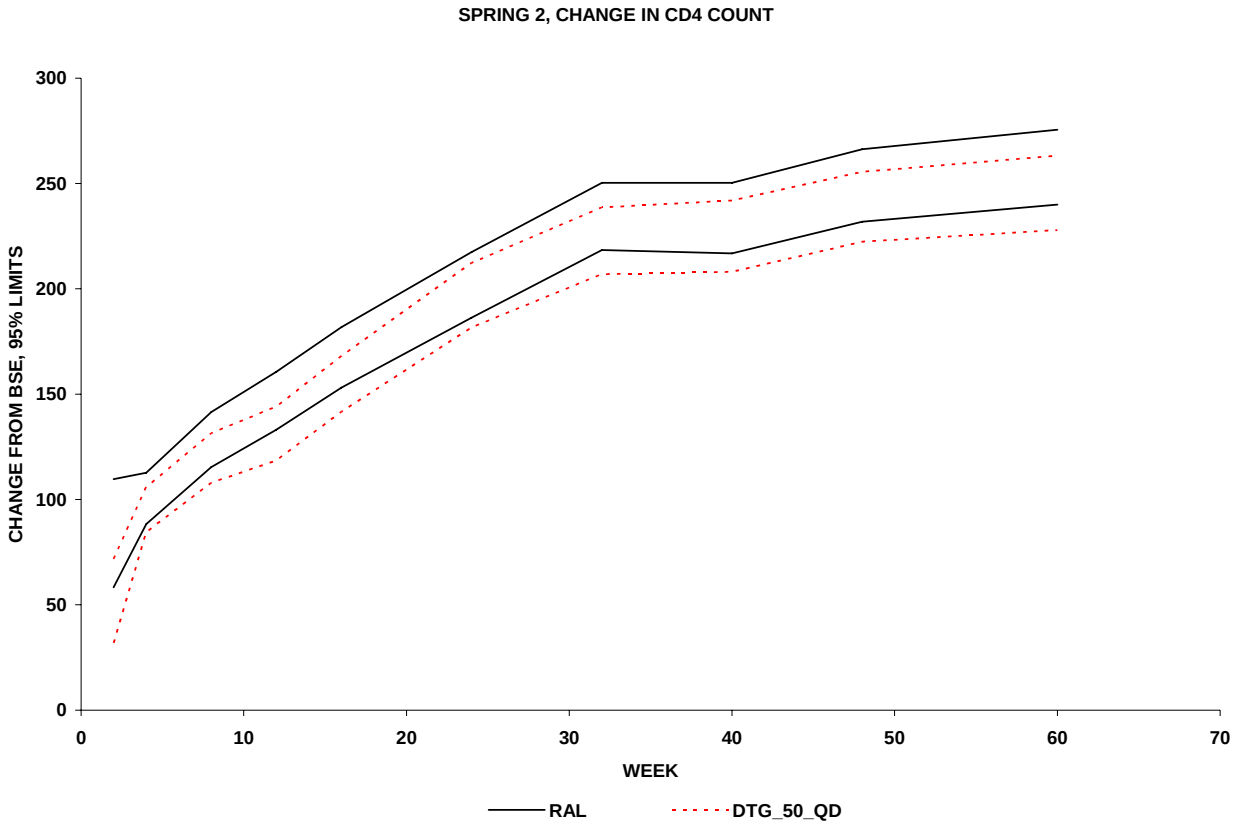
The first graph gives the change from baseline in all four arms of the Spring 1 trial. One will notice that all four doses of DTG are similar and slightly superior to EFV. There is not an apparent dose response relationship among the DTG doses as there was for HIV response.



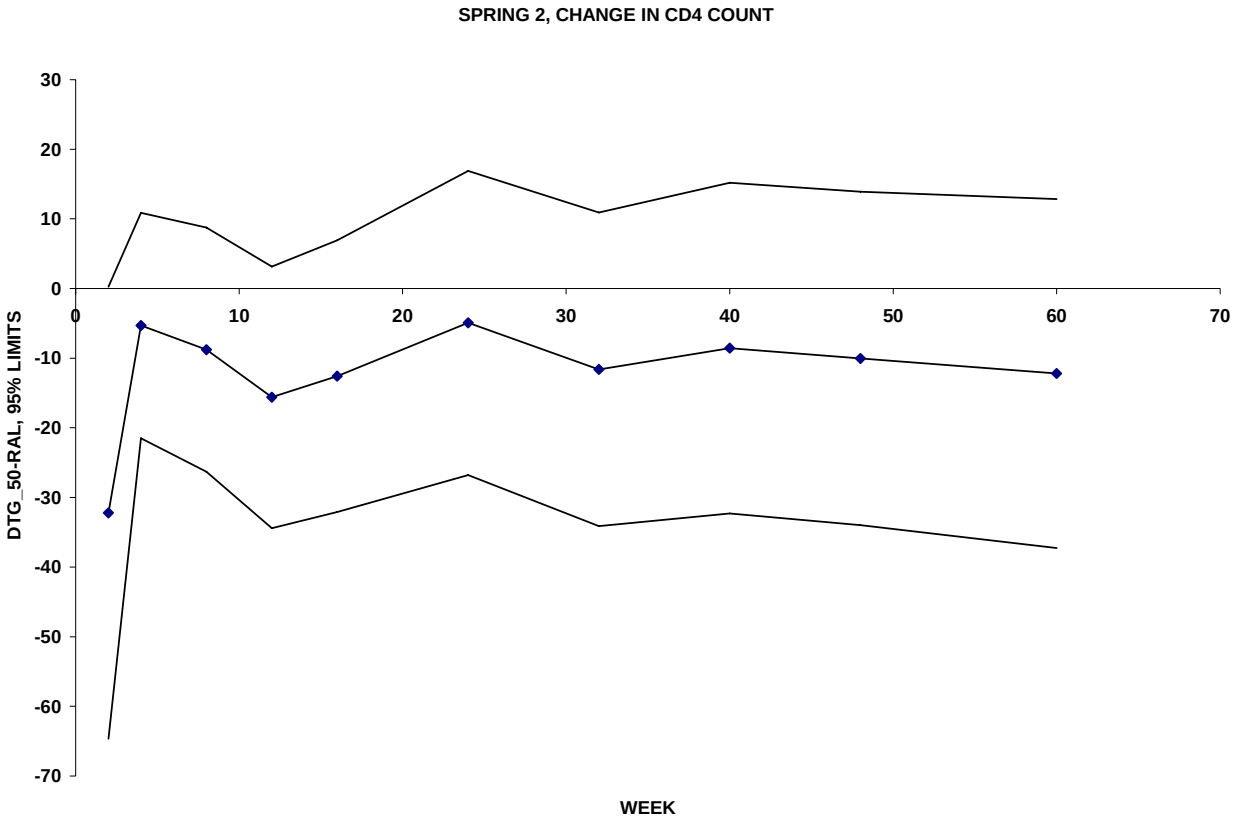
The second graph shows the 95% confidence limits for the difference DTG_50mg - EFV on the change from baseline in CD4 count. One will notice that, as was the case with HIV, the observed superiority of DTG to EFV is close to, but not at, statistical significance.



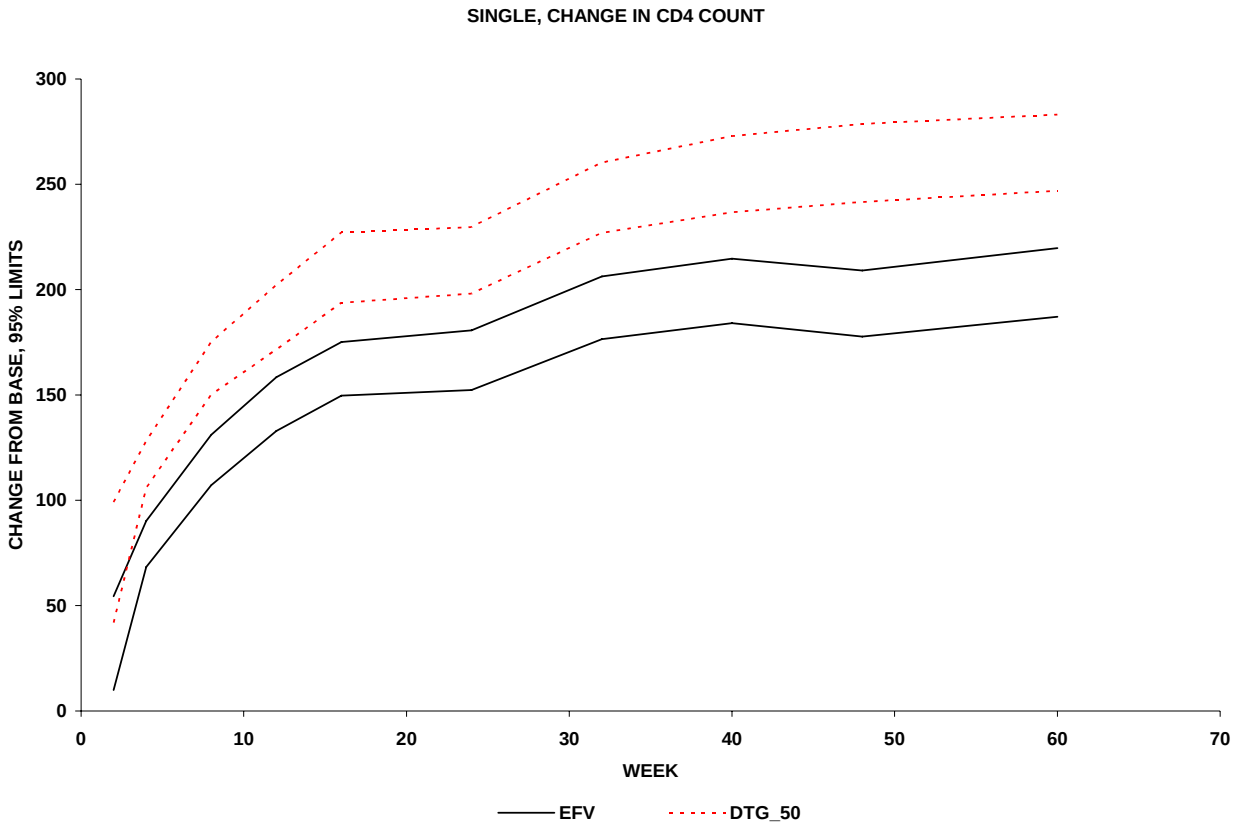
The next graph shows the 95% confidence bands for the change in CD4 count in the DTG and RAL arms of the Spring 2 trial. They nearly overlap perfectly.



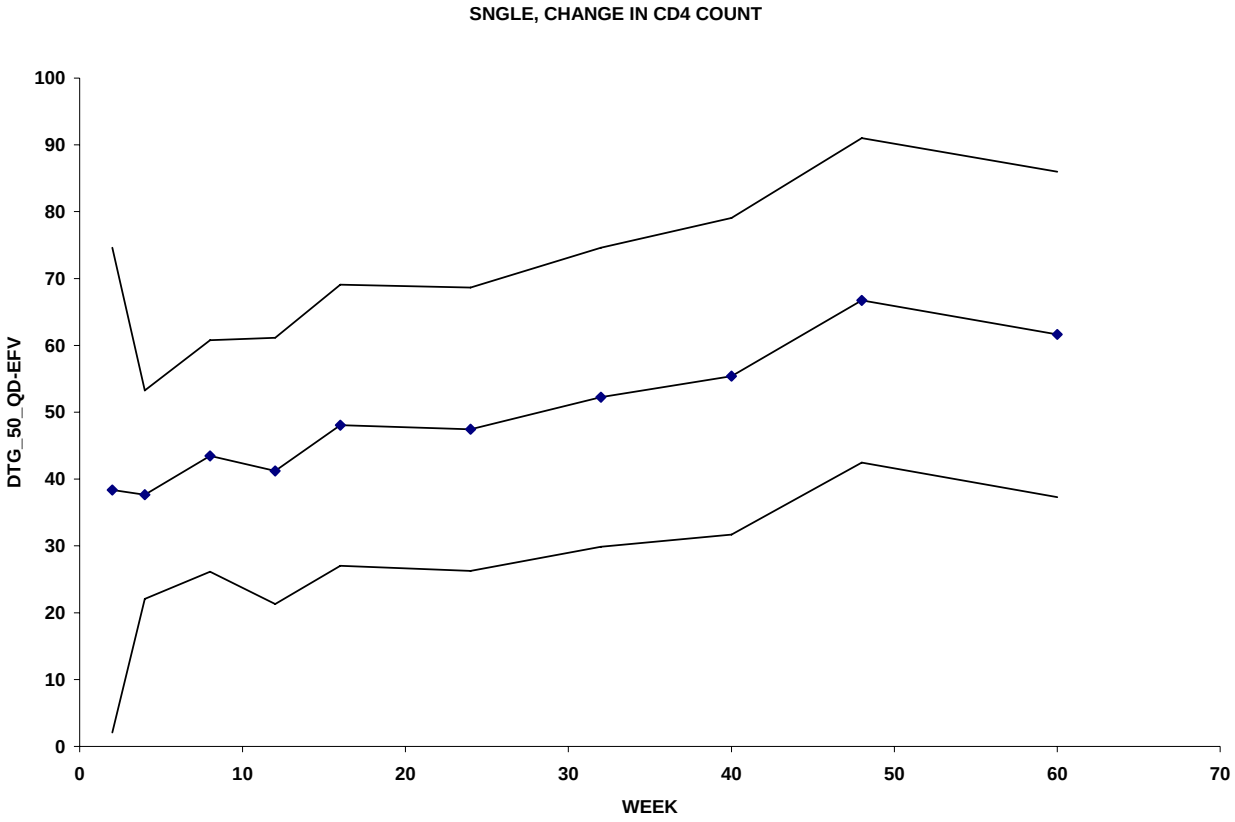
This graph shows the point estimate and 95% confidence limits for the difference, DTG-RAL, in change in CD4 count in the Spring 2 trial. One can be reasonably confident that the DTG regimen is no more than 30-35 cells/ml worse than the RAL regimen.



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.

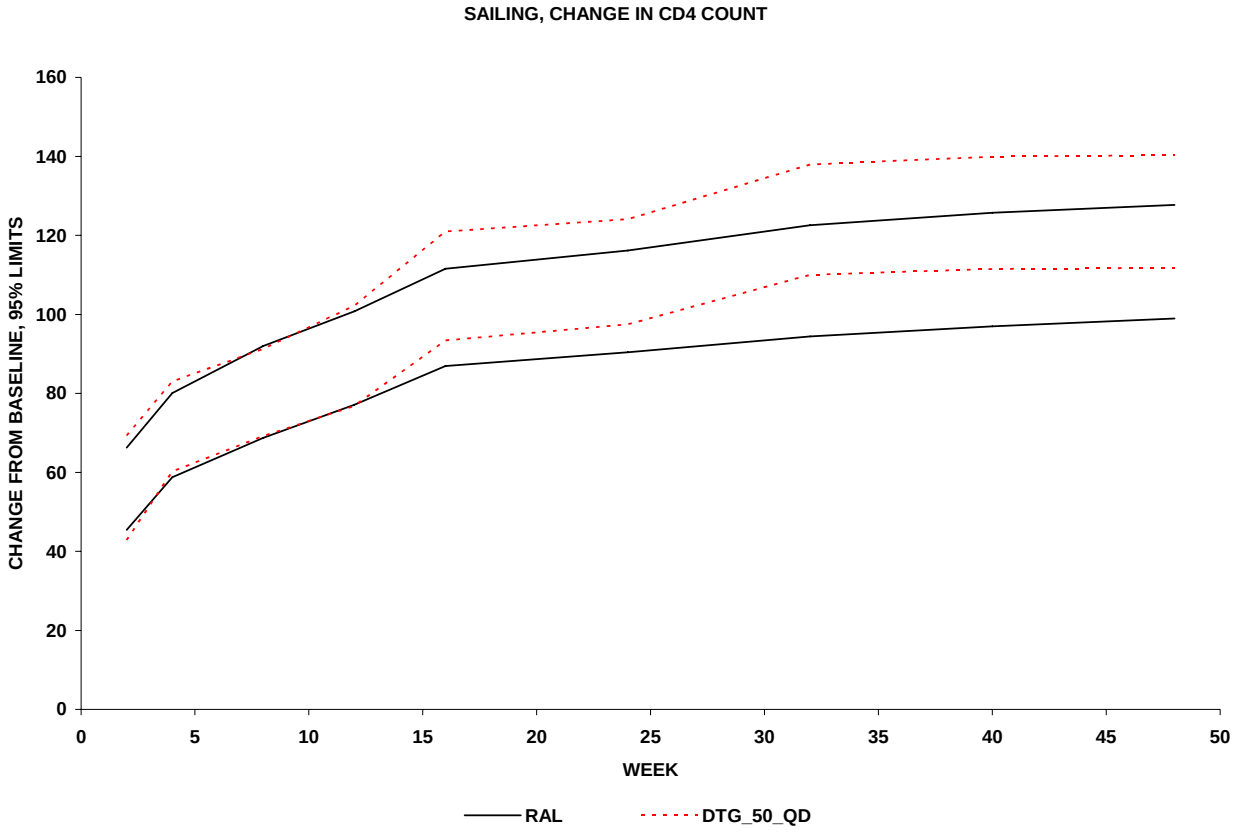


This graph gives the point estimate and 95% confidence limits for The difference, DTG-EFV, in change in CD4 count in the Single trial. The DTG regimen is statistically significantly superior throughout the trial. This confirms the findings with the HIV endpoints in this trial.

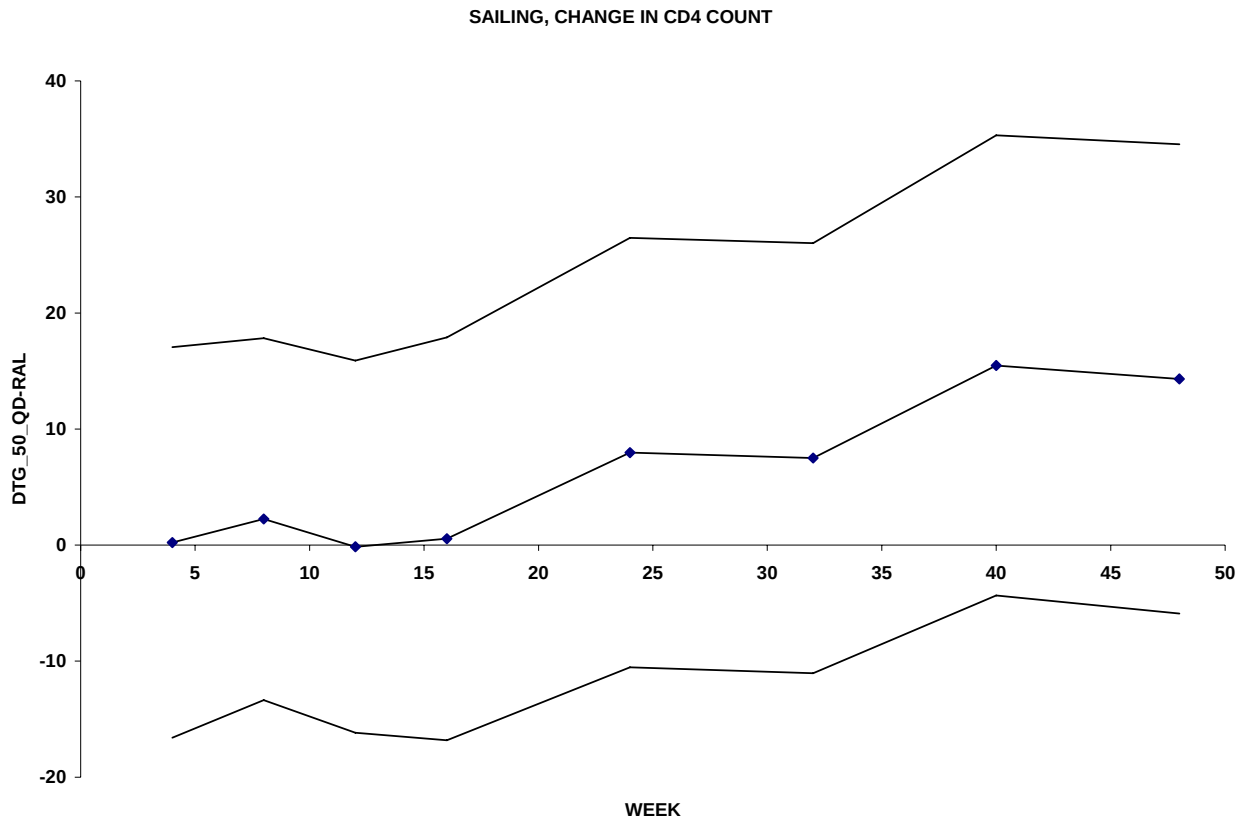


3.4.2 Two Class Resistant INI Naïve Trial

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.

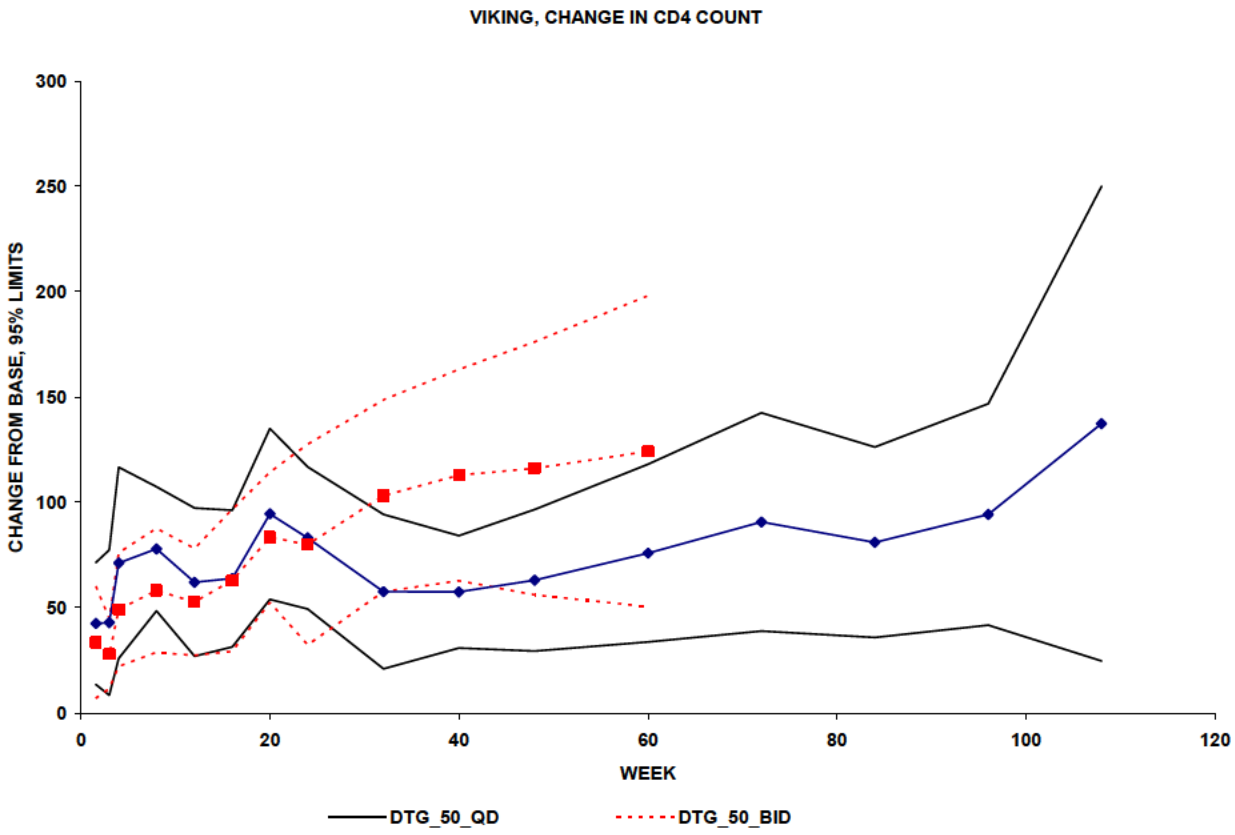


This graph shows the point estimate and 95% confidence limits for the difference, DTG-RAL, in change in CD4 count. As was the case in the Spring 2 trial and with the HIV endpoints in this trial, there is no statistically confirmed difference. Nonetheless, one can be confident that the DTG regimen is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

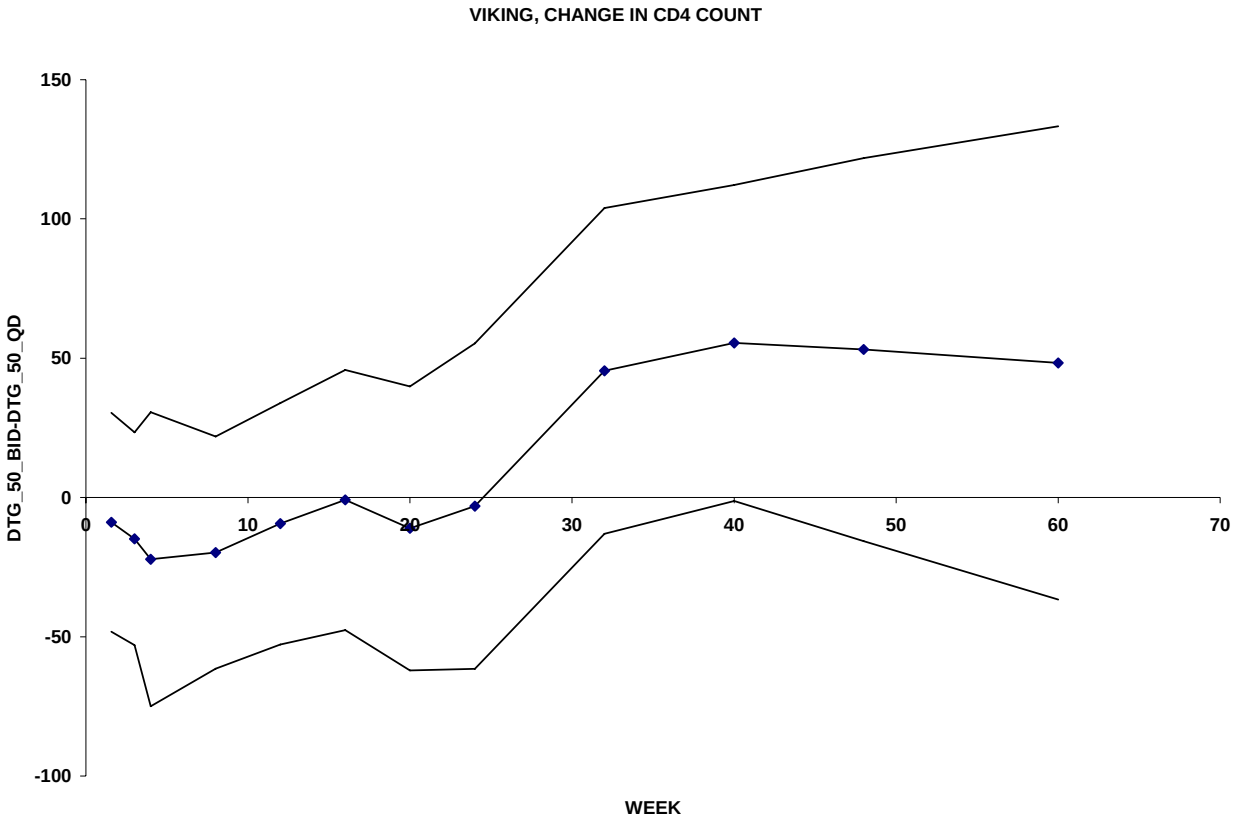


3.4.3 Two Class Resistant, INI Resistant Trials

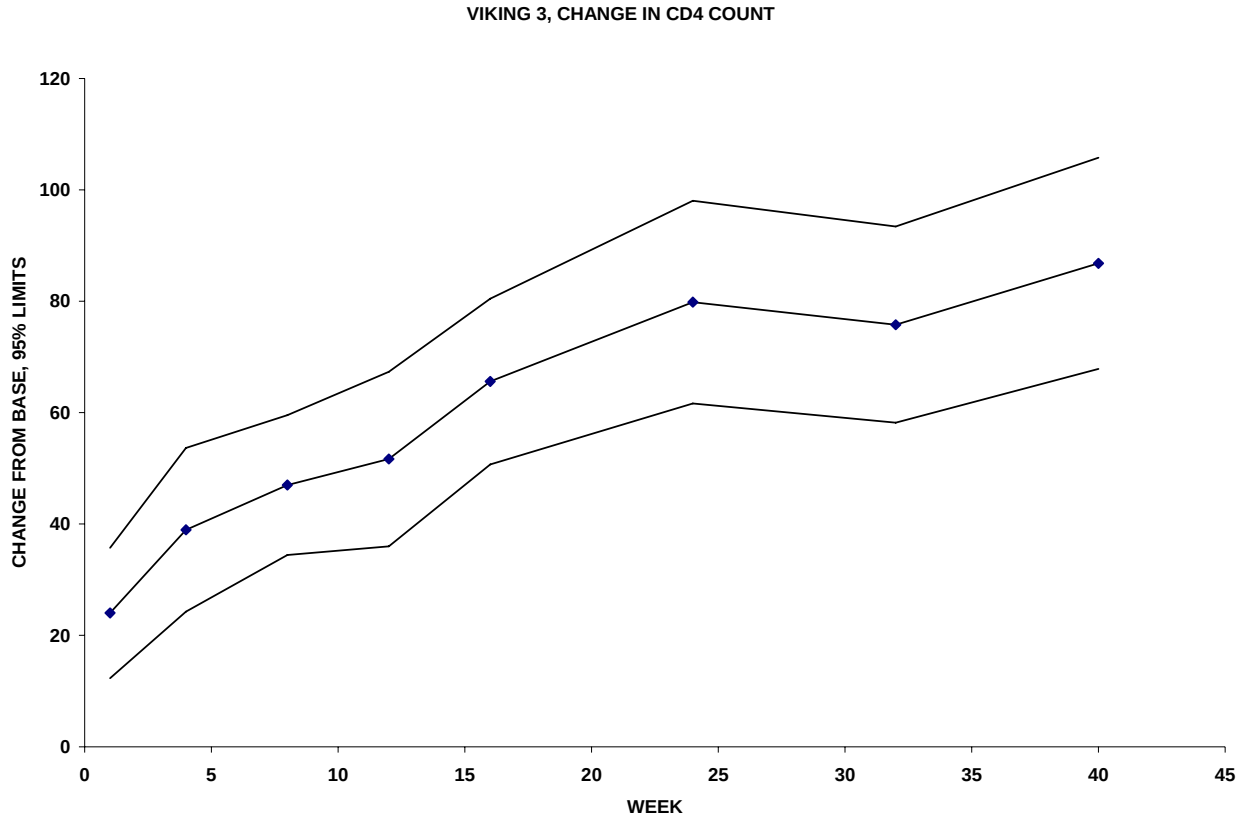
This graph shows the point estimate and the 95% confidence bounds for the two cohorts, DTG_50mg BID and QD, in the Viking trial. Because the QD cohort was recruited earlier, the band for that cohort extends later. Looking only at the 95% bands, the separation between the two cohorts is not as clear as 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 9% 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.

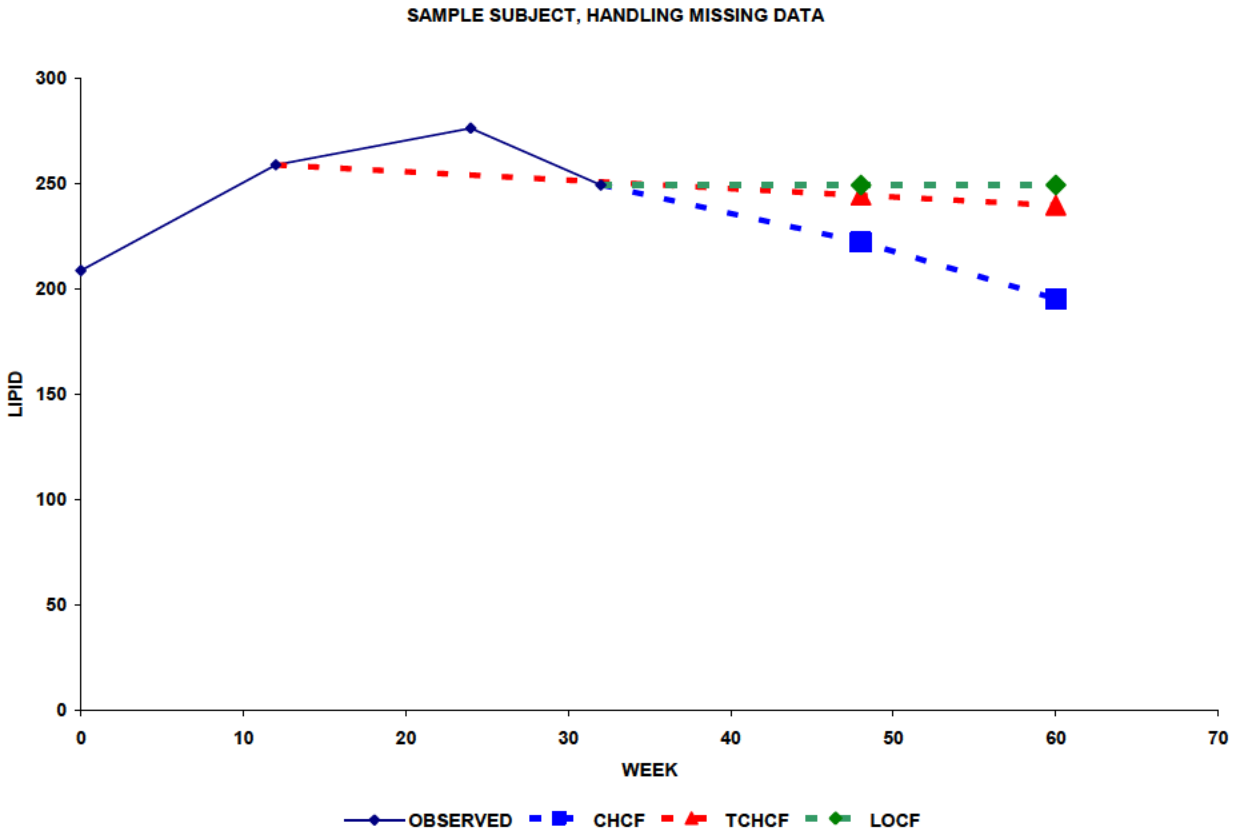
VISIT	CHOL
DAY_1	208.817
WEEK_12	259.087
WEEK_24	276.489
WEEK_32	249.420
WEEK_48	.
WEEK_60	.

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.


SAMPLE SUBJECT, HANDLING MISSING DATA
300
250
200
150
100
50
0
LIPID
0
10
20
30
40
50
60
70
WEEK
OBSERVED
CHCF
TCHCF
LOCF

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	354
WEEK_24	-0.49292	-1.93923	0.95340	3.07038	3.56330	354	350
WEEK_32	-0.03877	-1.52088	1.44334	2.73161	2.77039	341	344
WEEK_48	-0.00974	-1.51745	1.49797	2.68033	2.69007	322	335
WEEK_60	-0.46598	-2.70686	1.77491	2.33555	2.80153	143	151

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	371
WEEK_24	-0.33122	-1.71437	1.05193	2.88923	3.22045	381	369
WEEK_32	0.13573	-1.26747	1.53893	2.72580	2.59007	384	368
WEEK_48	0.06795	-1.32551	1.46141	2.63059	2.56264	378	370
WEEK_60	0.07364	-1.34744	1.49473	2.93176	2.85811	381	368

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

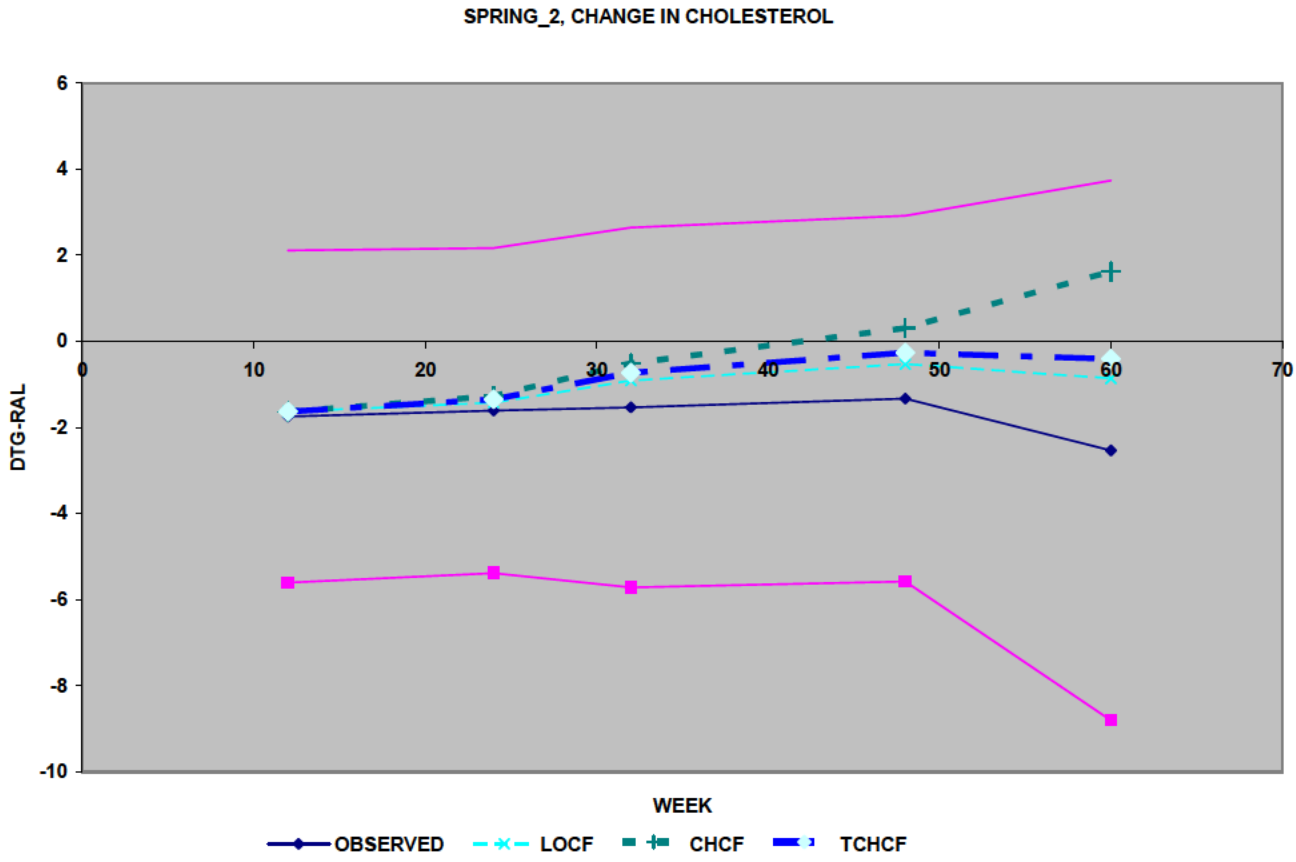
VISIT	DIFF_TRIG	LOWER	UPPER	CHG_TRIG_DTG	CHG_TRIG_RAL	N_RAL	N_DTG
WEEK_12	0.4868	-16.1241	17.0977	24.1296	23.6428	342	334
WEEK_24	11.7622	-9.6444	33.1688	36.6177	24.8555	346	336
WEEK_32	-1.7897	-29.0303	25.4509	38.9802	40.7699	343	336
WEEK_48	0.4322	-38.0203	38.8848	49.1231	48.6908	339	330

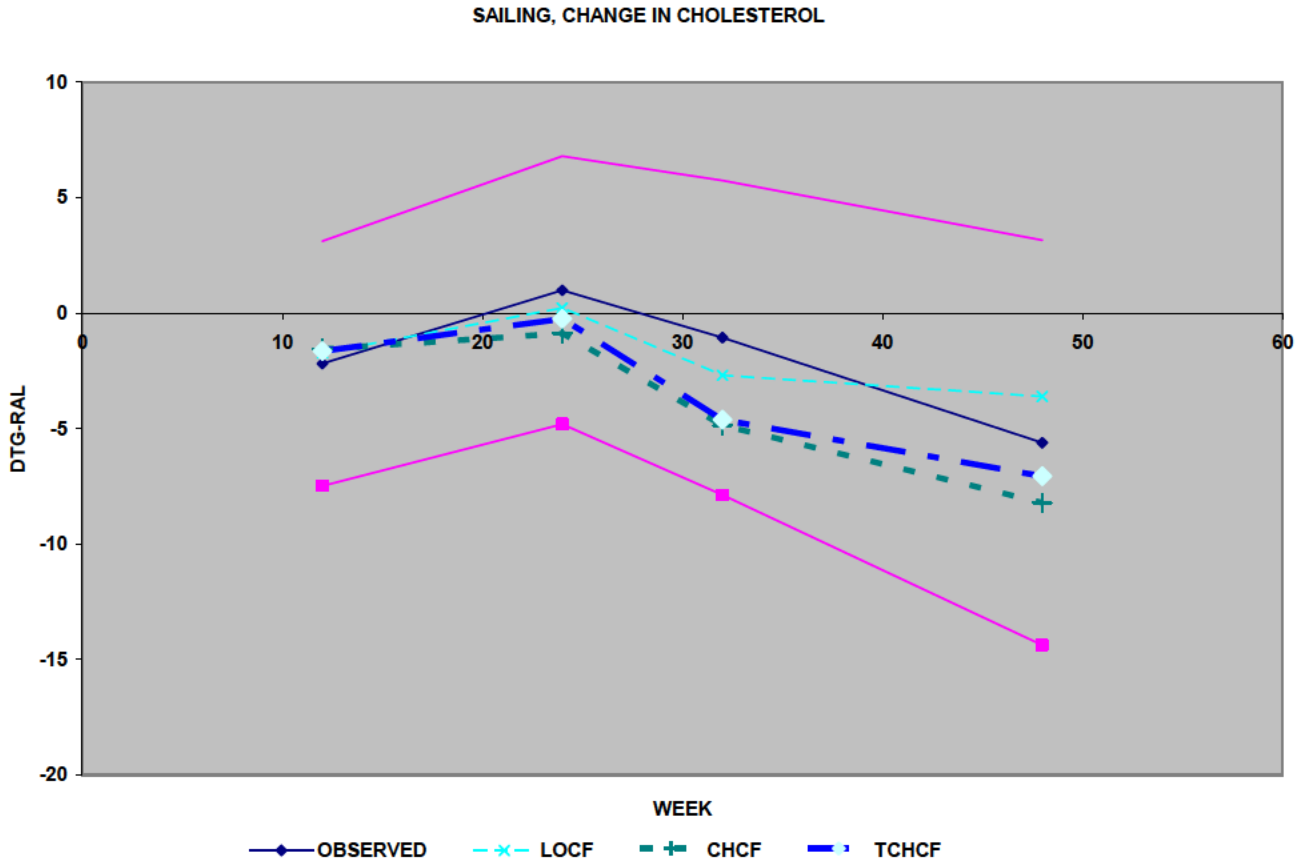
TWO_CHANGE_CF

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

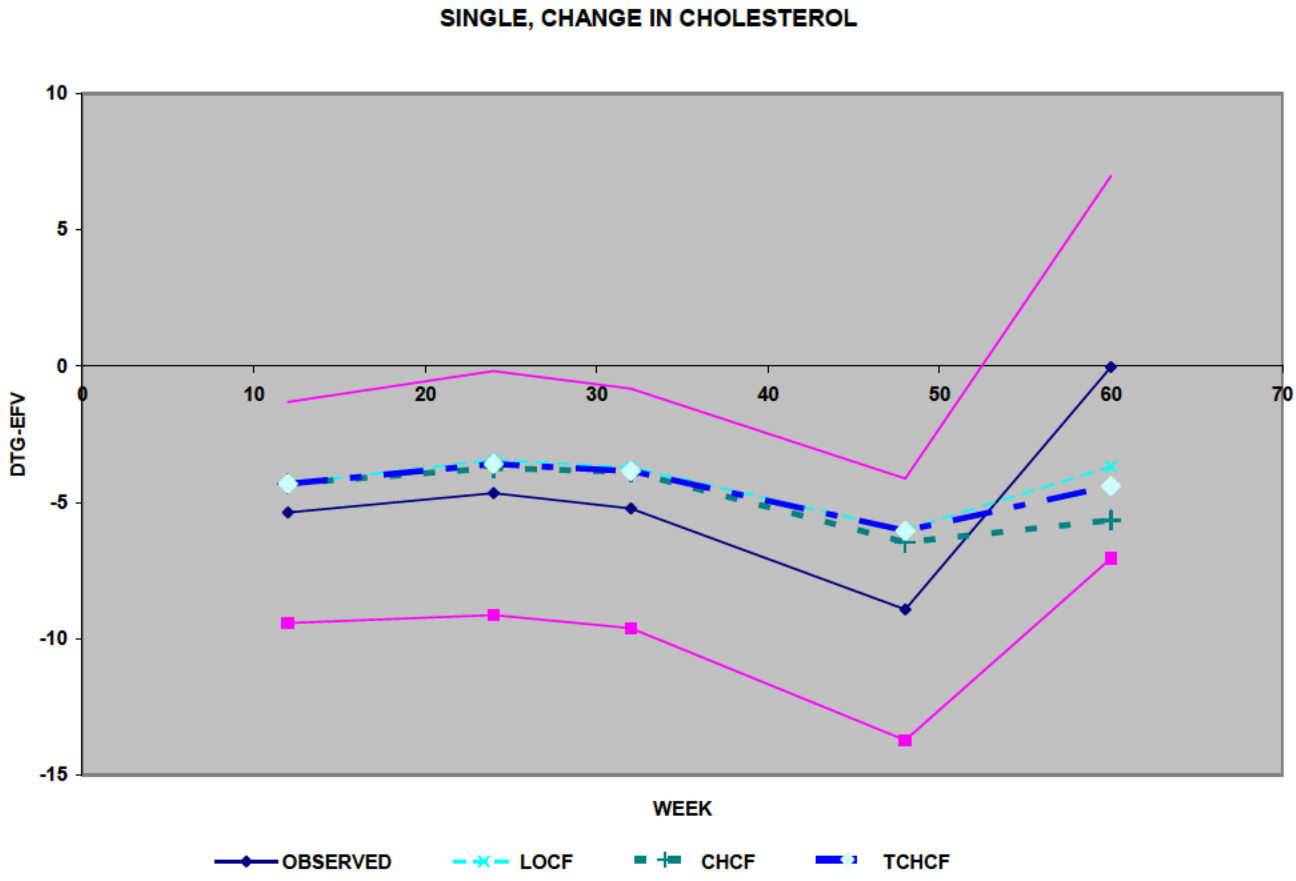
There are a lot of numbers in these tables that are hard to absorb all at once. The following graphs show the differences between DTG and control in change from baseline in each of the four lipids in each of the three trials. The four curves in the middle of each graph represent the four methods of handling 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.

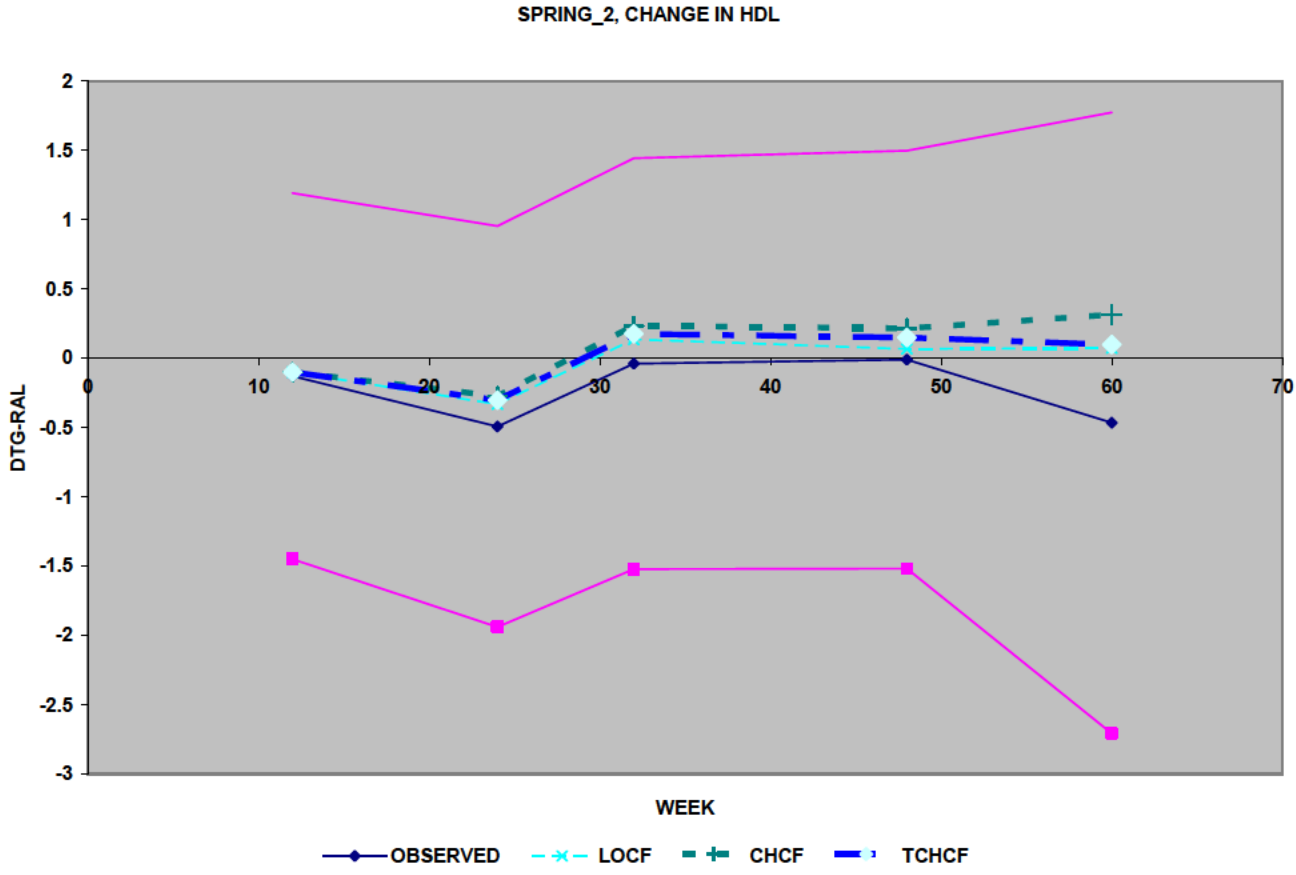


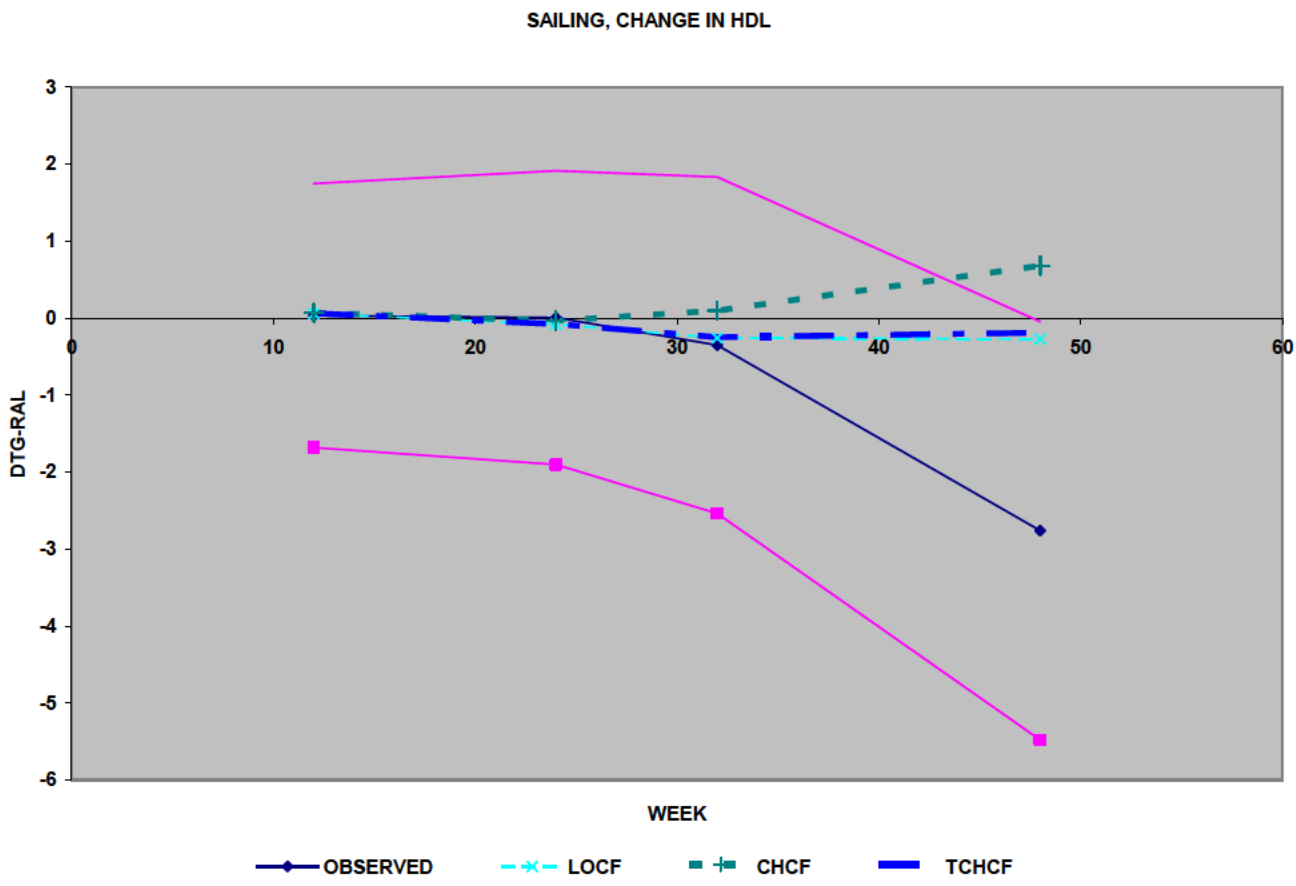

SAILING, CHANGE IN CHOLESTEROL
10
5
0
-5
-10
-15
-20
0
10
20
30
40
50
60
DTG-RAL
WEEK
OBSERVED
LOCF
CHCF
TCHCF

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.

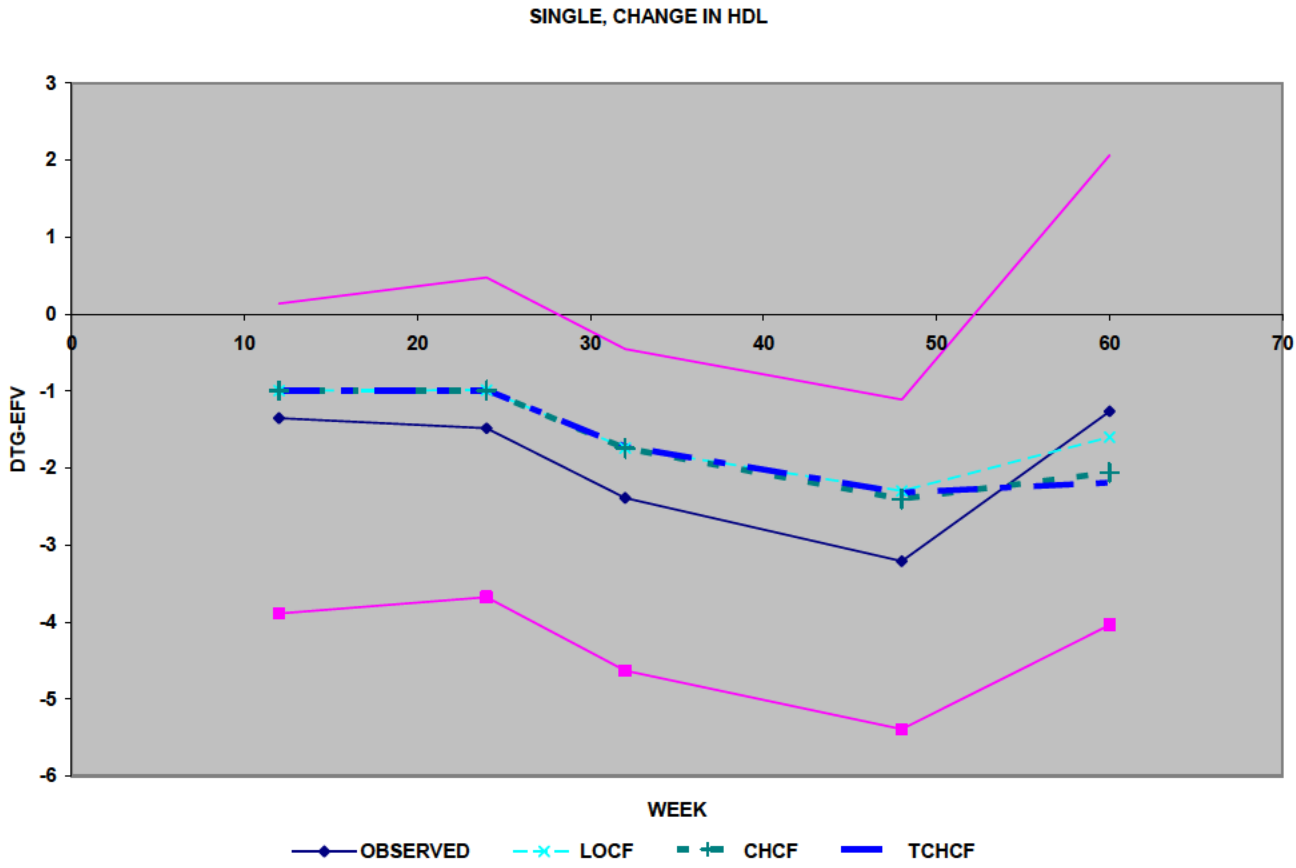


There was no statistically significant difference between DTG and RAL with respect to change from baseline in HDL. In fact, the point estimates for the DTG-RAL difference are nearly zero with the upper and lower 95% confidence bounds symmetric about zero.

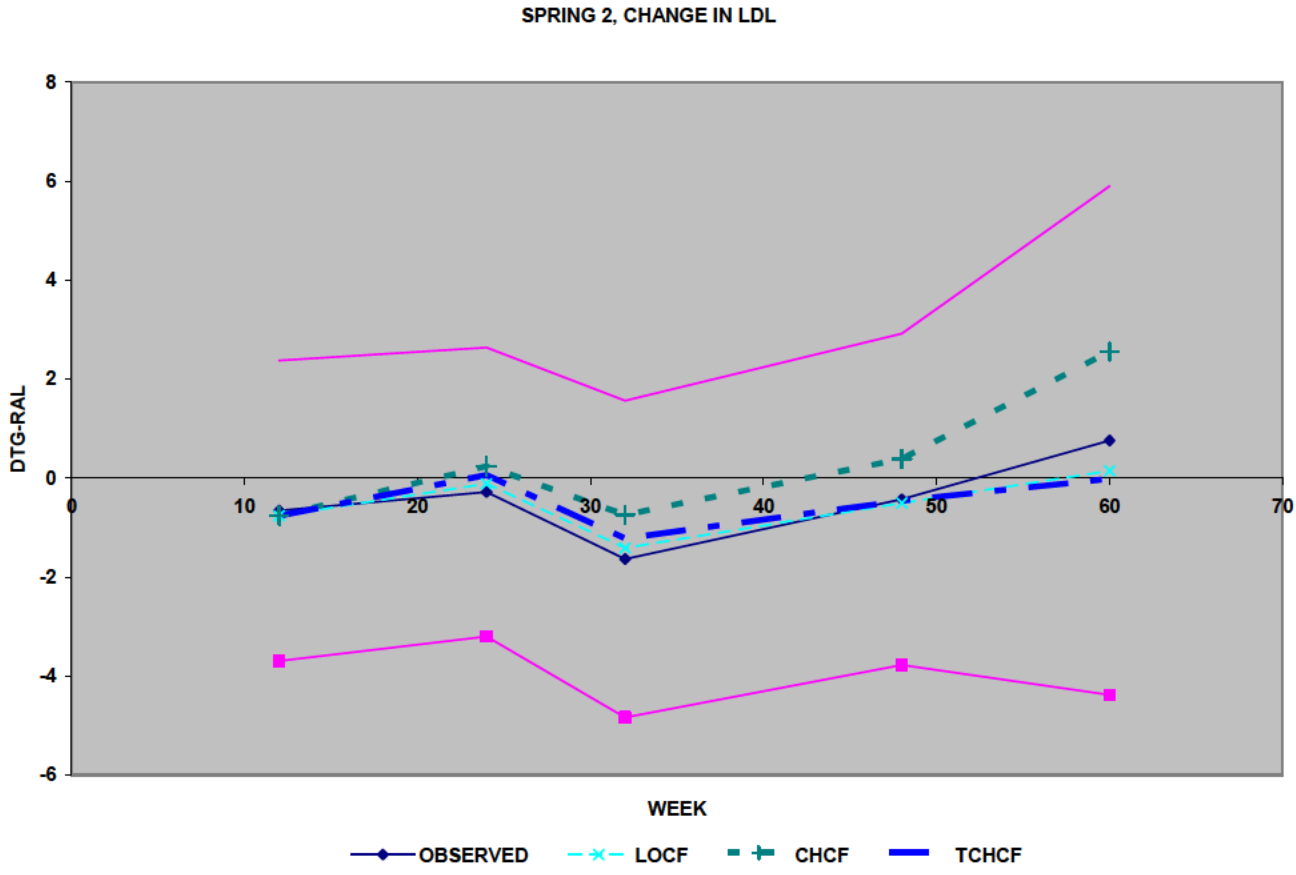


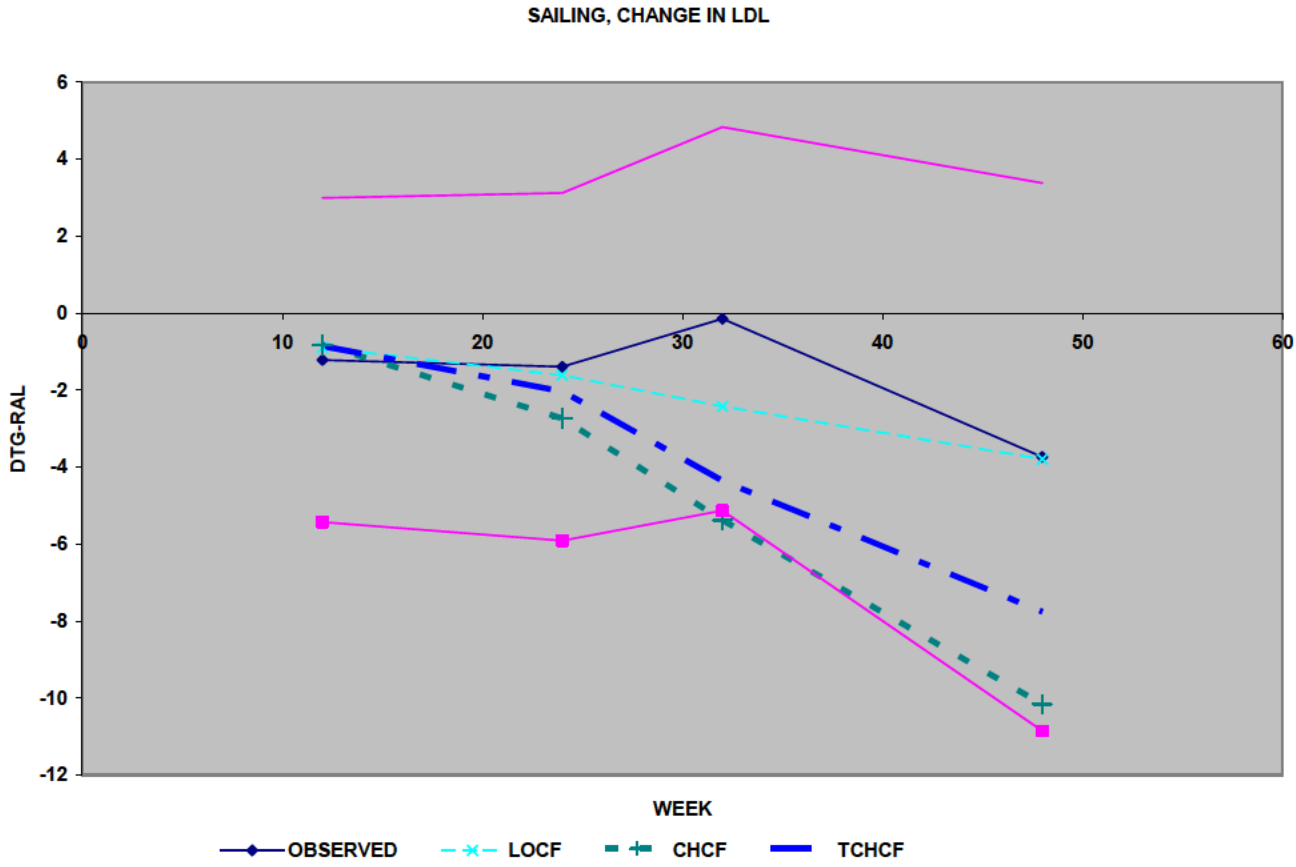


In contrast, there was a statistically significant decrease in change from baseline in HDL when DTG was compared to EFV in Single. The DTG arm showed about a 2 mg/dl greater decrease in HDL.

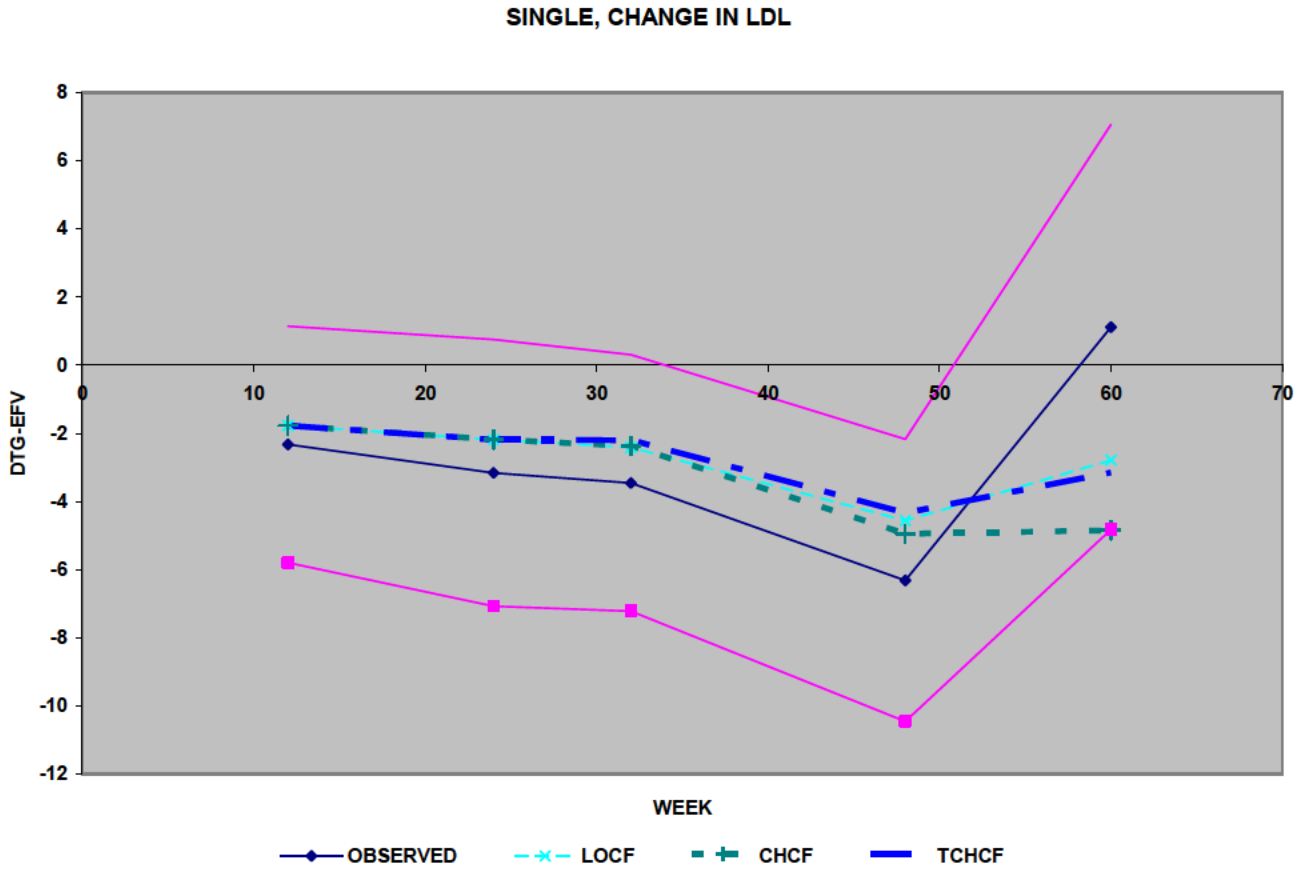


There is no statistically significant difference between DTG and RAL with respect to change from baseline in LDL either. Again, the point estimates are nearly zero, the method of handling missing data is of little consequence, and the 95% confidence limits are nearly symmetric about zero.

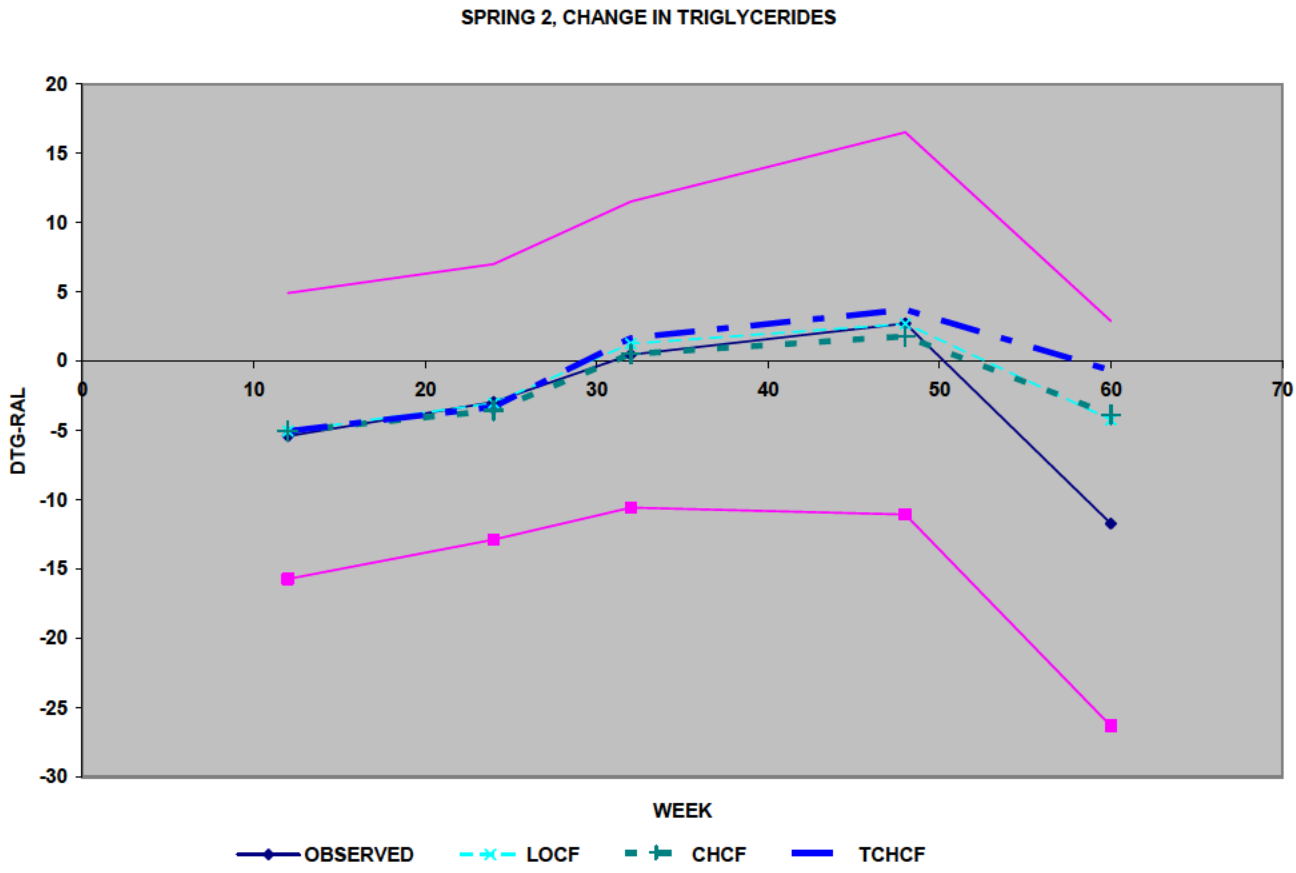


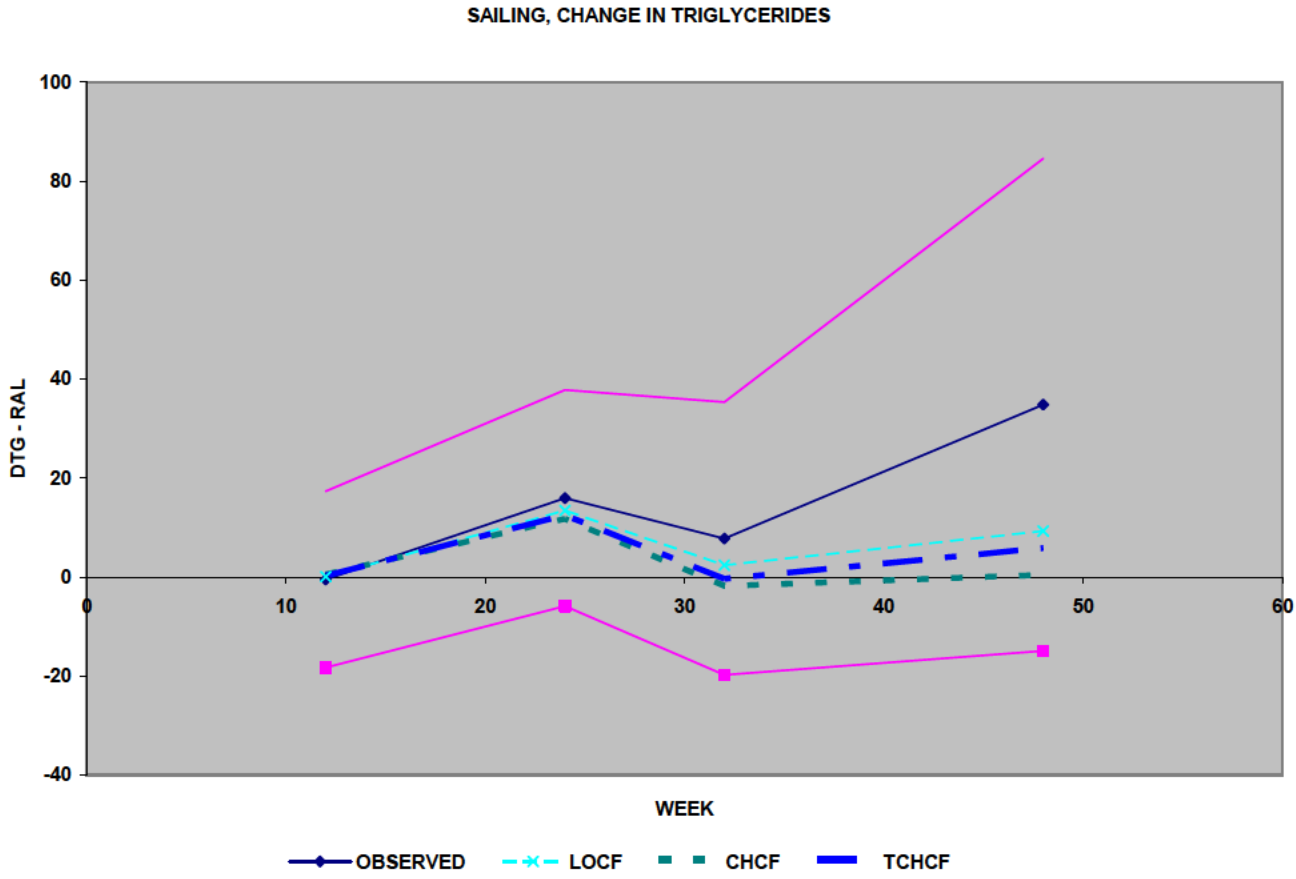

SAILING, CHANGE IN LDL
DTG-RAL
6
4
2
0
-2
-4
-6
-8
-10
-12
0
10
20
30
40
50
60
WEEK
OBSERVED
LOCF
CHCF
TCHCF

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.

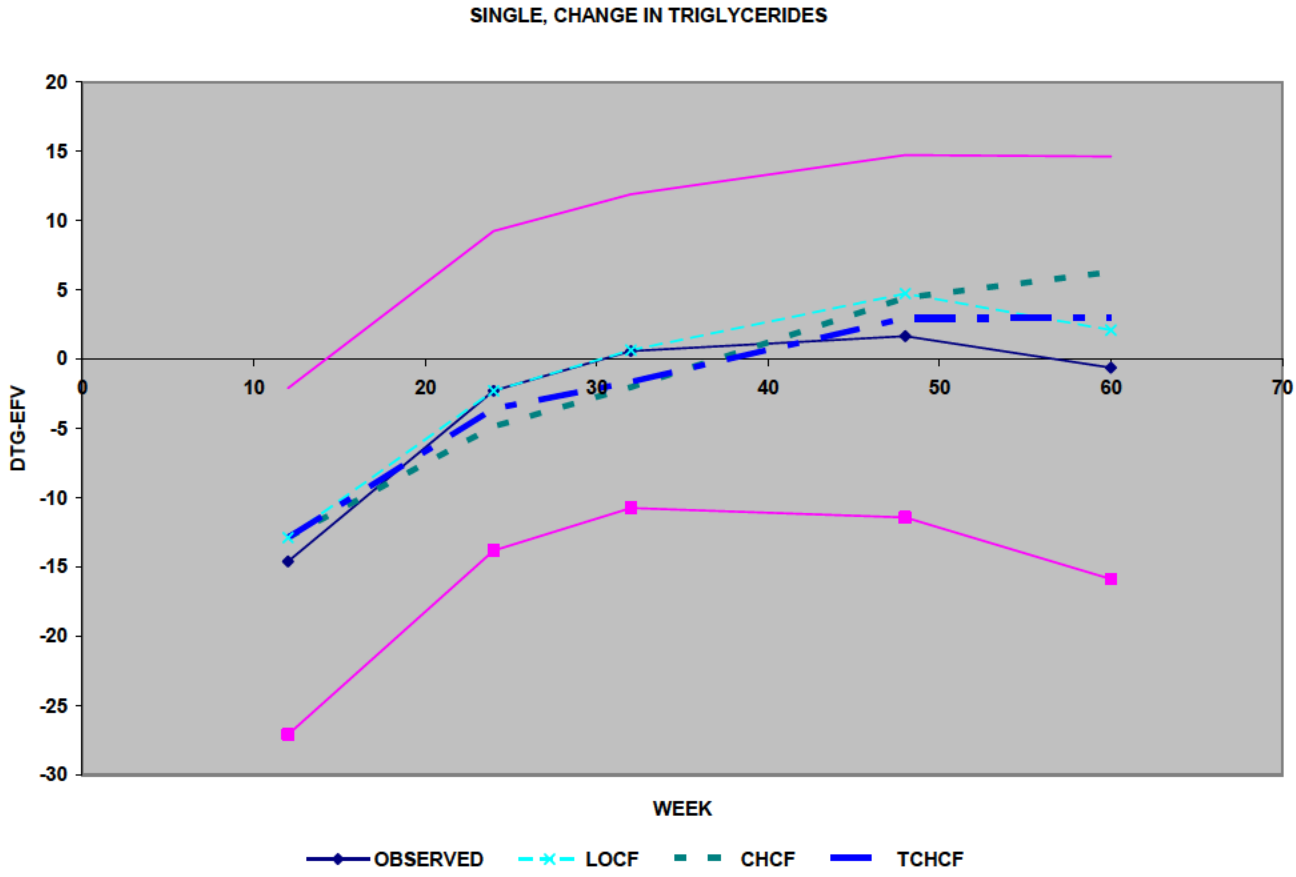


There doesn't appear to be any difference between DTG and RAL with respect to change from baseline in triglycerides. The confidence limits straddle zero although the point estimates show a slightly higher level in the DTG arm of about 3 mg/dl in Spring 2 and about 10 mg/dl in Sailing.




SAILING, CHANGE IN TRIGLYCERIDES
DTG - RAL
100
80
60
40
20
0
-20
-40
0
10
20
30
40
50
60
WEEK
OBSERVED
LOCF
CHCF
TCHCF

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 DIFF	95% LIMITS 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 DIFF	95% LIMITS 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 DIFF	95% LIMITS 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 DIFF	95% LIMITS 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 DIFF	95% LIMITS 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 DIFF	95% LIMITS 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 DIFF	95% LIMITS 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 DIFF	95% LIMITS LOWER	UPPER	DTG_50mg	RAL	PVALUE
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 DIFF	95% LIMITS 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 DIFF	95% LIMITS LOWER	UPPER	DTG 50mg_BID	50mg_QD	PVALUE
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

		95% LIMITS			
	MEAN	LOWER	UPPER	N	PVALUE
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

		95% LIMITS		
	MEAN	LOWER	UPPER	PVALUE
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 LOWER	UPPER	DTG	PLAC	N_P	N_D
BASELINE 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

BASELINE 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

BASELINE 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 DIFF	95% LIMITS LOWER	UPPER	DTG_10mg	EFV	PVALUE
RISK_FACTOR						
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 DIFF	95% LIMITS LOWER	UPPER	DTG_10mg	EFV	PVALUE
RISK_FACTOR						
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 DIFF	95% LIMITS LOWER	UPPER	DTG_10mg	EFV	PVALUE
RISK_FACTOR						
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 DIFF	95% LIMITS 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 DIFF	95% LIMITS 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 DIFF	95% LIMITS 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 DIFF	95% LIMITS 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 DIFF	95% LIMITS LOWER	UPPER	DTG 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 DIFF	95% LIMITS LOWER	UPPER	DTG 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 DIFF	95% LIMITS 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 LOWER	UPPER	DTG	PLAC	N_P	N_D
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 LOWER	UPPER	DTG	PLAC	N_P	N_D
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 DIFF	95% LIMITS 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 DIFF	95% LIMITS 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 DIFF	95% LIMITS 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 DIFF	95% LIMITS 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 DIFF	95% LIMITS 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 DIFF	95% LIMITS 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 DIFF	95% LIMITS LOWER	UPPER	DTG	PLAC	N_P	N_D
COUNTRY							
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 DIFF	95% LIMITS LOWER	UPPER	DTG 50mg_BID	50mg_QD	PVALUE
COUNTRY						
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 DIFF	95% LIMITS LOWER	UPPER	DTG 50mg_BID	50mg_QD	PVALUE
COUNTRY						
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

		95% LIMITS			
	MEAN	LOWER	UPPER	N	PVALUE
COUNTRY					
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

		95% LIMITS		
	MEAN	LOWER	UPPER	PVALUE
COUNTRY				
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 DIFF	95% LIMITS LOWER	UPPER	DTG_50mg	RAL	PVALUE
ABC EXPOSURE						
No	8.6%	2.1%	15.0%	260/321=81.0%	234/323=72.4%	
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

	MEAN DIFF	95% LIMITS LOWER	UPPER	DTG	PLAC	N_P	N_D
ABC EXPOSURE							
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

	MEAN DIFF	95% LIMITS LOWER	UPPER	DTG 50mg_BID	50mg_QD	PVALUE
ABC EXPOSURE						
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

	MEAN	95% LIMITS LOWER	UPPER	N	PVALUE
ABC EXPOSURE					
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 DIFF	95% LIMITS 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 DIFF	95% LIMITS LOWER	UPPER	DTG_50mg	RAL	PVALUE
BGSS42	BL GSS to 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 to 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 to 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 to 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 DIFF	95% LIMITS LOWER	UPPER	DTG	PLAC	N_P	N_D
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 DIFF	95% LIMITS LOWER	UPPER	DTG 50mg_BID	50mg_QD	PVALUE
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 DIFF	95% LIMITS LOWER	UPPER	DTG 50mg_BID	50mg_QD	PVALUE
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 DIFF	95% LIMITS LOWER	UPPER	DTG	PLAC	N_P	N_D
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 DIFF	95% LIMITS LOWER	UPPER	DTG 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 DIFF	95% LIMITS LOWER	UPPER	DTG 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 DIFF	95% LIMITS LOWER	UPPER	DTG	PLAC	N_P	N_D
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 DIFF	95% LIMITS LOWER	UPPER	DTG 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 DIFF	95% LIMITS LOWER	UPPER	DTG 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 DIFF	95% LIMITS 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 DIFF	95% LIMITS LOWER	UPPER	DTG 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 DIFF	95% LIMITS LOWER	UPPER	DTG 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

		MEAN	95% LIMITS LOWER	UPPER	N	PVALUE
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

		MEAN	95% LIMITS LOWER	UPPER	PVALUE
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

		95% LIMITS			
	MEAN	LOWER	UPPER	N	PVALUE
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		
	MEAN	LOWER	UPPER	PVALUE
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 LOWER	UPPER	PVALUE
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		
	MEAN	LOWER	UPPER	PVALUE
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

		95% LIMITS			
	MEAN	LOWER	UPPER	N	PVALUE
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

		95% LIMITS		
	MEAN	LOWER	UPPER	PVALUE
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.

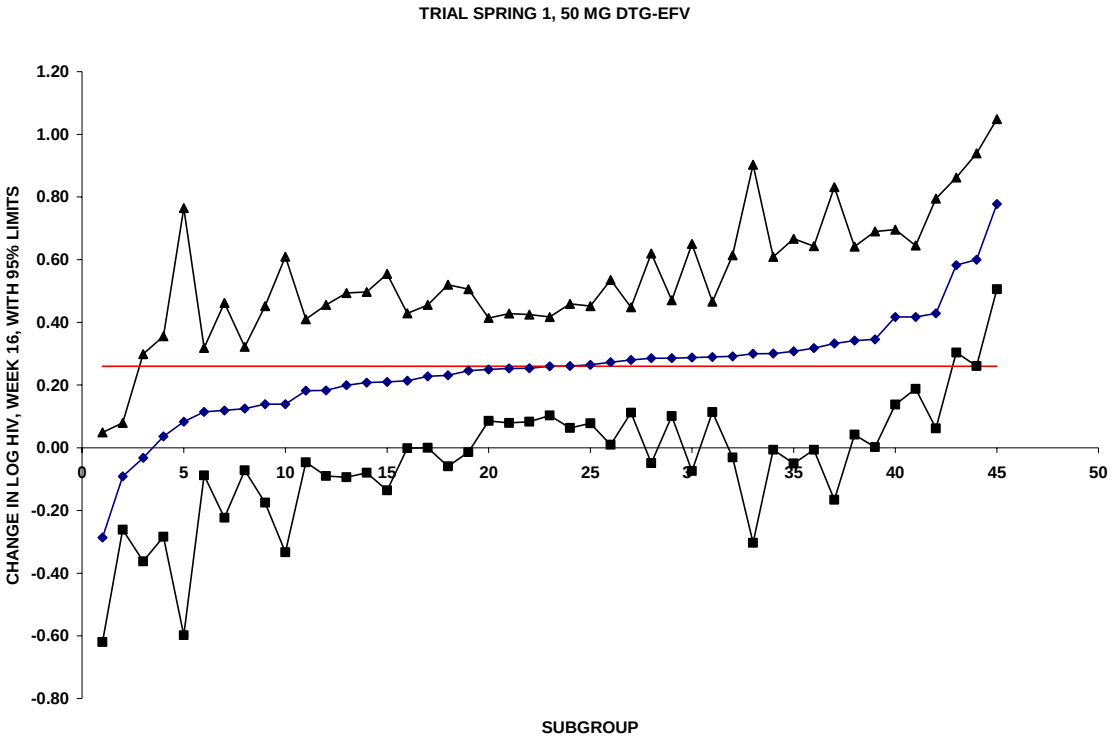
In the first graph, the subgroups are sorted by increasing value of the difference between DTG_50mg and control. (The control in Viking 3 is a constant zero.) In this graph, the plot includes the point estimate and upper and lower bounds for each subgroup plus a horizontal line corresponding to the point 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.

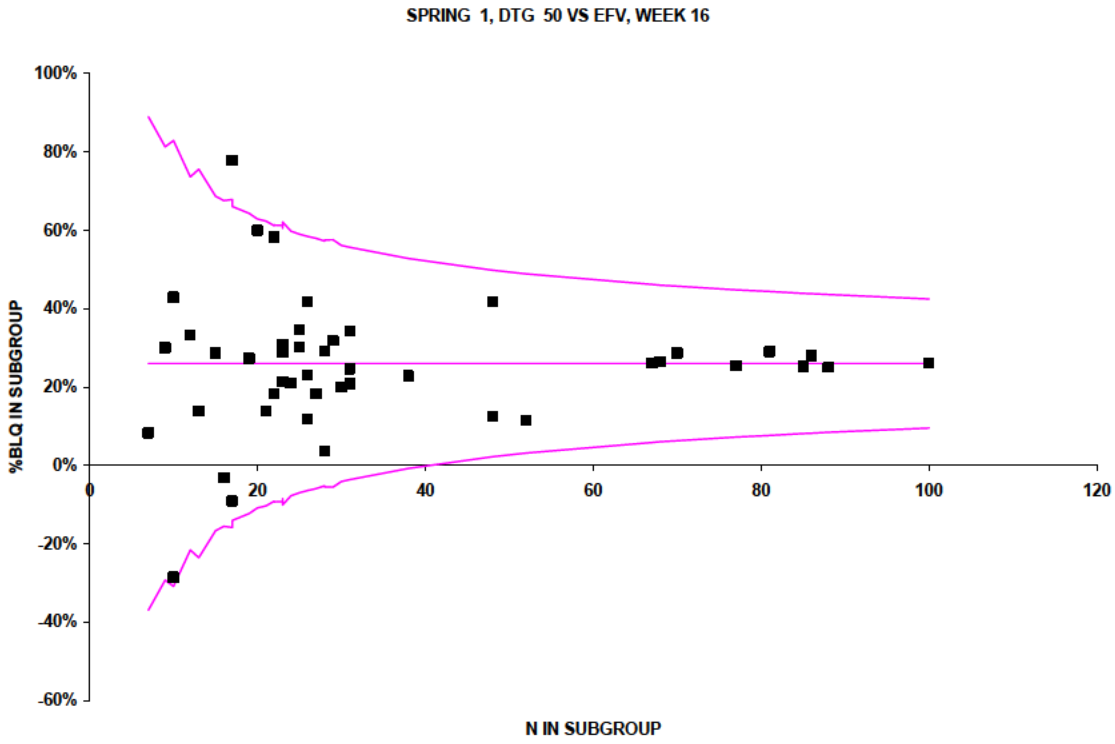
In the second graph, the point estimates for each subgroup are sorted by increasing sample size in the subgroup. Only the point estimates are plotted so each subgroup is represented by one discrete point. Three curves are also plotted. The horizontal line is the point estimate for all subjects taken 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

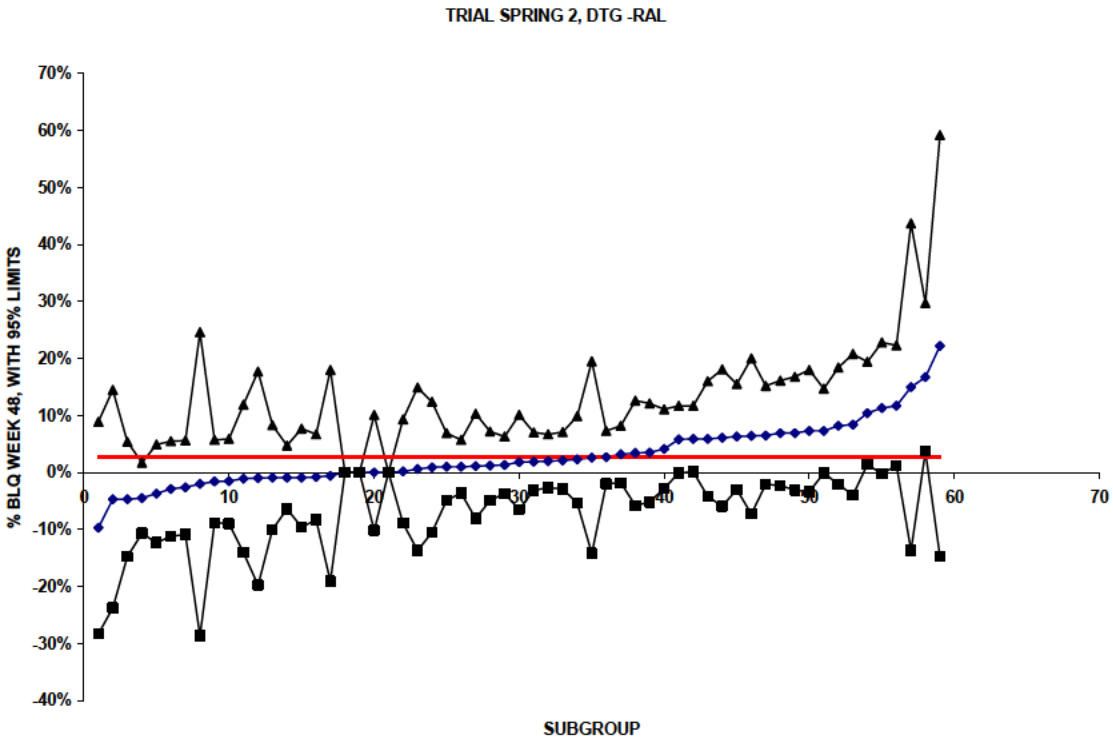
were exactly the same in, say, males and females, and any observed difference were just due to random sampling error, then the point estimate for males would lie between the upper and lower curves, as the point estimate for females. If the majority of the point representing individual subgroups lie within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

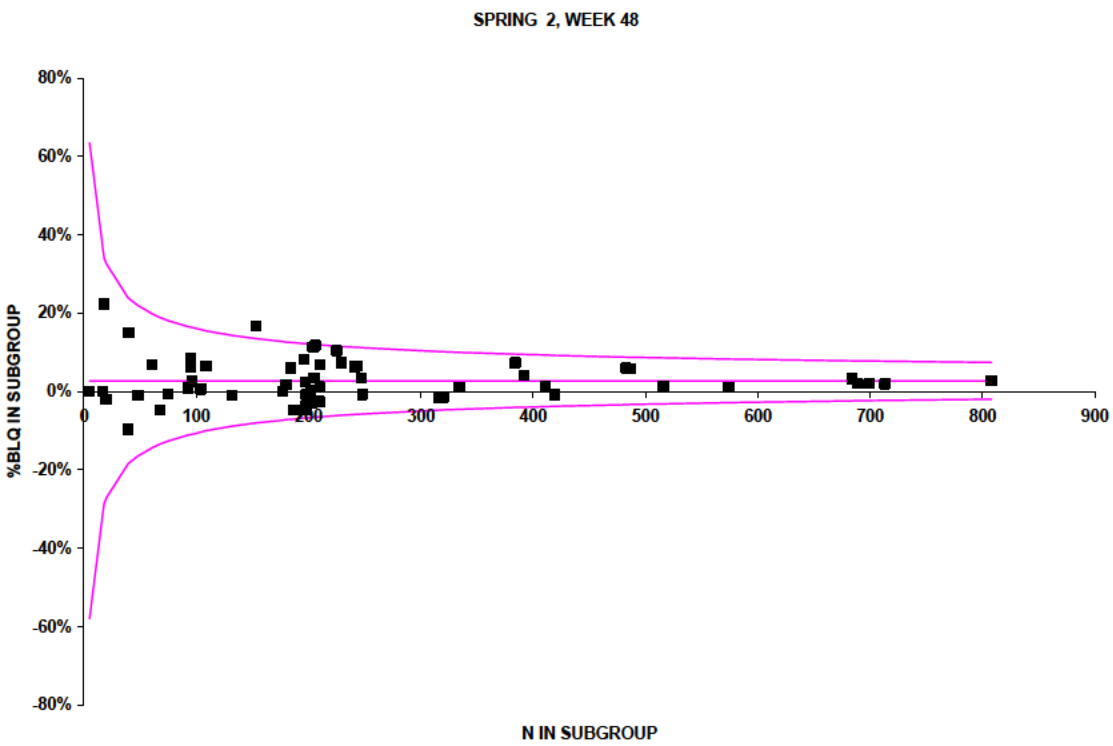
One will observe that the upper and lower curves in these graphs are not smooth but rather exhibit some jerks up and down. That is because the limits on difference between two samples would depend not merely on the total sample size= sum of the sample sizes in each arm but also on the sample sizes in 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.

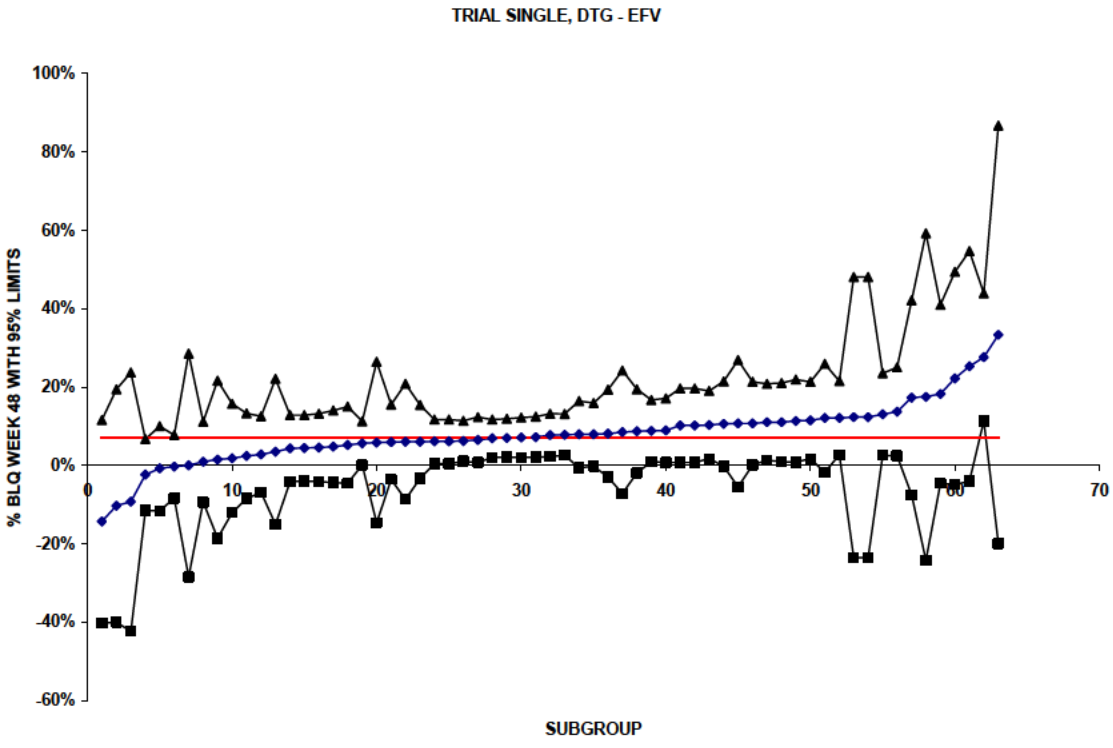
4.4.1 Treatment Naïve Trials

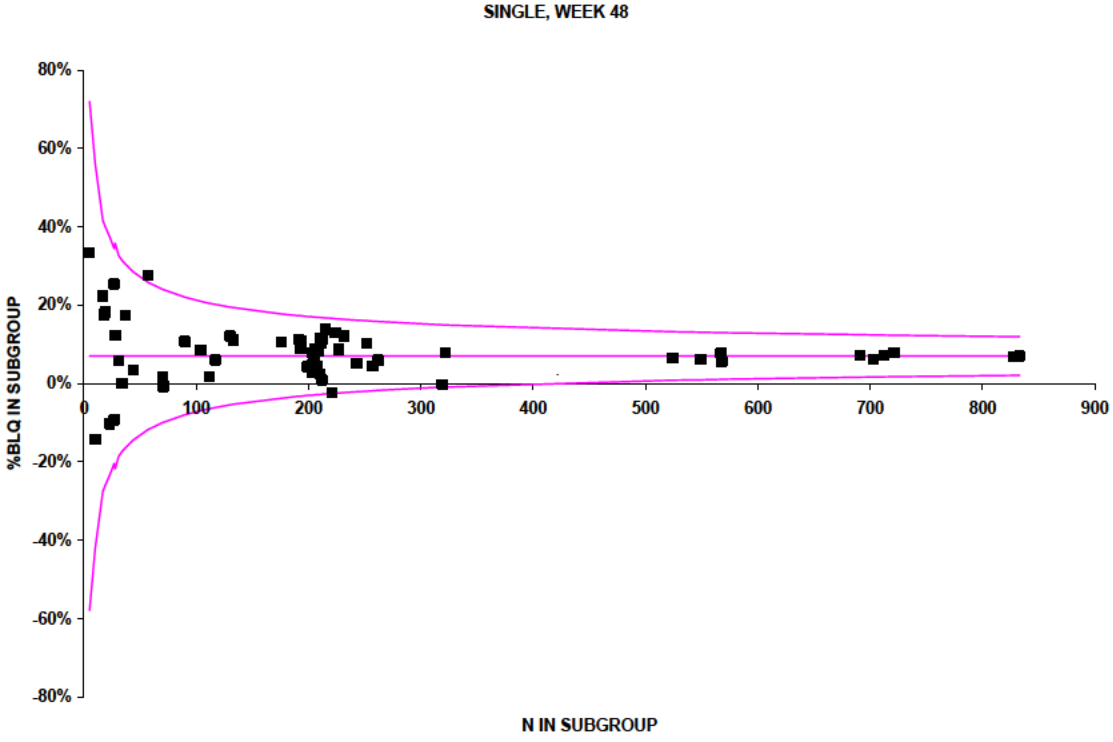




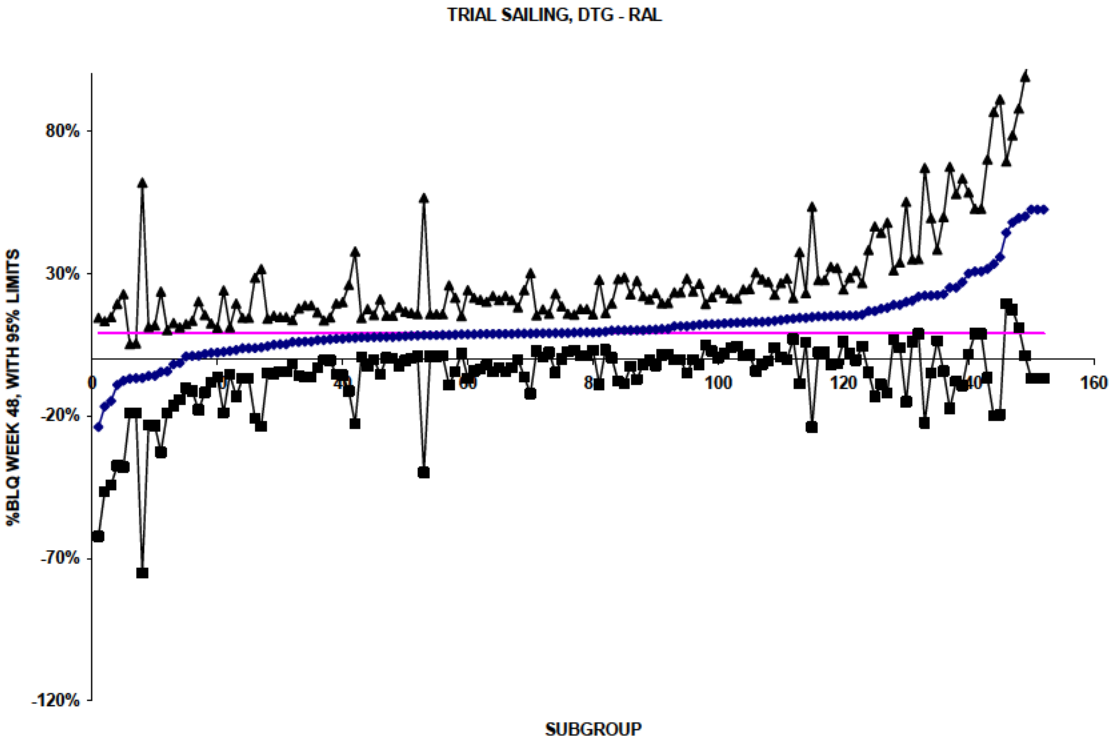


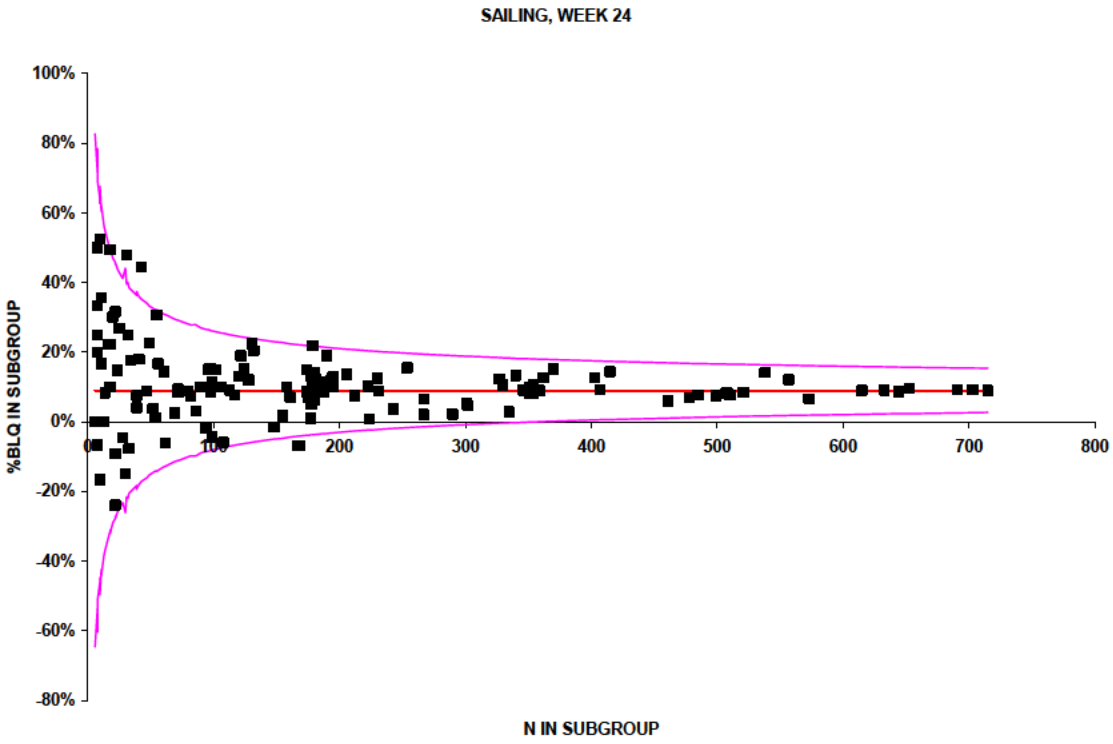



TRIAL SINGLE, DTG - EFV
% BLQ WEEK 48 WITH 95% LIMITS
100%
80%
60%
40%
20%
0%
-20%
-40%
-60%
0
10
20
30
40
50
60
70
SUBGROUP

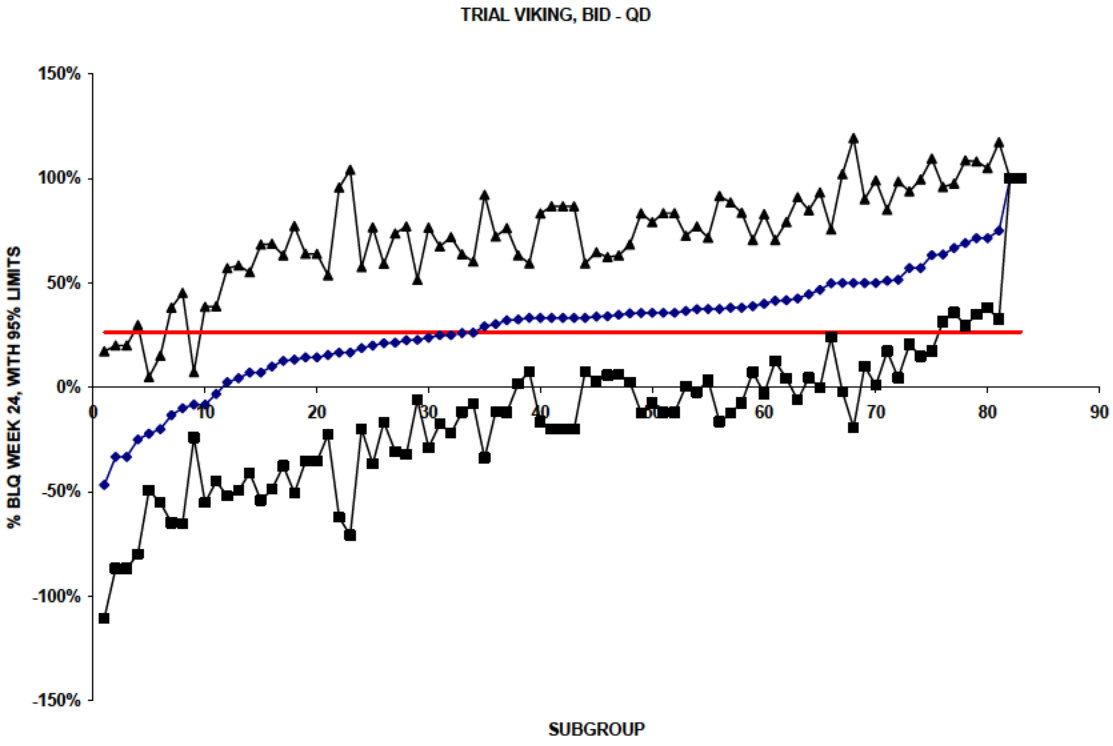

SINGLE, WEEK 48
%BLQ IN SUBGROUP
80%
60%
40%
20%
0%
-20%
-40%
-60%
-80%
0
100
200
300
400
500
600
700
800
900
N IN SUBGROUP

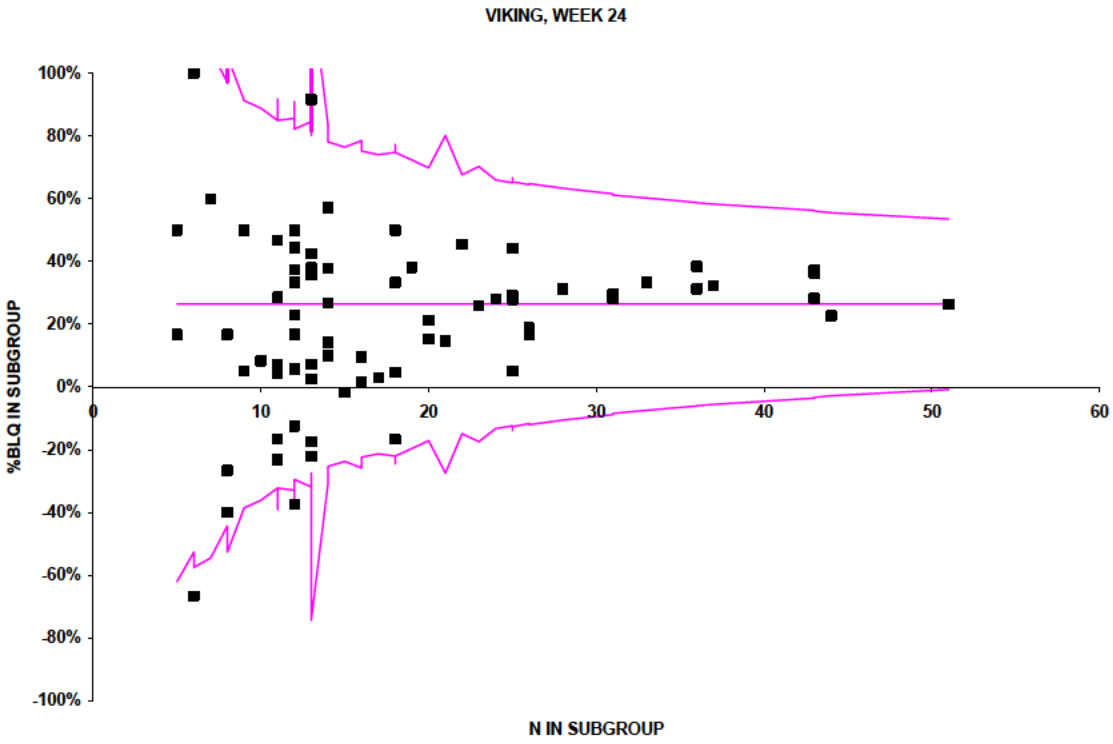
4.4.2 Two Class Resistant INI Naïve Trial

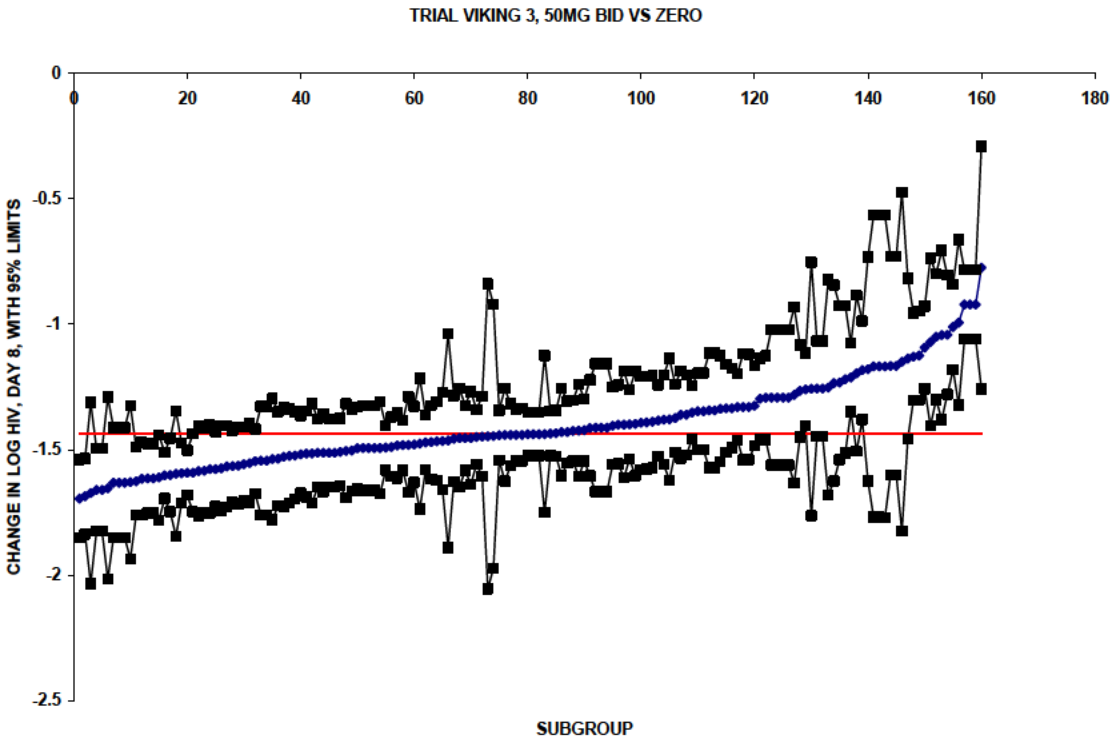


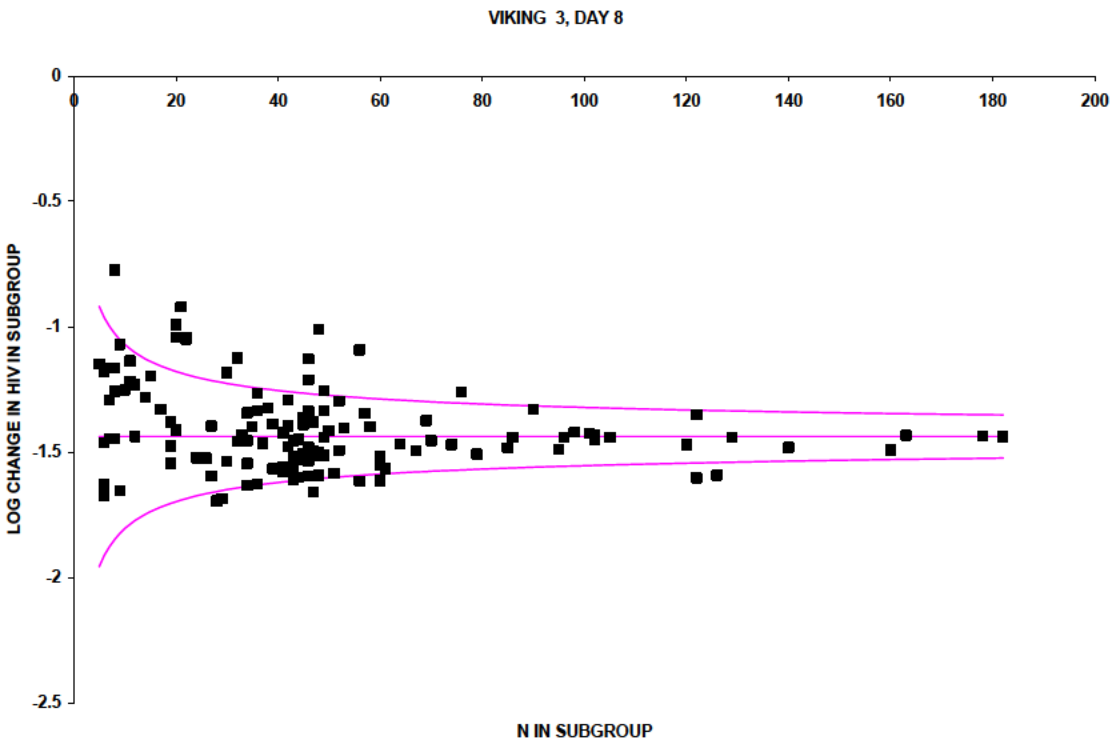

SAILING, WEEK 24
100%
80%
60%
40%
20%
0%
-20%
-40%
-60%
-80%
%BLQ IN SUBGROUP
0
100
200
300
400
500
600
700
800
N IN SUBGROUP

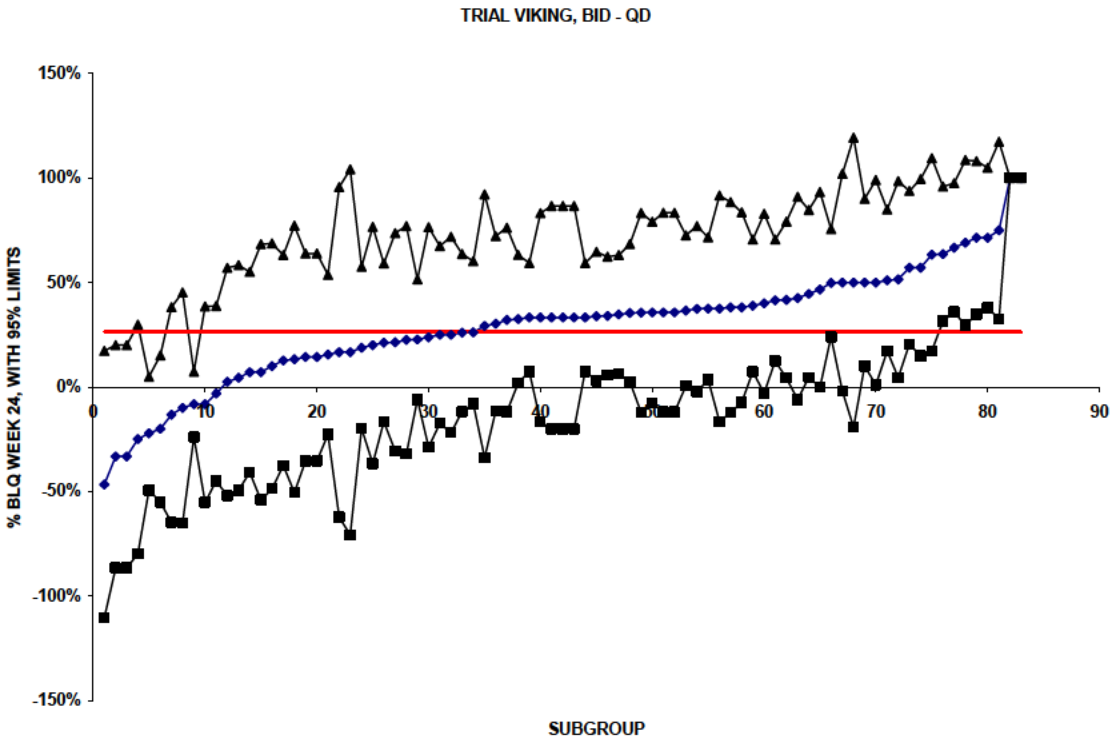
4.4.3 Two Class Resistant, INI Resistant Trials

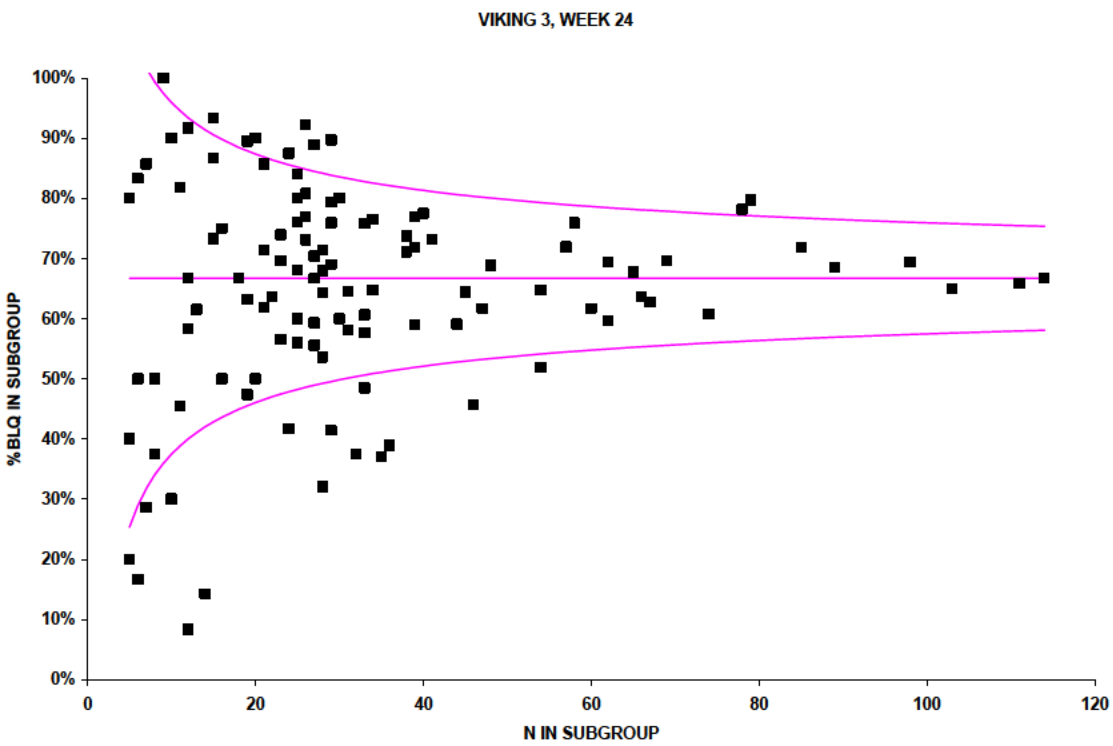



VIKING, WEEK 24
100%
80%
60%
40%
20%
0%
-20%
-40%
-60%
-80%
-100%
%BLQ IN SUBGROUP
0
10
20
30
40
50
60
N IN SUBGROUP


TRIAL VIKING 3, 50MG BID VS ZERO
CHANGE IN LOG HIV, DAY 8, WITH 95% LIMITS
0
-0.5
-1
-1.5
-2
-2.5
0
20
40
60
80
100
120
140
160
180
SUBGROUP


VIKING 3, DAY 8
LOG CHANGE IN HIV IN SUBGROUP
0
-0.5
-1
-1.5
-2
-2.5
0
20
40
60
80
100
120
140
160
180
200
N IN SUBGROUP





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 doe 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
HFD-530/Dr. Birnkrant
HFD-530/Dr. Murray
HFD-530/Dr. Marcus
HFD-530/Dr. Mullick
HFD-530/Dr. Carter
HFD-530/Mr. Mosaddegh
HFD-725/Dr. Hammerstrom
HFD-725/Dr. Soon
HFD-725/Dr. Lin
HFD-725/Dr. Huque
HFD-725/Dr. Patrician

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

/s/

THOMAS S HAMMERSTROM
05/08/2013

GUOXING SOON
05/15/2013