

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205551Orig1s000**

**STATISTICAL REVIEW(S)**

## STATISTICAL REVIEW AND EVALUATION

**NDA#:** 205551 SDN 001

**DRUG NAME:** Dolutegravir, Abacavir, 3TC FDC

**INDICATION:** Treatment of HIV Infection

**TYPE OF REVIEW:** Clinical

**APPLICANT:** ViiV Healthcare

**DATES:** Dec 21, 2013

**REVIEW PRIORITY:** Standard

**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), Yodit Belew,  
M.D. (HFD-530)

**PROJECT MANAGER:** Sohail Mosaddegh, (HFD-530)

## STATISTICAL REVIEW AND EVALUATION

NDA#: 205551

1. Executive Summary
2. Introduction
  - 2.1 Overview
  - 2.2 Data Sources
    - 2.2.1 Objectives in Trials
    - 2.2.2 Summary of Study Design
    - 2.2.3 Patient Accounting and Baseline Characteristics
      - 2.2.3.1 Trials with Treatment Naïve Patients
      - 2.2.3.2 Trials with Treatment Experienced, Integrase Inhibitor Naïve Patients
      - 2.2.3.4 Summary
    - 2.2.4 Summary of Methods of Assessment
      - 2.2.4.1 Schedule of Measurements
      - 2.2.4.2 Assessment of Treatment Effects
    - 2.2.5 Summary of Statistical Analysis
    - 2.2.6 Summary of Applicant's Results
      - 2.2.6.1 Trials with Treatment Naïve Patients
      - 2.2.6.2 Trials with Treatment Experienced, Integrase Inhibitor Naïve Patients
    - 2.2.7 Summary of Applicant's Conclusions
3. Statistical Evaluation
  - 3.1 Primary Efficacy Results
    - 3.1.1 Replication of Applicant's Primary Results
    - 3.1.3 Reasons for Failure
  - 3.2 Time Course of Viral Load
    - 3.2.1 Treatment Naïve Trials
    - 3.2.2 Two Class Resistant INI Naïve Trials
  - 3.3 Results with ABC/3TC Specifically
  - 3.4 Change in CD4 Count
    - 3.4.1 Treatment Naïve Trials
    - 3.4.2 Two Class Resistant INI Naïve Trial
4. Results in Special Populations
  - 4.1 Gender, Race, and Age
    - 4.1.1 Treatment Naïve Trials
    - 4.1.2 Two Class Resistant INI Naïve Trial

- 4.2 Baseline HIV, CD4, CDC Class
  - 4.2.1 Treatment Naïve Trials
  - 4.2.2 Two Class Resistant INI Naïve Trials
- 4.3 Demographic Covariates
  - 4.3.1 Treatment Naïve Trials
  - 4.3.2 Two Class Resistant INI Naïve Trial
- 4.4 Prior ART Exposure Covariates
  - 4.4.1 Two Class Resistant INI Naïve Trials
- 4.5 Baseline Resistance Covariates
  - 4.5.1 Two Class Resistant INI Naïve Trial: Baseline Sensitivity Scores
- 5. Summary and Conclusions

## 1. Executive Summary

The applicant submitted nine trials in support of the efficacy of dolutegravir (DTG) as part of a multi-drug regimen for the treatment of HIV-1. Four of these trials (ING113086 or Spring 2, ING114467 or Single, ING111762 or Sailing, and ING114915 or Flamingo) 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, one (ING116070) is a phase 3B open-label, single arm, 13 subject study of concentrations in serum and cerebrospinal fluid, and the other three (ING111521, ING112276 or Spring 1, and ING112961 or Viking) are phase 2 single arm or dose ranging studies. Seven of these trials have been discussed in a previous review. The current review gives longer term data on three of the large, randomized, controlled trials (Spring 2, Single, and Sailing) and also 24 week data on a new, large randomized controlled trial (Flamingo).

Six of the trials (ING111521, ING116070, ING112276 or Spring 1, ING113086 or Spring 2, ING114467 or Single, and ING114915 or Flamingo) 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.

One of the pivotal trials (Single, 4467) tested subjects randomized to DTG 50 mg qd or raltegravir (RAL) 400 mg qd with all subjects receiving the abacavir (ABC)\3TC background that will be part of the fixed dose combination (FDC). Two of the phase 3 trials (Spring\_2 3086 and Flamingo 4915) compared DTG 50 mg qd to either RAL 400 mg qd or darunavir 800 mg qd with a ritonavir booster of 100 mg qd (DRV/r) but had a choice of two background regimens, either the ABC/3TC of the FDC or tenofovir (TDF) 300 mg qd and FTC 200 mg qd. The fourth pivotal trial (Sailing, 1762) compared DTG 50 mg qd to RAL 400 mg qd with an investigator chosen background regimen of two NRTIs. Finally, the phase 2 study Spring 1 (2276) compared DTG 50 mg qd to EFV (and two lower DTG doses) with a background of either ABC/3TC or TDF/FTC.

In total, the number of subjects receiving the FDC whose indication is sought (DTG/ABC/3TC) and followed long enough for efficacy data to be collected was 687: 414 in Single (4467), 169 in Spring 2 (3086), 79 in Flamingo (4915), 8 in Sailing (1762), and 17 in Spring 1 (2276).

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 previous review. The current data shows that this statistically significant superiority is maintained to 96 weeks.

In the second pivotal trial, trial Spring 2, DTG at 50mg QD was statistically non-inferior to raltegravir (RAL) at week 48 in the previous review. Again, the current review shows that the DTG regimen remains no more than 5% worse than RAL out to 96 weeks.

At 24 weeks, the third large, randomized, open-label, phase 3B trial, trial Flamingo, showed DTG at 50mg QD was statistically significantly superior to DAR/rtv.

In the one pivotal trial (Sailing) in treatment experienced, two class resistant, integrase inhibitor (INI) naïve patients trial, DTG at 50mg QD was slightly 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 at week 24. The new data in this NDA show that by week 48, the DTG regimen was statistically significantly superior to RAL.

The general pattern of convincing efficacy was also confirmed when one focused exclusively on subjects who received the ABC/3TC background proposed in this NDA.

In the previous NDA, the applicant had 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. In the current NDA, the efficacy of DTG 50mg QD has been confirmed to 96 weeks in treatment naïve patients and to 48 weeks in two class resistant, INI naïve patients.

## 2. Introduction

### 2.1 Overview

The applicant submitted nine trials in support of the efficacy of dolutegravir (DTG) as part of a multi-drug regimen for the treatment of HIV-1. Four of these trials (ING113086 or Spring 2, ING114467 or Single, ING111762 or Sailing, and ING114915 or Flamingo) 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, one (ING116070) is a phase 3B open-label, single arm, 13 subject study of concentrations in serum and cerebrospinal fluid, 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 nine trials will be identified by their last four digits or by their name.

Six of the trials (ING111521, ING116070, ING112276 or Spring 1, ING113086 or Spring 2, ING114467 or Single, and ING114915 or Flamingo) 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.

One of the pivotal trials (Single, 4467) tested subjects randomized to DTG 50 mg qd or raltegravir (RAL) 400 mg qd with all subjects receiving the abacavir (ABC)\3TC background that will be part of the fixed dose combination (FDC). Two of the pivotal trials (Spring 2 3086 and Flamingo 4915) compared DTG 50 mg qd to either RAL 400 mg qd or darunavir 800 mg qd with a ritonavir booster of 100 mg qd (DRV/r) but had a choice of two background regimens, either the ABC/3TC of the FDC or tenofovir (TDF) 300 mg qd and FTC 200 mg qd. The fourth pivotal trial (Sailing, 1762) compared DTG 50 mg qd to RAL 400 mg qd with an investigator chosen background regimen of two NRTIs. Finally, the phase 2 study Spring 1 (2276) compared DTG 50 mg qd to EFV (and two lower DTG doses) with a background of either ABC/3TC or TDF/FTC.

In total, the number of subjects receiving the FDC whose indication is sought (DTG/ABC/3TC) and followed long enough for efficacy data to be collected was 687: 414 in Single (4467), 169 in Spring 2 (3086), 79 in Flamingo (4915), 8 in Sailing (1762), and 17 in Spring 1 (2276).

The Single, Spring 2 and Sailing trials were initially analyzed in NDA 204790 for DTG alone but additional longer term data is presented in this NDA for all three of them. The Flamingo trial is analyzed for the first time in this review. All of the Spring 1 data was previously analyzed in NDA 204790 but the conclusions are repeated in this review.

Trials 1521, Viking (2961), and Viking 3 (2574) were analyzed as part of NDA 204790 and are not relevant to the current NDA for the FDC. Trial 6070 is also too small, short, and uncontrolled for use in determining efficacy. These four trials will not be discussed further.

## **2.2 Data Sources**

### **2.2.1 Objectives in Trials**

The primary objective of the five trials reviewed below was to establish the efficacy of dolutegravir at 50 mg once daily in ART naïve or 2 class resistant, integrase inhibitor (INI) naïve HIV-1 infected patients. Additional emphasis will be placed on the performance of DTG with the background regimen of ABC\3TC because this is the combination contained in the FDC.

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. Trial 4915 (also called Flamingo) is a phase 3B study in the treatment naïve population. There is also a supportive phase 2 study in the treatment naïve population: 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.

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

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 4915 (also called Flamingo) was a randomized, multi-center, open label, active controlled trial with subjects who were ART naïve. 468 subjects were randomized 1:1 to either DTG 50 mg qd or darunavir/ritonavir (DRV/r) 800/100` 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.

Trial 1762 (also called Sailing) was 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).

## 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, SINGLE, AND FLAMINGO)

	SPRING 2		SINGLE		FLAMINGO	
	DTG QD	RAL	DTG QD	ATRIPLA	DTG QD	DRV\R
Randomized	413	414	422	422	243	245
Treated	411	411	414	419	242	242
Week 48						
Ongoing	364	355	363	335	224	213
Withdrew	47	56	51	84	18	29
LOE	16	24	14	13	2	2
AE	10	7	10	42	4	10
LTFU	4	7	14	9	6	10
Other	17	18	13	20	6	7
Week 96						
Completed/						
Ongoing	348	332	341	303		
Withdrew	63	79	73	116		
LOE	17	25	18	15		
AE	10	10	14	52		
LTFU	6	10	17	18		
Other	39	34	24	31		

(Protocol defined liver endpoint included as AE, LOE=lack of efficacy, 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 subjects: 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%

In trial 4915 (Flamingo), 64 investigational sites enrolled subjects: 6 in France, 3 in Germany, 5 in Italy, 3 in Romania, 5 in Russia, 5 in Spain, 3 in Switzerland, 3 in Puerto Rico and 31 in the US. Number and percent of total enrollment in each country is given in table 2.2.3.1 D.

TABLE 2.2.3.1 D  
NUMBER AND PERCENT OF SUBJECTS IN EACH COUNTRY  
FLAMINGO TRIAL 4915

COUNTRY	NUMBER	PERCENT
USA	2506	43.7%
France	633	11%
Germany	240	4.2%
Italy	582	10.1%
Puerto Rico	156	2.7%
Romania	239	4.2%
Russia	213	3.7%
Spain	1029	17.9%
Switzerland	143	2.5%

The three 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.

Subjects in trial 4915 (Flamingo) had a median age of 34 years, were 85% male, were 19% Hispanic, were 72% White and 23% Black, and were 84% CDC class A. 70% identified homosexual activity as their risk factor, 29% heterosexual contact and 2% injectable drug use. Median baseline HIV-1 RNA was 4.49 log copies/ml, median baseline CD4 count was 395. 13 subjects had hepatitis B, 32 had hepatitis C and one had both.

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.

### 2.2.3.4 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		MEDIAN BASELINE	
		CLASS A	CLASS C	HIV-1 RNA	CD4 COUNT
Naïve					
Spring 2	822	86%	2%	4.55	360
Single	833	83%	4%	4.68	338
Spring 1	208	87%	1%	4.5	308
Flamingo	484	84%	4%	4.49	395
2-Class Resistant, INI Naïve					
Sailing	715	31%	46%	4.18	200

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

### **2.2.4.1 Schedule of Measurements**

The five trials reviewed here 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 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 endpoints in the three phase 3 trials with treatment naïve subjects, Spring 2, Single and Flamingo, were HIV-1 RNA observed BLQ at week 48 (regardless of subsequent confirmation or prior rebound, i.e. snapshot) and HIV-1 RNA observed BLQ at week 96.

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.

## **2.2.5 Summary of Statistical Analysis**

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 the three phase 3 trials in naïve subjects, Spring 2, Single and Flamingo, used percent observed suppressed to BLQ at week 48 and week 96. In all 3 trials, the DTG and

control arms (RAL in Spring 2, EFV in Single, DRV/r in Flamingo) 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 and Flamingo, baseline HIV-1 RNA and baseline CD4 count in Single). Non-inferiority to RAL, EFV or DRV/r was declared if the lower confidence bound for the week 48 differences was  $>-10\%$ . In the two trials started earlier, 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 48 with a CMH confidence interval (week 24 was used in the previous NDA 204790). 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.

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

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

The results for trial Spring 1 (2276) are given in tables 2.2.6 A and B. 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 A 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 A  
 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%*

\* = statistically significantly superior to EFV

TABLE 2.2.6 B  
 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 C and D. The first table gives the percent with snapshot viral suppression in the two arms at weeks 48 and 96, 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 and fourth rows 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 weeks 48 and 96. At both weeks 48 and 96, 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 C  
 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%
Week_96	332/411=81%	314/411=76%	4.5%	-1.1%,10.0%
	332/403=82%	314/405=78%	4.9%	-0.6%,10.3%

TABLE 2.2.6 D  
 SPRING 2 TRIAL (3086) HIV RNA RESULTS  
 SUPPRESSIONS AND FAILURES AT WEEKS 48,96

	DTG 50mg qd	RAL
N	411	411
Week 48		
Success	361 88%	351 85%
>50, new ART or		
Disc. LOE	20 5%	31 8%
Discontinued		
AE	9 2%	6 1%
Other	21 5%	23 6%
Week 96		
Success	332 81%	314 76%
>50, new ART or		
Disc. LOE	22 5%	43 8%
Missed Visit	7 2%	3 1%
Discontinued		
AE	10 2%	10 2%
Other	40 10%	41 10%

The results for trial Single (4467) are given in tables 2.2.6 E and F. The first table gives the percent with snapshot viral suppression in the two arms at weeks 48 and 96, 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 weeks 48 and 96. The protocol specified primary comparison of non-inferiority of the DTG regimen to the EFV regimen was established at both weeks 48 and 96. In fact, the DTG regimen was statistically significantly superior at both times.

TABLE 2.2.6 E  
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%
Week_96	332/414=80%	303/419=72%	8.0%	2.3%,13.8%

TABLE 2.2.6 F  
SINGLE TRIAL (4467) HIV RNA RESULTS  
SUPPRESSIONS AND FAILURES AT WEEKS 48, 96

	DTG 50mg qd	EFV
N	414	419
Week 48		
Success	364 88%	338 81%
Missed Visit	0	1 <1%
>50, new ART or Disc. LOE	21 5%	26 6%
Discontinued		
AE	9 2%	40 10%
Other	20 5%	14 3%
Week 96		
Success	332 80%	303 72%
Missed Visit	2 <1%	0
>50, new ART or Disc. LOE	31 7%	33 8%
Discontinued		
AE	13 3%	48 11%
Other	36 9%	35 8%

The results for trial Flamingo (4915) are given in tables 2.2.6 G and H. The first table gives the percent with snapshot viral suppression in the two arms at weeks 48. together with the DTG-DRV 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 DRV/r regimen was established. In fact, the DTG regimen was statistically significantly superior.

TABLE 2.2.6 G  
 FLAMINGO TRIAL (4915) HIV RNA RESULTS  
 OBSERVED HIV-1 RNA<50 C/ML

	DTG 50mg qd	DRV/r	Adjusted Difference	95% Confidence Limits
Week_48	217/242=90%	200/242=83%	7.1%	0.9%,13.2%

TABLE 2.2.6 H  
 FLAMINGO TRIAL (4915) HIV RNA RESULTS  
 SUPPRESSIONS AND FAILURES AT WEEK 48

	DTG 50mg qd	DRV/r
N	242	242
Week 48		
Success	217 90%	200 83%
Missed Visit	1 <1%	4 2%
>50, new ART or Disc. LOE	15 6%	18 7%
Discontinued		
AE	3 1%	9 4%
Other	6 2%	11 5%

### **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 I and J. 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 weeks 24 and 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 table gives a breakdown of the reasons for failure at weeks 24 and 48. 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 I  
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	251/354=71%	230/361=64%	7.4%	0.7%,14.2%

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

	DTG 50mg qd	RAL
N	354	361
Week 24		
Success	281 79%	252 70%
Missed 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%
Week 48		
Success	251 71%	230 64%
Missed Visit	7 2%	4 1%
>50 at Week 48		
or new ART	45 13%	58 16%
Discontinued		
LOE	26 7%	42 12%
AE	6 2%	9 2%
Other	16 5%	14 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 and three phase 3 trials. The phase 2 trials, trial 1521 and Spring 1, have been discussed in NDA 204790. The effectiveness of DTG 50mg qd in the naïve population was confirmed in two pivotal trials, Spring 2 with a RAL (raltegravir) control and Single with an EFV (efavirenz) control. This NDA extends the data from those two trials out to 96 weeks without changing the conclusions of substantial efficacy relative to the controls. In addition, a third, open-label, trial, Flamingo, further confirms the efficacy of DTG relative to a third control drug, DRV/r (darunavir boosted with ritonavir), out to 24 weeks.

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, as was reported in NDA 204790. This trial now has complete data out 48 weeks, which confirms the preliminary finding in NDA 204790 that DTG 50mg qd is non-inferior to RAL with respect to viral suppression.

With respect to subjects who were treatment experienced and INI resistant, no new data is available in this NDA. NDA 204790 has already provided reasonably good evidence of efficacy of DTG at 50mg bid in this highly experienced population.

### **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 percent BLQ at the designated primary time points: weeks 24, 48, or 96. 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.

The applicant also discovered that one physician in Russia (Kozyrev) was guilty of GCP (good clinical practice) violations. The subjects from this site were included in the applicant provided datasets for three trials, Spring 2, Flamingo, and Sailing. In all the analyses in this review, the subjects from this site were excluded.

There is also an issue that affects the computation of the confidence intervals for percent BLQ. For the four randomized pivotal trials, Spring 2, Single, Flamingo, 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. FDA statisticians recommend the use of the weighted average of within-stratum results.

The weights used in the Mantel-Haenszel procedure are  $N/pq$ , where  $N$  = sample size in the stratum and  $p$  and  $q$  are the proportions of successes and failures within the stratum. This means that a stratum gets higher weight both when it has more observations and when the success rate is higher (as opposed to success-failure proportions closer to 50:50). Simply pooling the results is equivalent to weighting the strata just by their sample sizes.

Table 3.1 A gives the comparison of the results for the major endpoints from applicant's efficacy review and the FDA reconstruction of the results using the datasets with individual visits. The applicant's point estimates and 95% confidence intervals are compared with the FDA's computations, using both the Mantel-Haenszel weighting and simple pooling to compute the confidence intervals.

TABLE 3.1 A  
COMPARISON OF APPLICANT AND FDA %BLQ AND CONFIDENCE LIMITS

	MEAN DIFF	95% LIMITS LOWER UPPER		DTG_50mg	CONTROL
SPRING_2_3086					
%BLQ_WEEK_48					
Applicant	2.6%	-1.9%	7.2%	356/403=88%	347/405=86%
FDA MH	1.8%	-2.4%	6.0%	355/403=88%	346/405=85%
Pool	2.9%	-1.7%	7.5%		
%BLQ_WEEK_96					
Applicant	4.9%	-0.6%	10.3%	332/403=81%	314/405=76%
FDA MH	4.5%	-0.8%	9.9%	332/403=82%	315/405=78%
Pool	4.6%	-0.9%	10.1%		
SINGLE_4467					
%BLQ_WEEK_48					
Applicant	7.4%	2.5%	12.3%	364/414=88%	338/419=81%
FDA MH	6.6%	1.8%	11.4%	364/414=87.9%	339/419=80.9%
Pool	6.8%	1.9%	11.7%		
%BLQ_WEEK_96					
Applicant	8.0%	2.3%	13.8%	332/414=80%	303/419=72%
FDA MH	8.7%	3.0%	14.4%	333/414=80%	303/419=72%
Pool	8.1%	2.4%	13.9%		
FLAMINGO_4915					
%BLQ_WEEK_24					
Applicant	.	.	.	218/242=90%	196/242=81%
FDA MH	6.0%	0.5%	11.5%	218/242=90%	195/242=81%
Pool	9.5%	3.3%	15.8%		
%BLQ_WEEK_48					
Applicant	7.1%	0.9%	13.2%	217/242=90%	200/242=83%
FDA MH	6.5%	0.6%	12.5%	218/242=90%	200/242=83%
Pool	7.4%	1.4%	13.5%		
SAILING_1762					
%BLQ_WEEK_24					
Applicant	9.7%	3.4%	15.9%	281/354=79%	252/361=70%
FDA MH	6.1%	0.2%	12.1%	283/354=79%	255/361=70%
Pool	7.5%	1.2%	13.7%		
%BLQ_WEEK_48					
Applicant	7.4%	0.7%	14.2%	251/354=71%	230/361=64%
FDA MH	6.6%	0.1%	13.2%	256/354=72%	235/361=65%
Pool	8.1%	2.4%	13.9%		

\* Flamingo had 1 failure on DTG at the Kozyrev site  
Sailing had 3 failures on DTG and 1 on RAL at the Kozyrev site.  
These 5 subjects are excluded in this table

One can see that for all the results, the results are inconsequentially different. 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, to DAR in Flamigno, and to RAL in Sailing.

### 3.1.3 Reasons for Failure

Tables 3.1 C and D give the breakdown of successes and failures by reason in the four trials (Spring 2, Single, Flamingo, and Sailing) of this NDA. Results from weeks 24 and 48 in Spring 2 and Single and week 24 in Sailing from the NDA 204790 review are included.

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%
SPRING_2_WEEK_96_RAL_VS_DTG_50mg				
(excluding Kozyrev)				
OUTCOME	DTG_50mg_QD		RAL	
Success	332	82.4%	315	77.8%
Viral_Failure	21	5.2%	40	9.9%
AE/Death	9	2.2%	10	2.5%
Other_Reason	34	8.4%	37	9.1%
Missing_in_window_but_on_study	7	1.7%	3	0.7%

TABLE 3.1 C

## OUTCOMES IN TREATMENT NAÏVE TRIALS (cont.)

## 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%

## SINGLE\_WEEK\_96\_EFV\_VS\_DTG\_50mg

OUTCOME	DTG_50mg_QD		EFV	
Success	322	77.8%	294	70.2%
Viral_Failure	42	10.1%	42	10.0%
AE/Death	13	3.1%	48	11.5%
Other_Reason	36	8.7%	35	8.4%
Missing_in_window_but_on_study	1	0.2%	.	.

FLAMINGO\_WEEK\_24\_DRV\RTV\_VS\_DTG\_50mg  
(excluding Kozyrev)

OUTCOME	DTG_50mg_QD		DRV/R	
Success	218	90.1%	195	80.6%
Viral_Failure	19	7.9%	35	14.5%
AE/Death	2	0.8%	6	2.5%
Other_Reason	2	0.8%	5	2.1%
Missing_in_window_but_on_study	1	0.4%	1	0.4%

FLAMINGO\_WEEK\_48\_DRV\RTV\_VS\_DTG\_50mg  
(excluding Kozyrev)

OUTCOME	DTG_50mg_QD		DRV/R	
Success	218	90.1%	200	82.6%
Viral_Failure	14	5.8%	18	7.4%
AE/Death	3	1.2%	9	3.7%
Other_Reason	6	2.5%	11	4.5%
Missing_in_window_but_on_study	1	0.4%	4	1.7%

TABLE 3.1 D

## OUTCOMES IN TWO CLASS RESISTANT, INI NAÏVE TRIAL

## SAILING\_WEEK\_24\_RAL\_VS\_DTG\_50mg

(including Kōzyrev)

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

## SAILING\_WEEK\_24\_RAL\_VS\_DTG\_50mg

(excluding Kōzyrev)

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

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

(excluding Kōzyrev)

OUTCOME	DTG_50mg_QD		RAL	
Success	256	72.3%	235	65.1%
Viral_Failure	67	18.9%	96	26.6%
AE/Death	9	2.5%	12	3.3%
Other_Reason	16	4.5%	14	3.9%
Missing_in_window_but_on_study	6	1.7%	4	1.1%

### **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 in all four trial in both populations studied. 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 96 weeks.

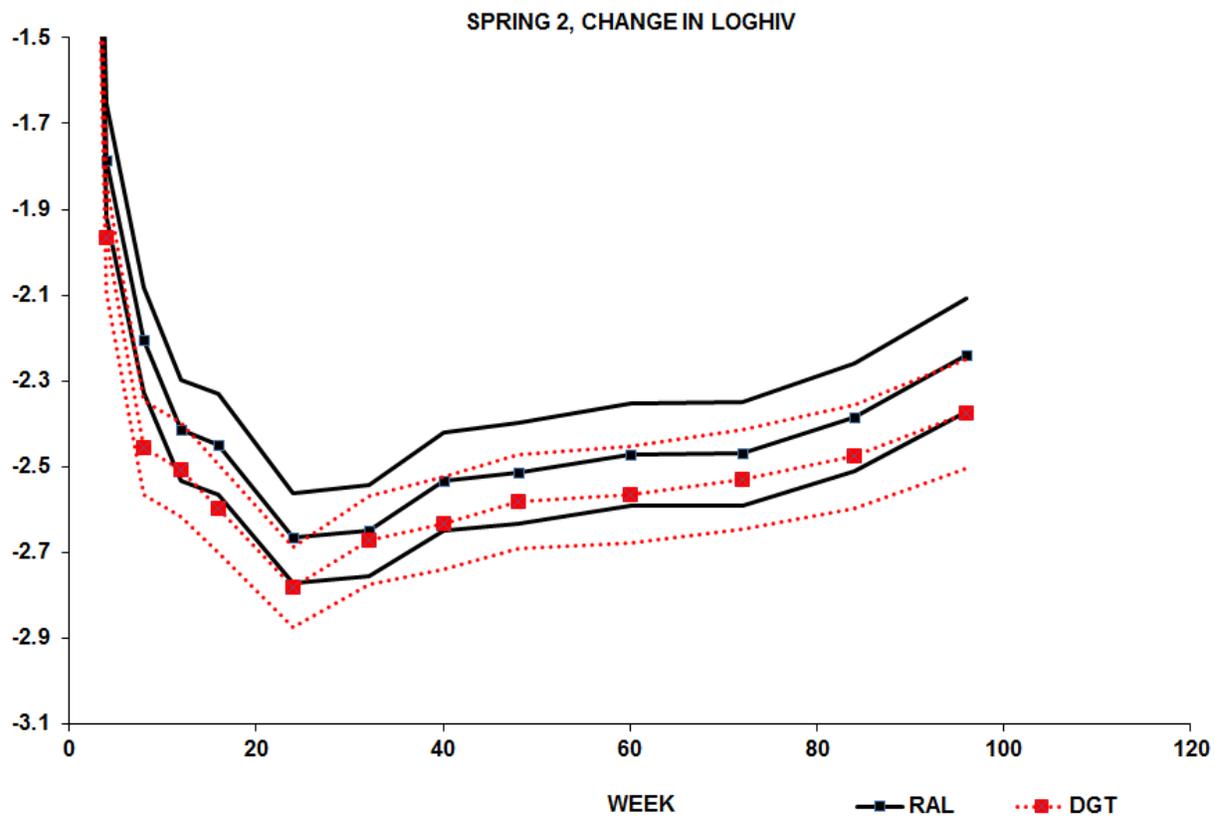
In trial Single, it is important to notice that the DTG 50mg QD arm was statistically significantly superior to the EFV arm throughout the first 96 weeks with respect to both endpoints examined, change in log HIV and percent BLQ.

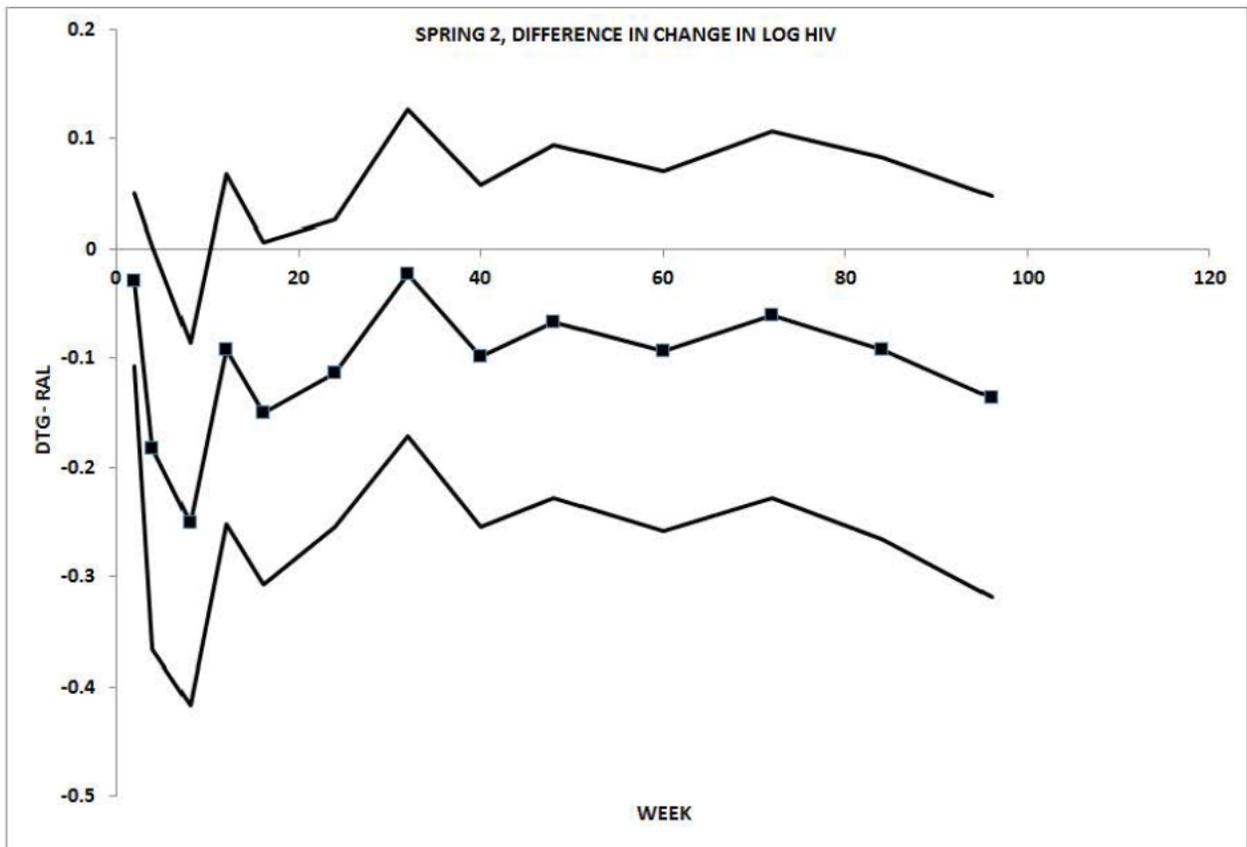
In trial Flamingo, DTG 50mg QD was slightly, but not statistically significantly, superior to DRV/R throughout the trial. The lower 95% confidence bound for the difference exceeded -10%, establishing non-inferiority to DRV/R throughout the first 96 weeks.

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.

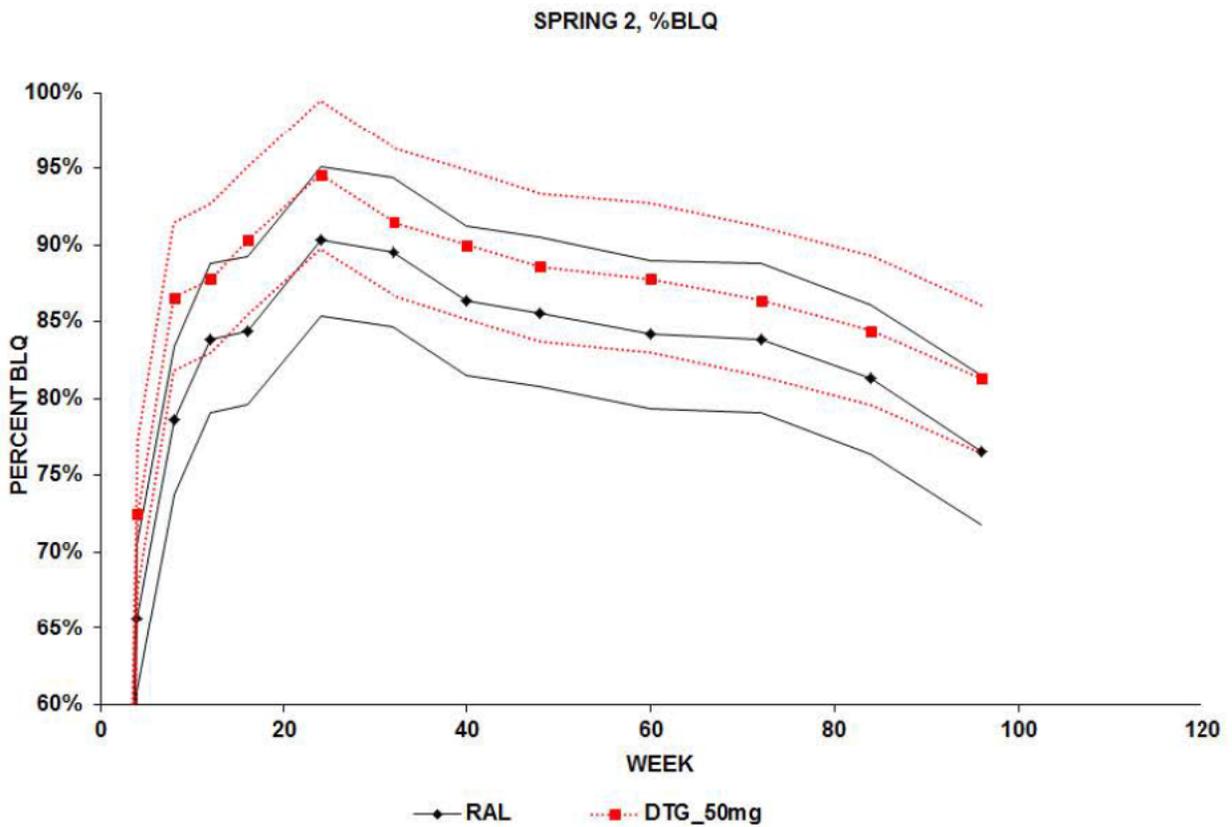
### 3.2.1 Treatment Naïve Trials

The first 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.

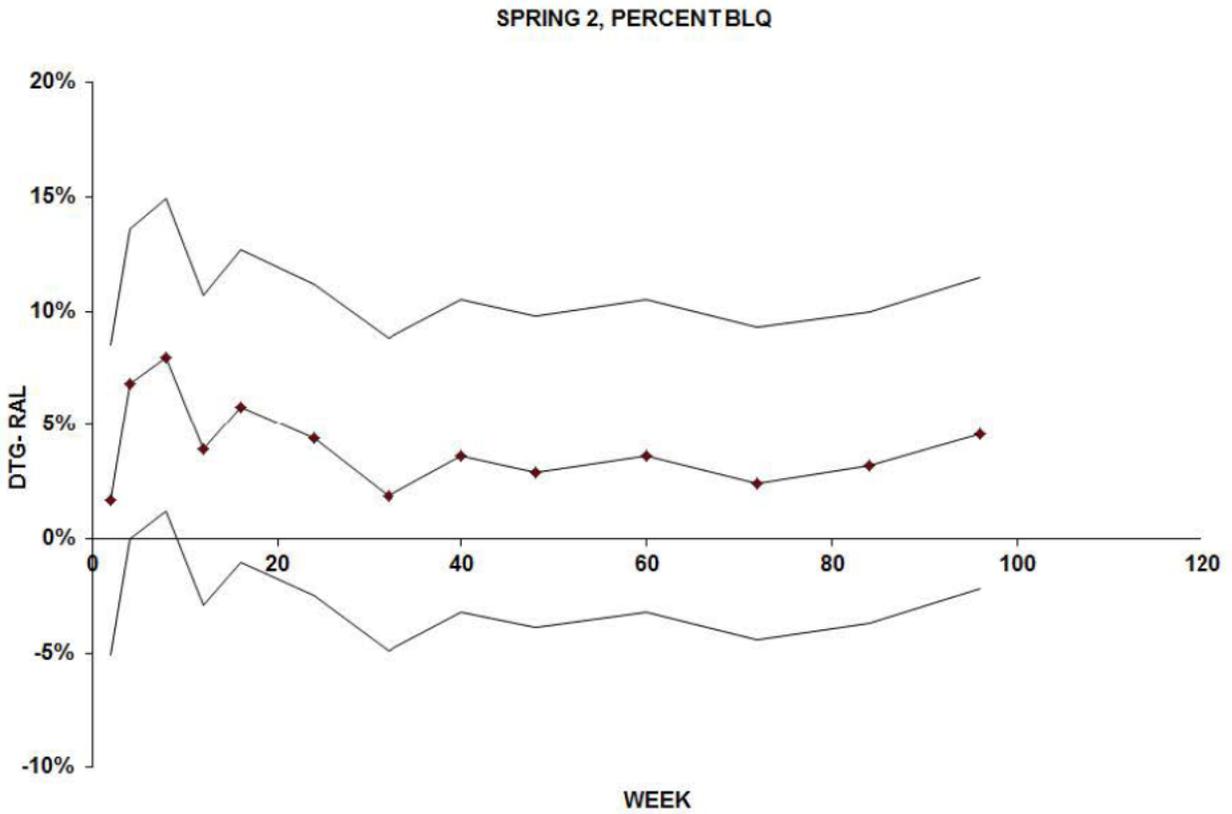




The next two graphs will show the %BLQ for the DTG and RAL arms in trial Spring 2 and the point estimates and 95% confidence limits for their difference.

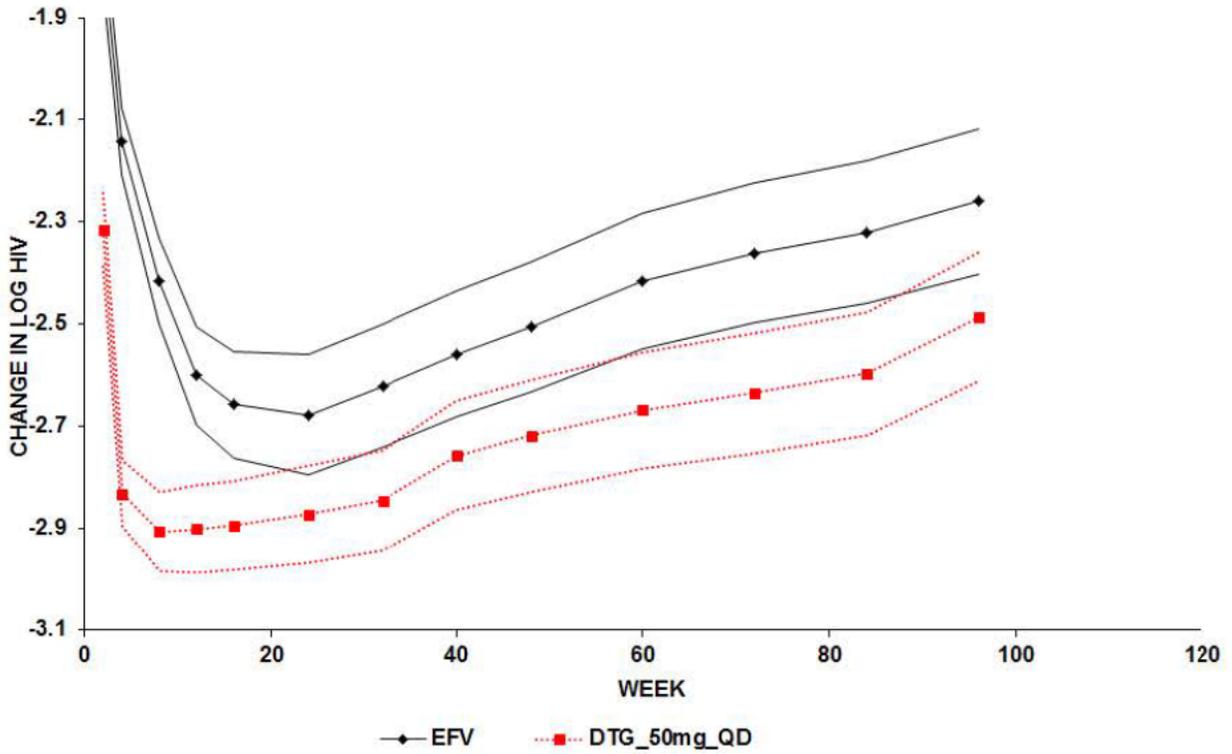


In this graph of the 95% confidence limits around the DTG-RAL difference, one does see that the lower bound exceeds -10%, providing statistically convincing evidence of non-inferiority throughout the first 48 weeks.

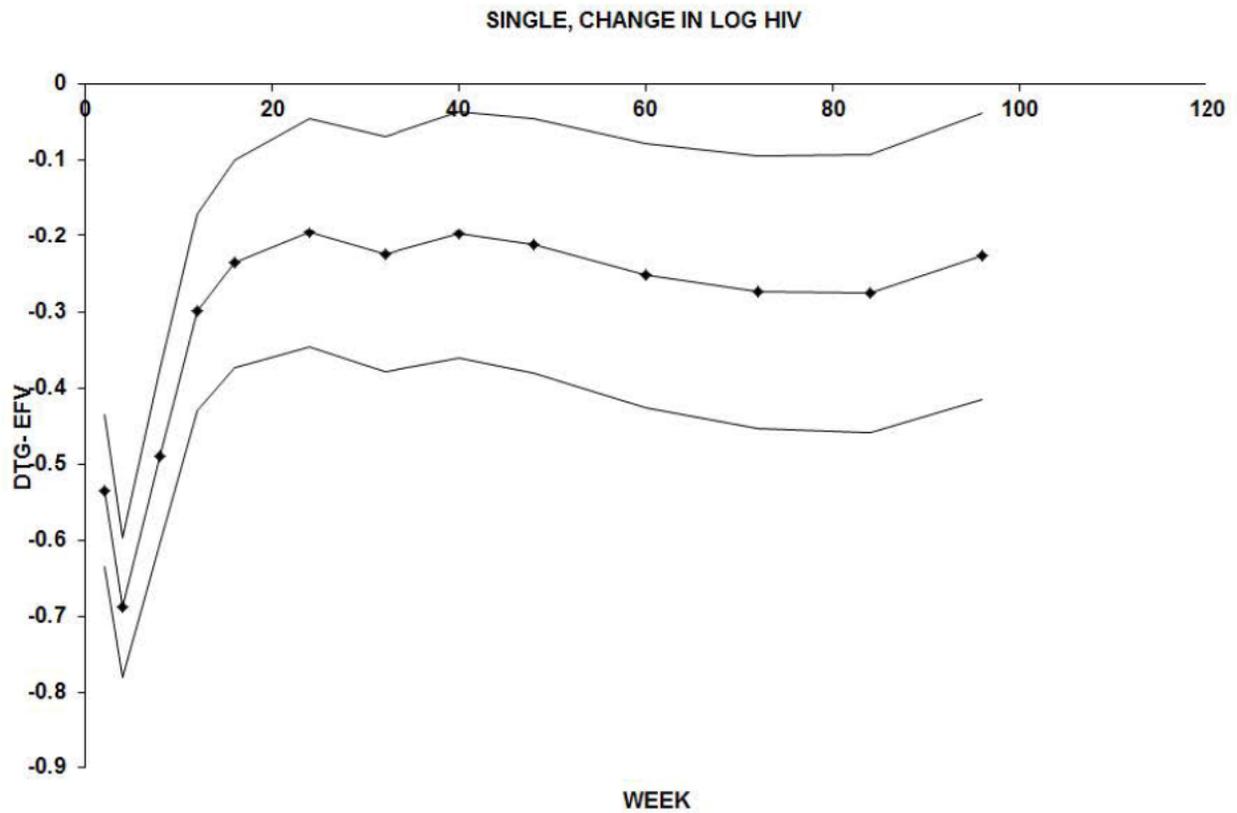


The next four graphs will repeat the previous four graphs for the second pivotal trial in treatment naïve subjects, Single. Change in log HIV and the 95% limits for change in log HIV are given first.

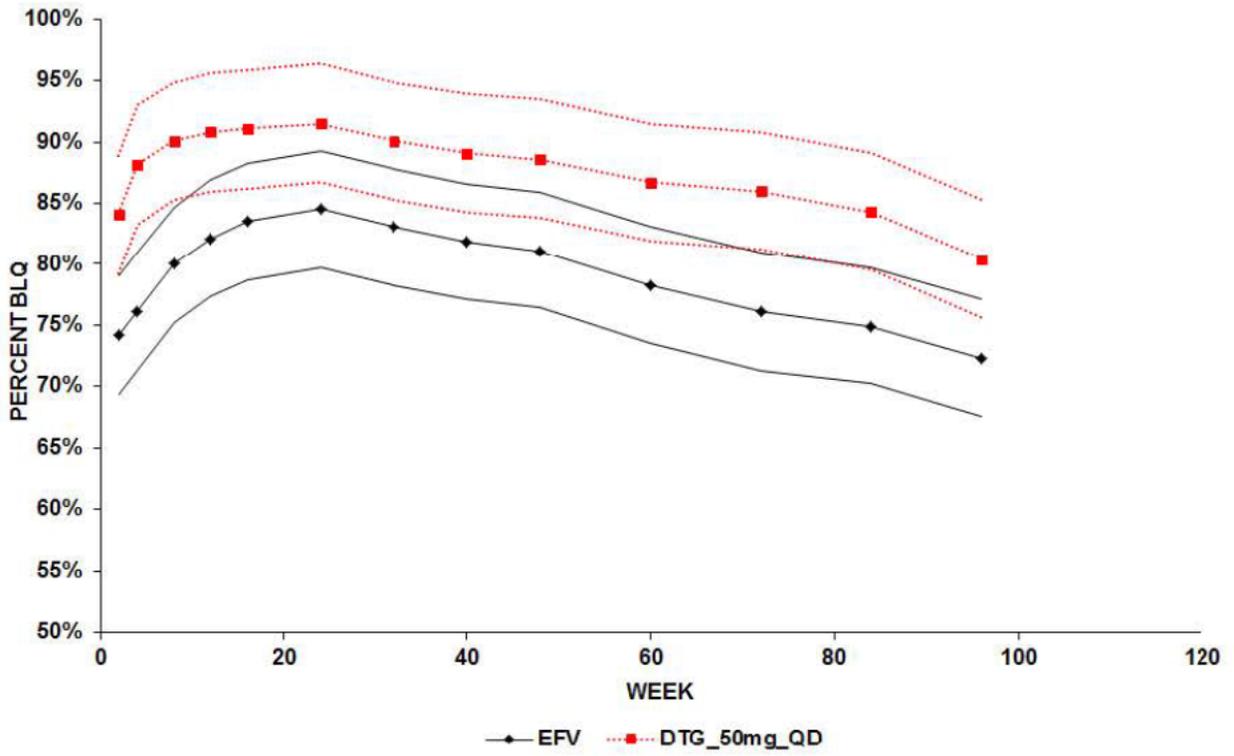
**SINGLE, CHANGE IN LOGHIV**



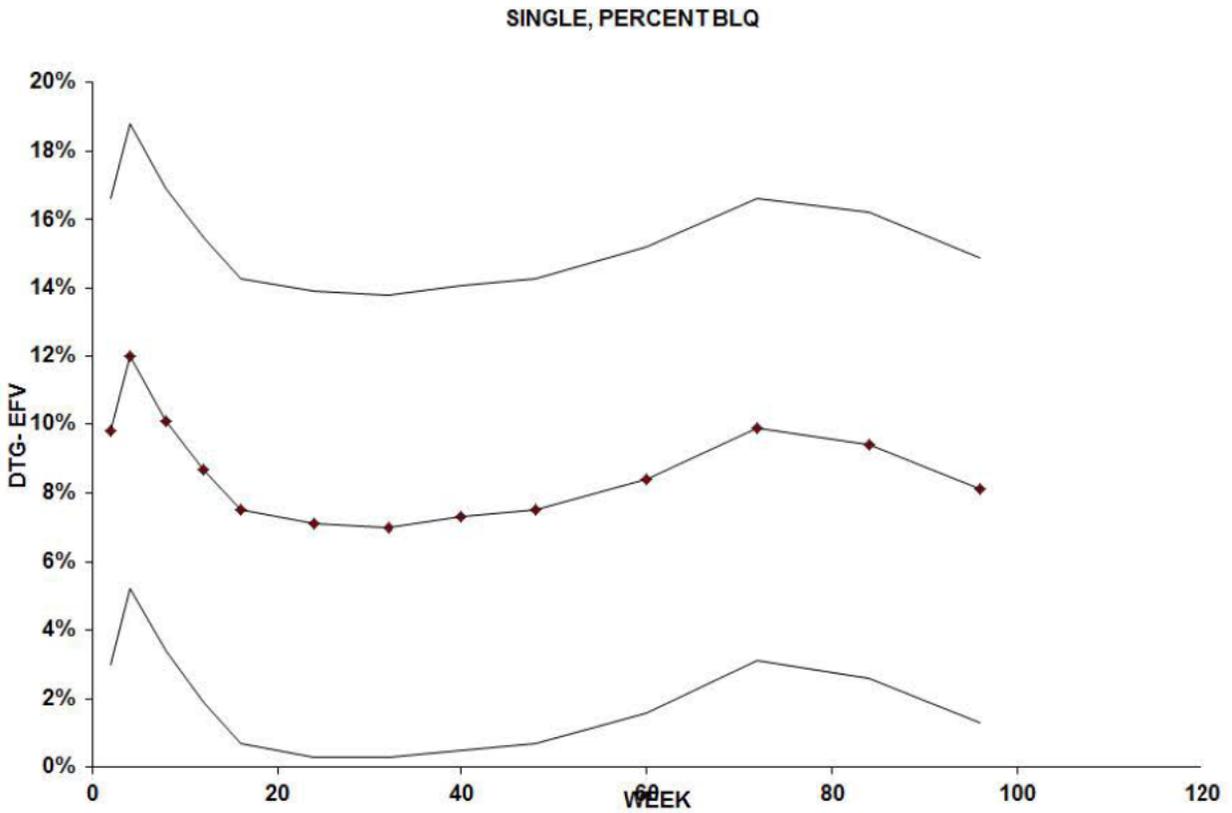
It is important to notice that the DTG 50mg QD arm was statistically significantly superior to the EFV arm throughout the first 96 weeks. Recall negative values in the difference correspond to larger decrease in viral load with DTG.



SINGLE, PERCENTBLQ

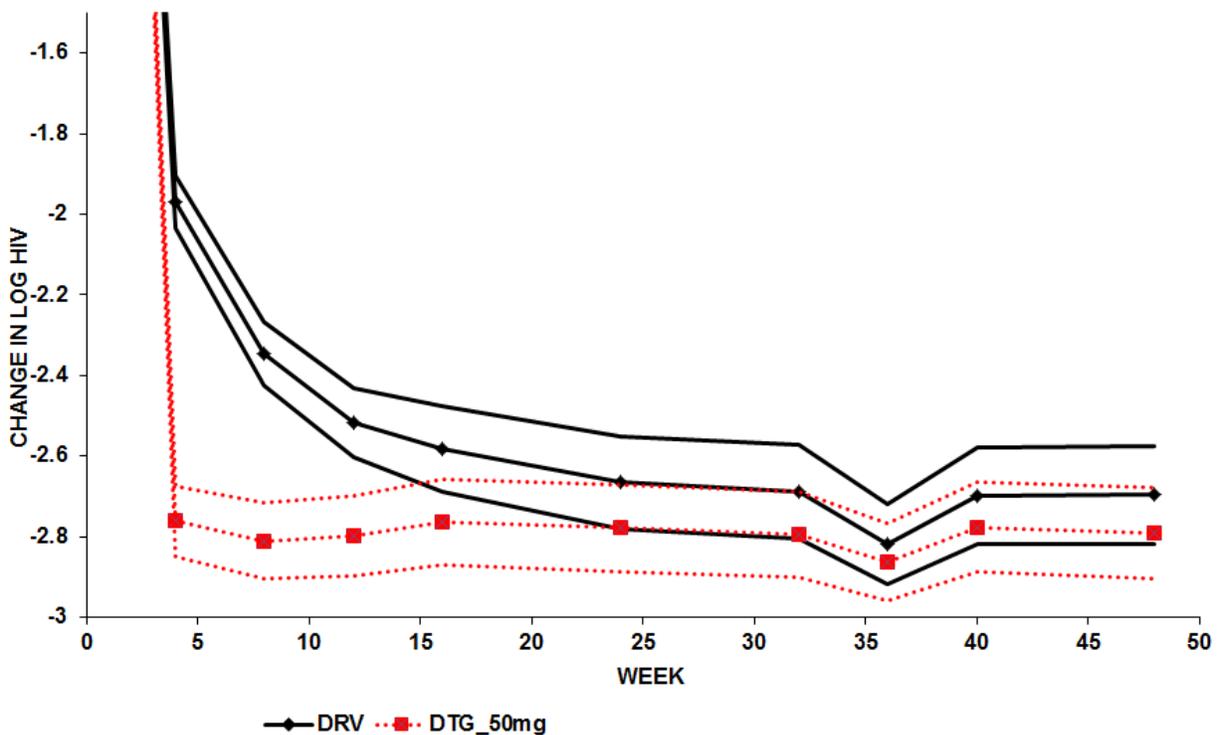


Again, the plot of 95% confidence limits for the difference in %BLQ shows a statistically significant superiority of DTG to EFV.

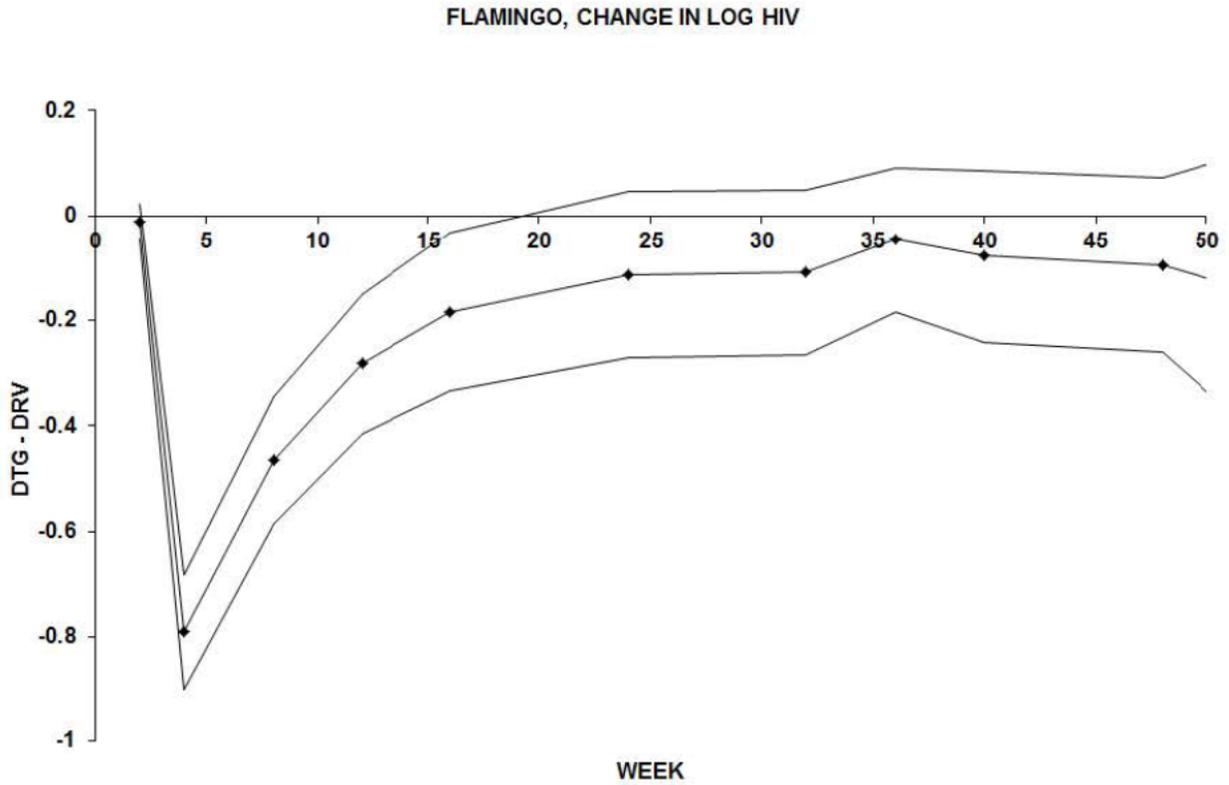


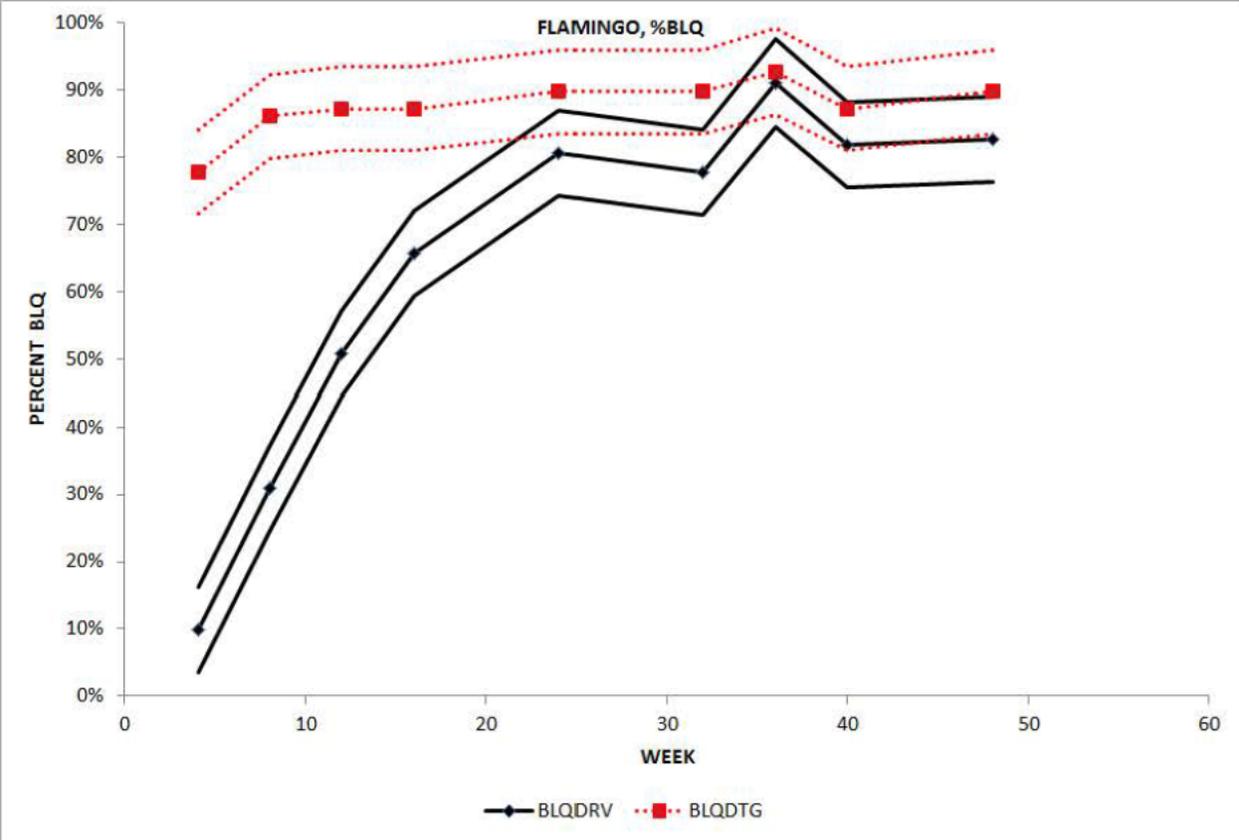
The next four graphs will repeat the previous four graphs for the third trial in treatment naïve subjects, Flamingo. Change in log HIV and the 95% limits for change in log HIV are given first.

### TRIAL FLAMINGO

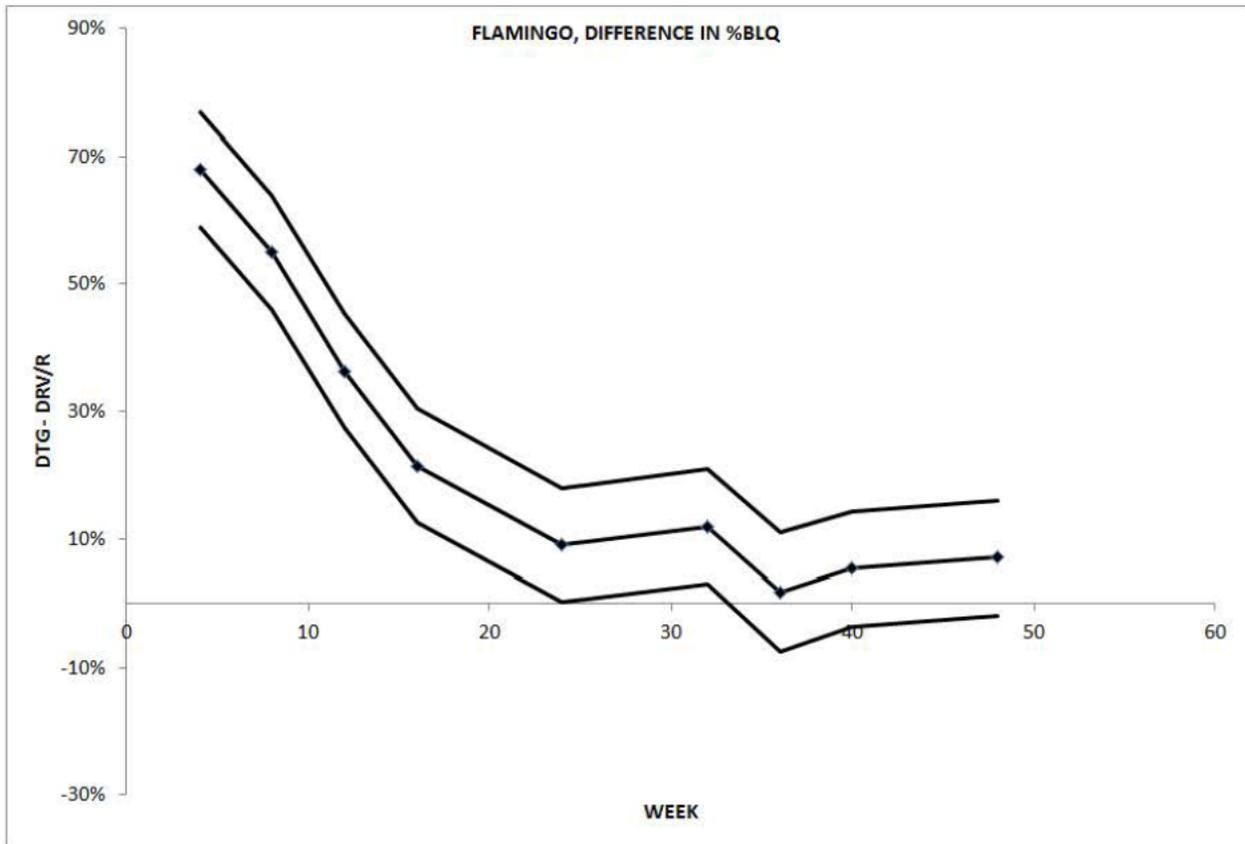


One will notice that the DTG 50mg QD arm was close to, but not quite, statistically significantly superior to the DRV/r arm throughout the first 48 weeks. Recall negative values in the difference correspond to larger decrease in viral load with DTG.



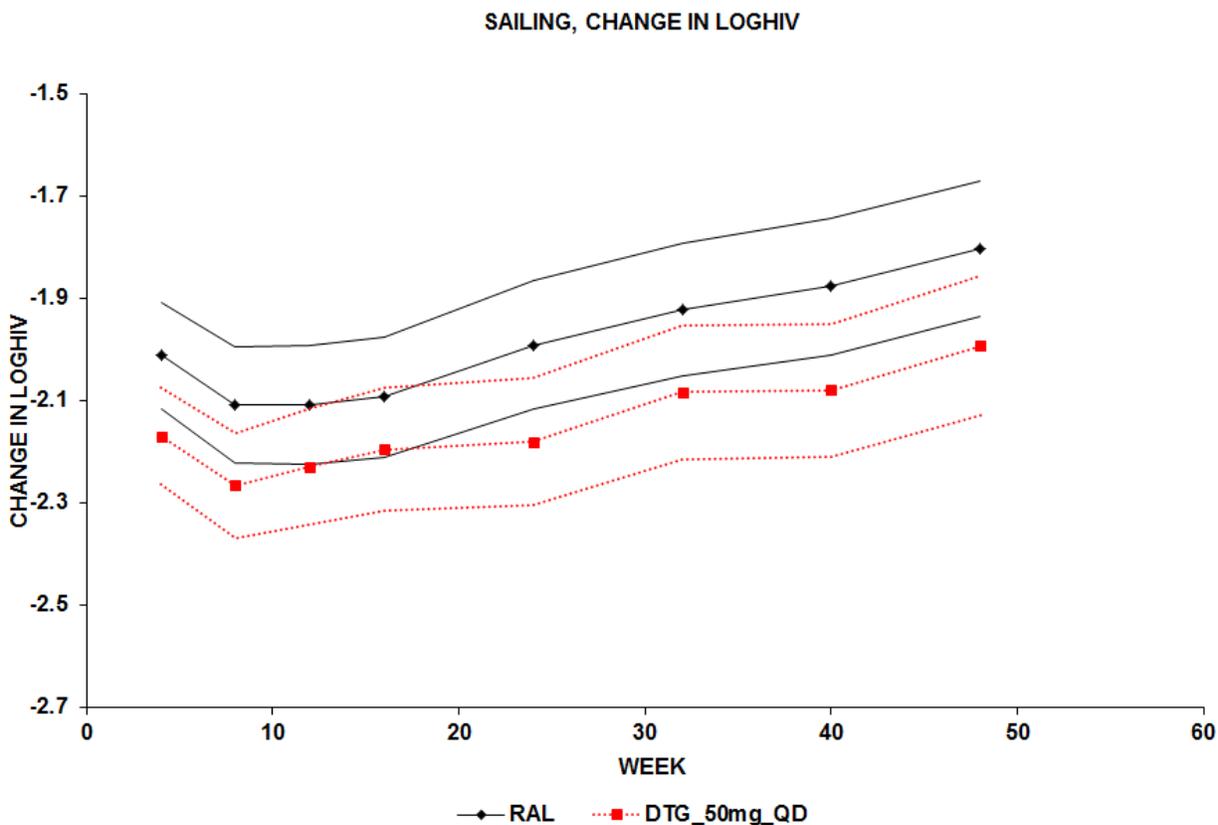


The plot of 95% confidence limits for the difference in %BLQ shows a statistically significant superiority of DTG to DRV/R out to about 24 weeks and a superiority not quite statistically significant out to 48 weeks.

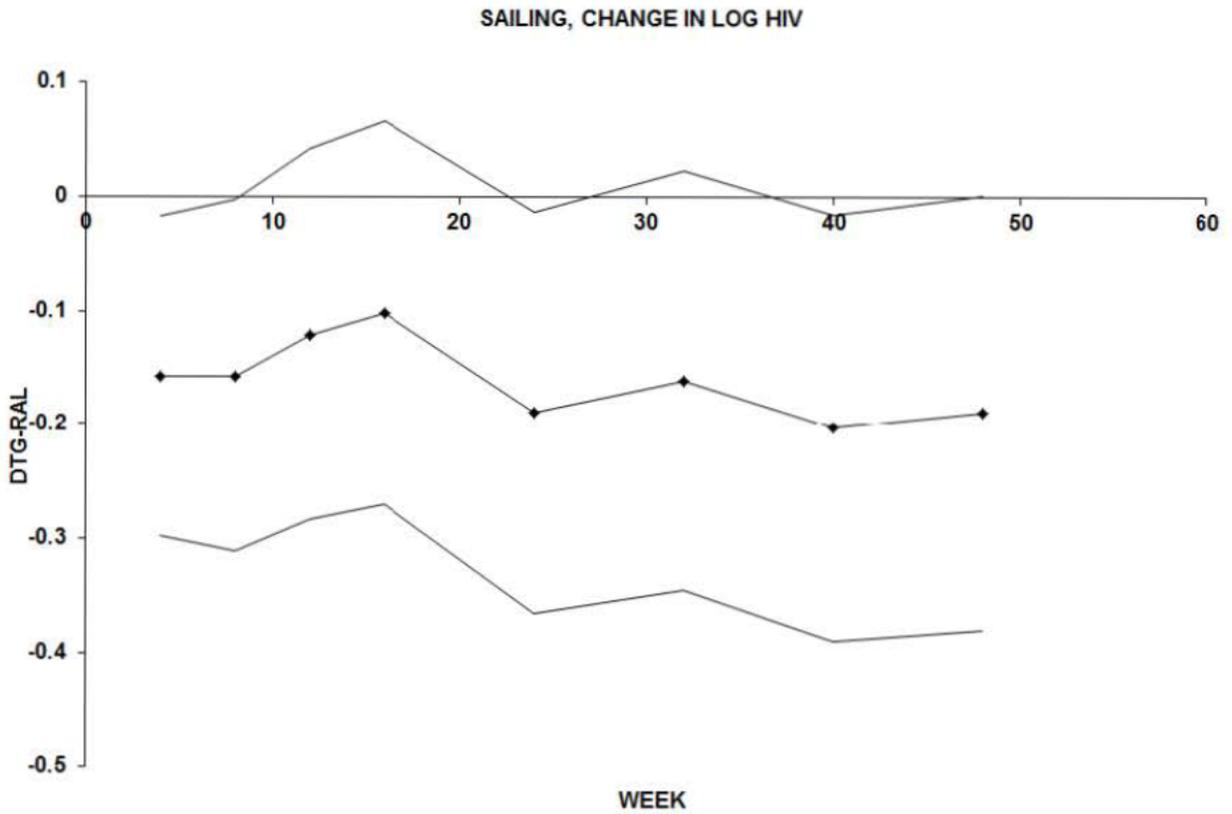


### 3.2.2 Two Class Resistant INI Naïve Trials

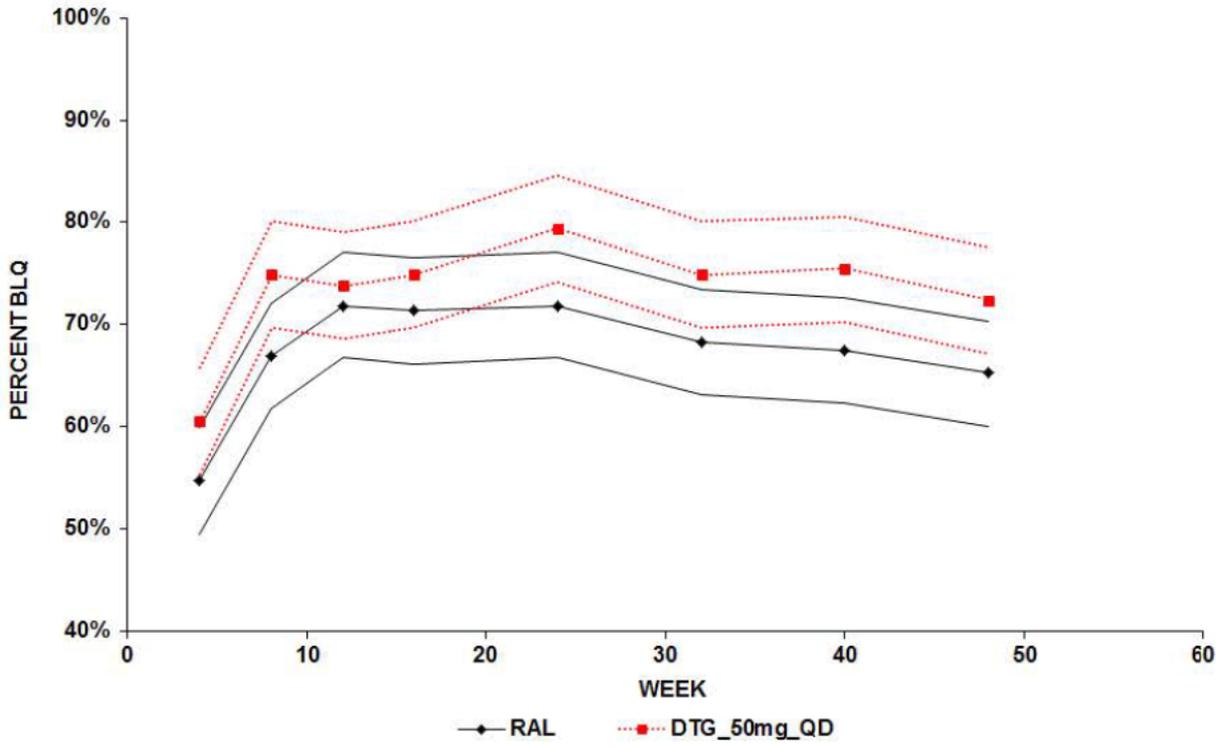
The next four graphs will give the time course of change in log HIV for DTG and RAL in the Sailing trial, the 95% confidence limits for the difference in change in log HIV, the %BLQ over time in both arms, and the 95% confidence limits for the difference in %BLQ.



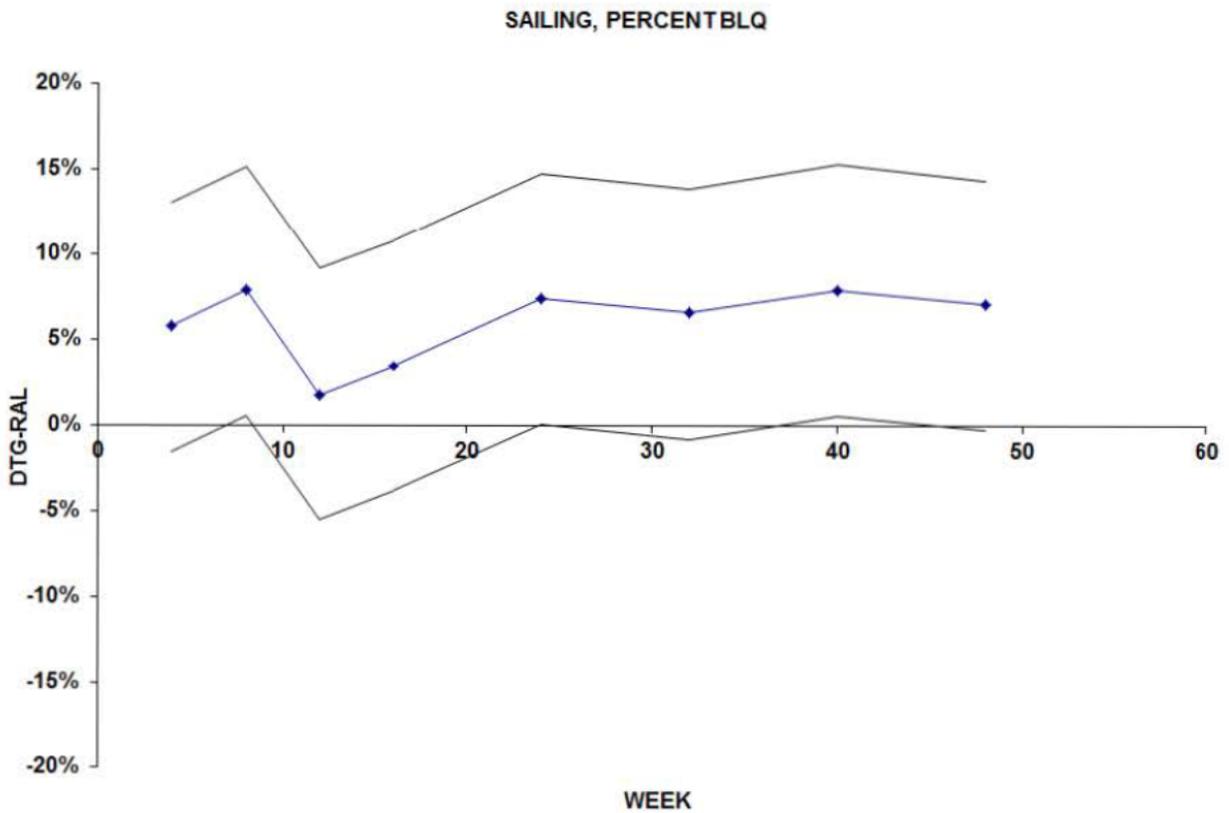
It is worth noting in this graph of the 95% confidence limits on the difference in the change in log HIV that the DTG 50mg QD arm is intermittently statistically significantly superior to the RAL arm.



SAILING, PERCENTBLQ



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%.



### 3.3 Results with ABC/3TC Specifically

Table 3.3 A gives the summary of percent BLQ on the specific combination of DTG/ABC/3TC in FDC which is the subject of the current NDA. All four trials were pooled together but only subjects for whom the background was ABC/3TC were included. The control arm is either EFV, DAR/r, or RAL plus ABC/3TC. The table gives the percent BLQ in each group together with the DTG-control difference and the 95% limits for the difference. The results were computed by week for all trials and by week and trial separately. Data from Single only appear in the pooled analysis because of the small number of ABC/3TC subjects in that trial.

TABLE 3.3 A  
 POOLED TRIALS, %BLQ  
 SUBJECTS WITH ABC/3TC BACKGROUND

WEEK	MEAN DIFFERENCE	95% CONFIDENCE LIMITS		DTG/ABC/3TC	CONTROL
Week_24	4.0%	-0.5%	8.6%	263/280=93.9%	249/277=89.9%
Week_48	0.6%	-4.3%	5.5%	249/274=90.9%	242/268=90.3%
Week_96	0.5%	-8.0%	8.9%	128/154=83.1%	124/150=82.7%
WEEK_24					
FLAMINGO	4.0%	-4.4%	12.3%	78/83=94.0%	72/80=90.0%
SAILING	7.7%	-12.3%	27.6%	25/31=80.6%	27/37=73.0%
SPRING_2	2.0%	-2.5%	6.6%	160/166=96.4%	150/159=94.3%
WEEK_48					
FLAMINGO	0.4%	-6.5%	7.3%	77/81=95.1%	71/75=94.7%
SAILING	4.3%	-16.1%	24.7%	23/29=79.3%	27/36=75.0%
SPRING_2	-0.9%	-7.0%	5.3%	149/164=90.9%	144/157=91.7%
WEEK_96					
SPRING_2	0.5%	-8.0%	8.9%	128/154=83.1%	124/150=82.7%

The DTG FDC combination is always estimated to be as good as the control plus ABC/3TC and with 95% confidence is always no more than 8% worse than the control.

### **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.

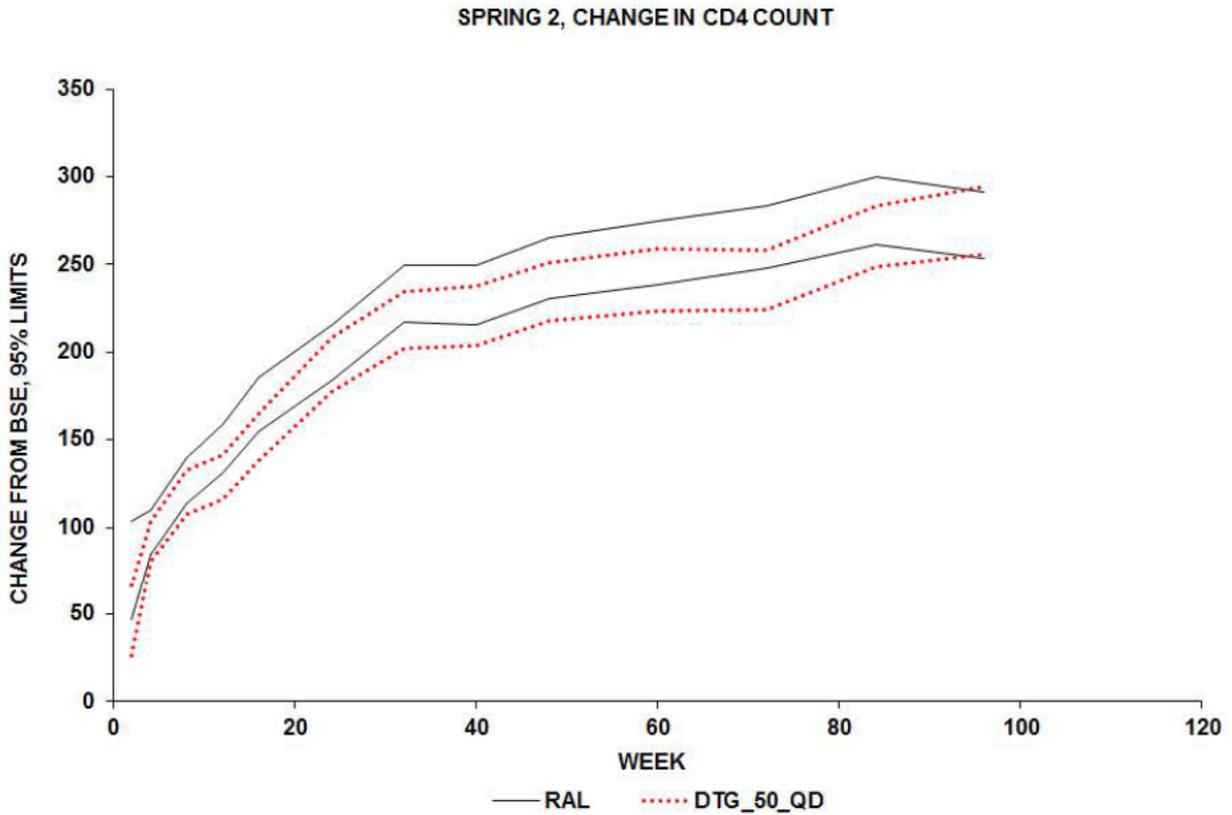
One should observe these salient features in the following graphs. The CD4 count for the DTG and RAL regimens are nearly identical. This holds for both the Spring 2 trial in treatment naïve subjects and in the Sailing trial in two class resistant, INI naïve subjects. One can be reasonably confident that the DTG regimen is no more than 30-35 cells/ml worse than the RAL regimen.

In the Flamingo trial in treatment naïve subjects, the DTG and DRV/r CD4 responses are nearly identical, as was the case with DTG and RAL. One can also be confident that the DTG regimen is no more than 20-30 cells/ml worse than the DRV/r regimen among the naïve subjects.

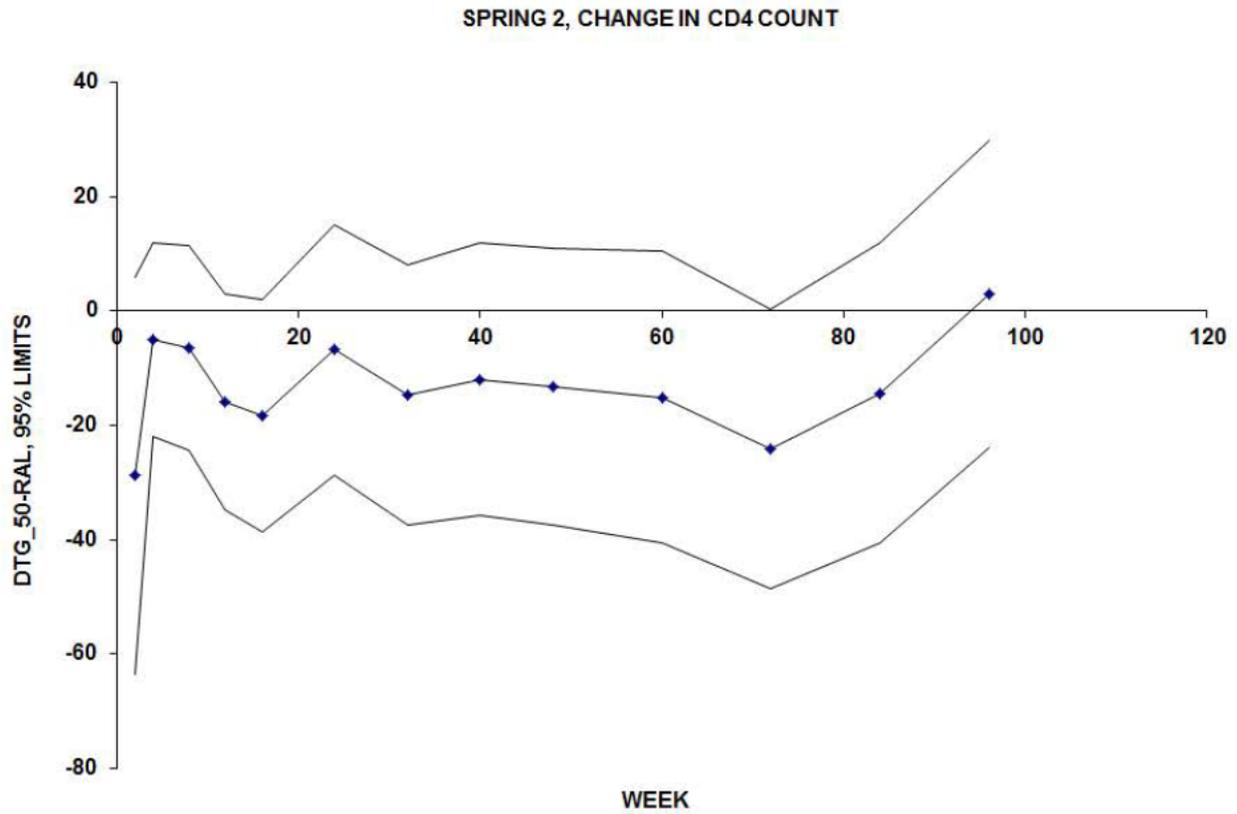
In the Single trial, the DTG regimen is statistically significantly superior to the EFV regimen throughout the 96 weeks of the trial. This confirms the findings with the HIV endpoints in this trial.

### 3.4.1 Treatment Naïve Trials

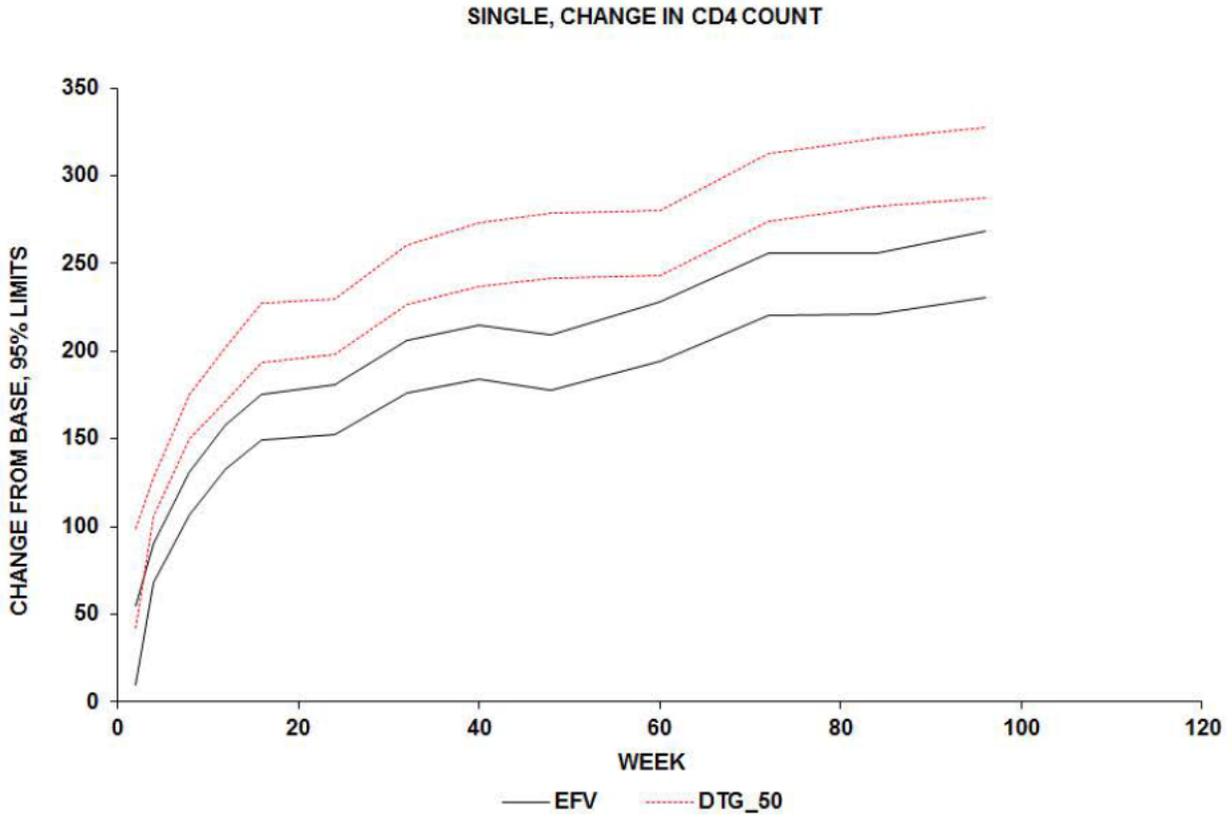
The first graph shows the 95% confidence bands for the change in CD4 count in the DTG and RAL arms of the Spring 2 trial. They nearly overlap perfectly out to week 96.



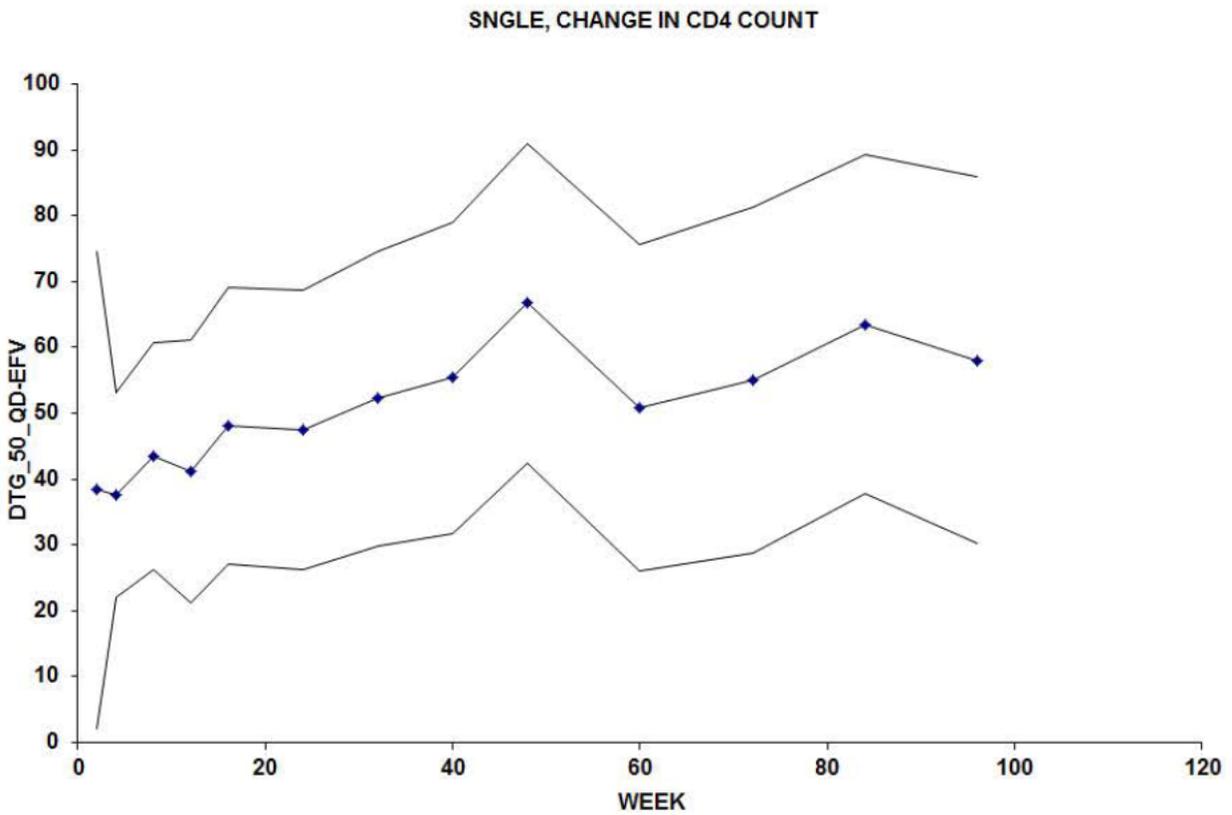
This graph shows the point estimate and 95% confidence limits for the difference, DTG-RAL, in change in CD4 count in the Spring 2 trial. One can be reasonably confident that the DTG regimen is no more than 30-35 cells/ml worse than the RAL regimen.



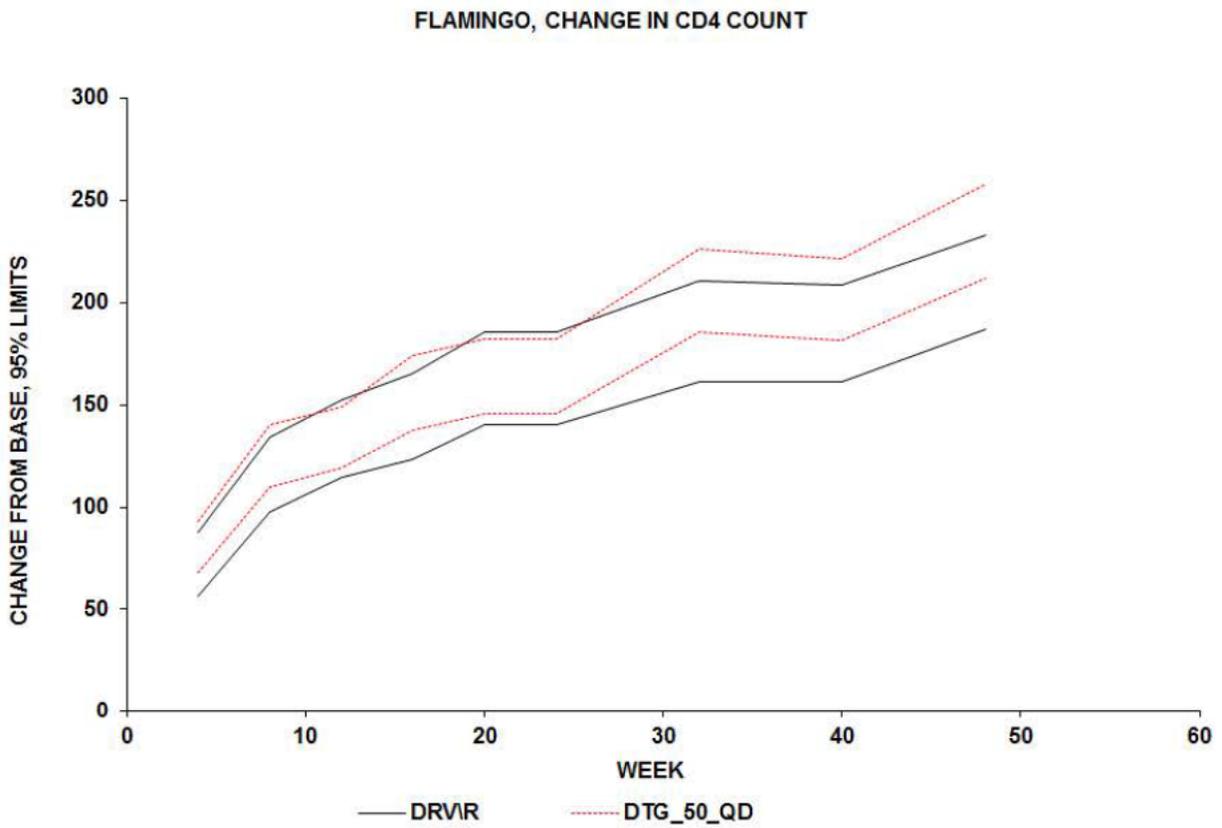
This graph shows the 95% confidence bounds for the change in CD4 count in the DTG and EFV arms of the Single trial. One will notice that the bands do not overlap and that the DTG regimen is superior.



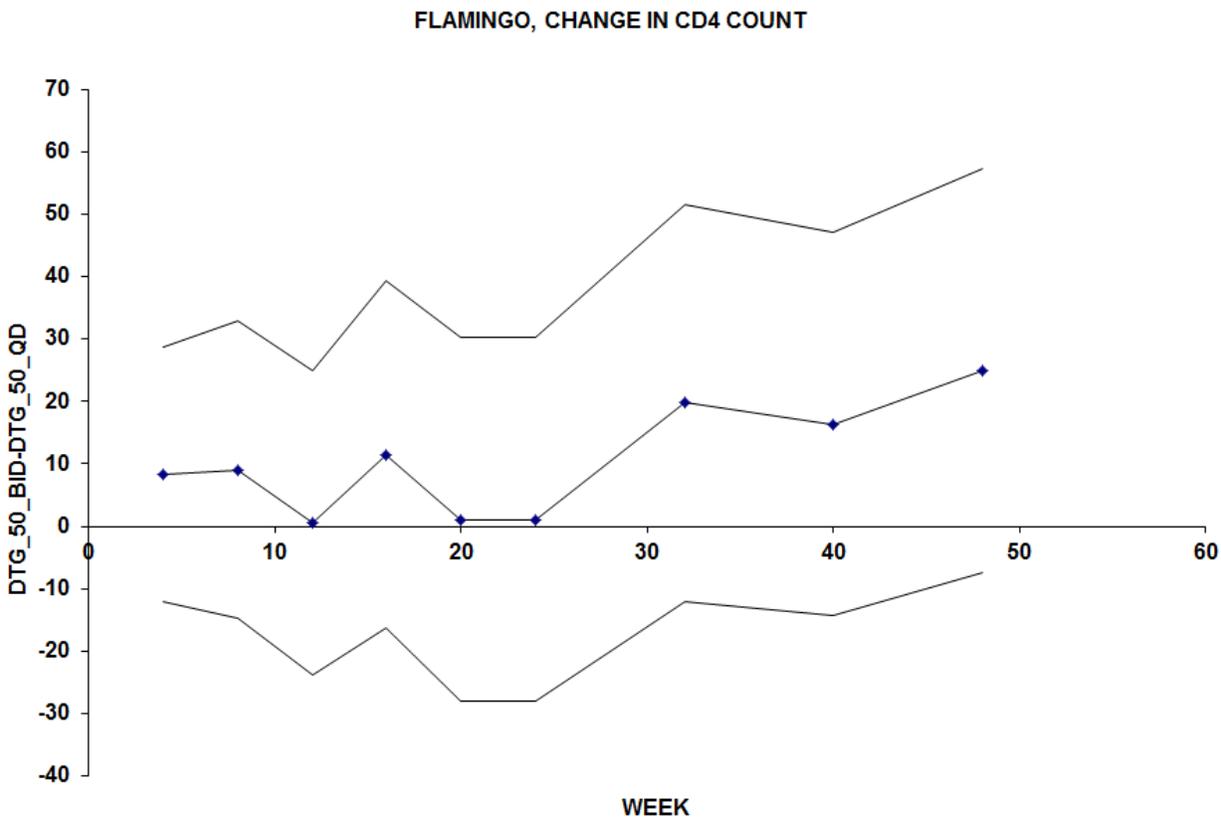
This graph gives the point estimate and 95% confidence limits for The difference, DTG-EFV, in change in CD4 count in the Single trial. The DTG regimen is statistically significantly superior throughout the trial. This confirms the findings with the HIV endpoints in this trial.



This graph shows the 95% confidence bounds for the change in CD4 count in the DTG and DRV/r arms of the flamingo trial. One will notice that the bands nearly overlap.

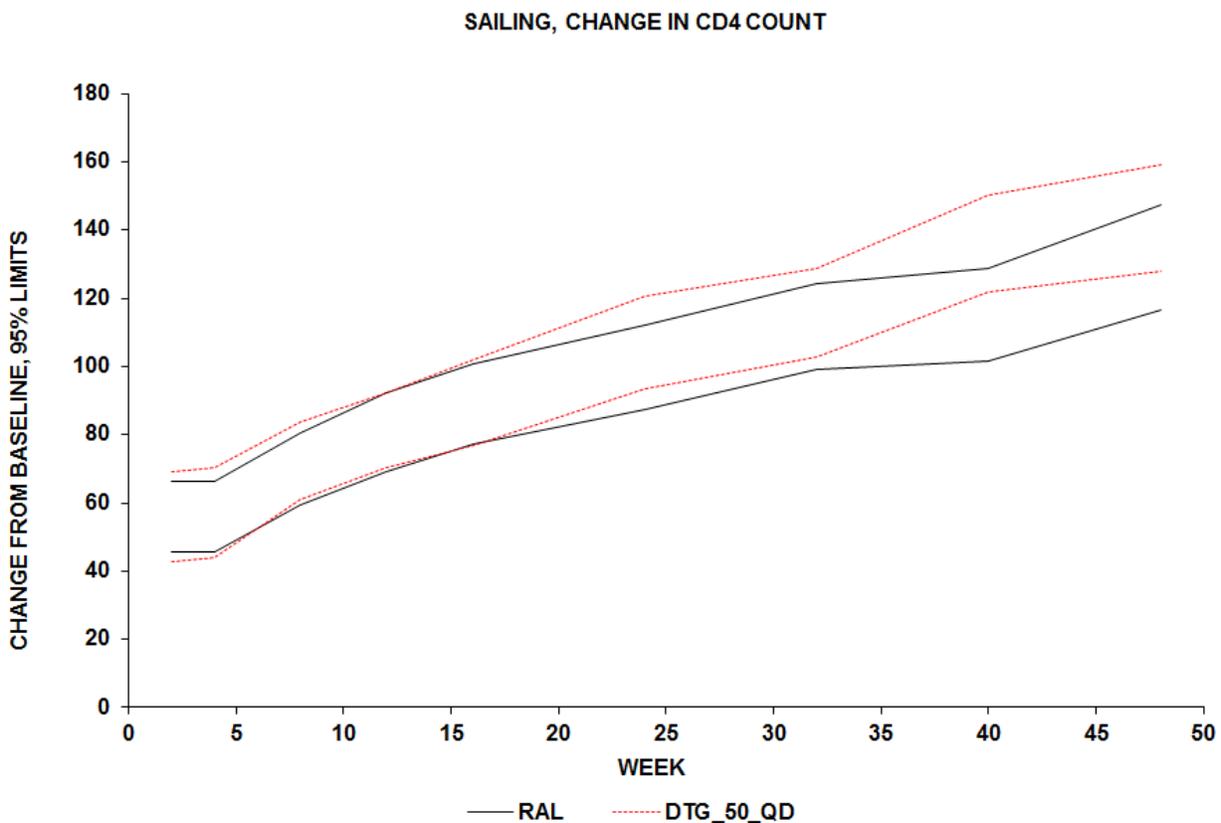


This graph gives the point estimate and 95% confidence limits for the difference, DTG-DRV, in change in CD4 count in the Flamingo trial. The DTG regimen is slightly superior throughout the trial but not to a statistically significant extent. One can be confident that DTG is no worse than 20-30 cells worse than DRV/R in the amount of improvement in CD4 count.

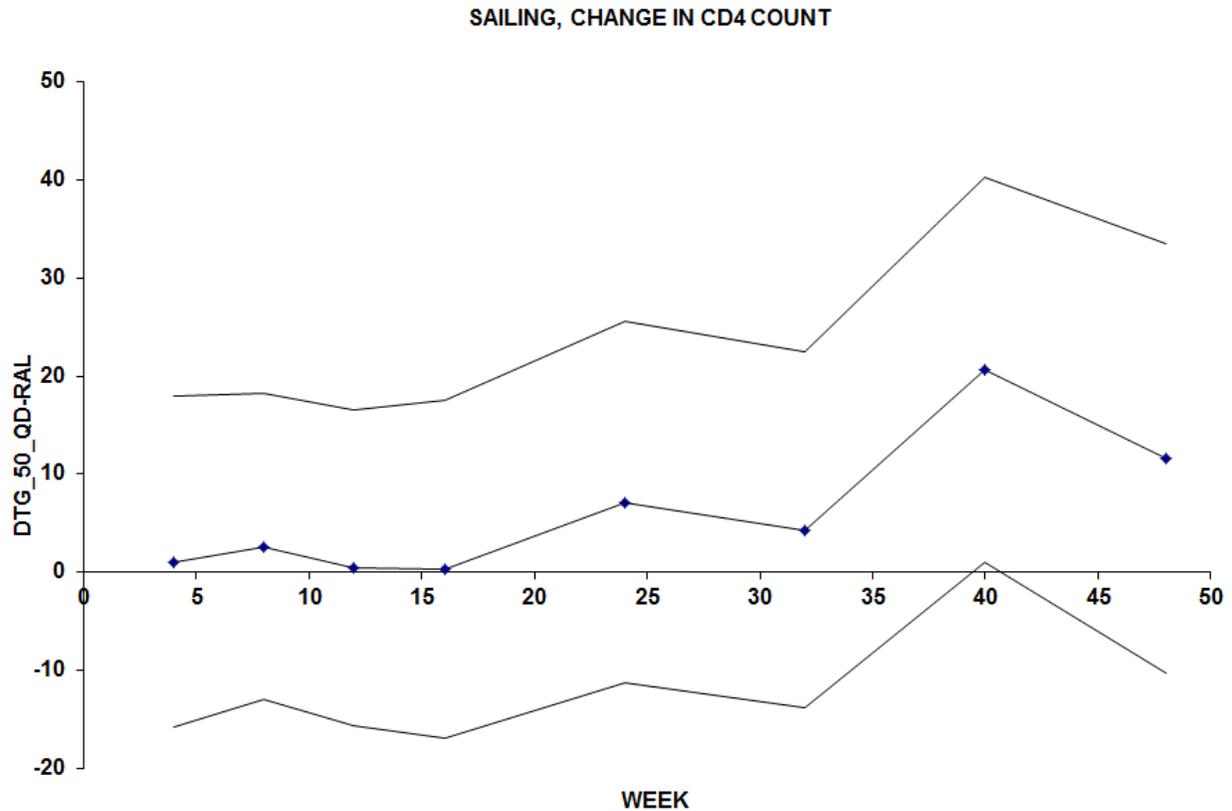


### 3.4.2 Two Class Resistant INI Naive Trial

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.



## 4. Results in Special Populations

The review for NDA 204790 contains an exploration of possible interactions between baseline covariates and the primary endpoint of percent with viral suppression at the time of the report. There was little evidence of interactions between treatment and any interesting covariates. For details, see the review of NDA 204790. The remainder of this section extends findings to week 96 (Spring 2 and Single) or week 48 (Sailing and Flamingo). Nothing consequently different from the previous review has been found in the way of interactions.

### 4.1 Gender, Race, and Age

The following tables give the results of analyzing the primary endpoints of all four 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.

For percent BLQ, the arm means are presented as ratios of counts and as percents. For Spring 2, Single, Sailing, and Flamingo there is one table each. Notice that each table takes several pages because of the number of sub-groups.

### 4.1.1 Treatment Naïve Trials

SPRING_2_3086_%BLQ_WEEK_96						
SUBGROUP	MEAN	95% LIMITS		DTG	CONTROL	
	DIFF	LOWER	UPPER			
ALL	4.6%	-0.9%	10.1%	332/403=82.4%	315/405=77.8%	
STRAT						
<100_K_ABC/3TC	-1.6%	-11.4%	8.2%	99/124=79.8%	101/124=81.5%	0.14
<100_K_TDF/FTC	3.8%	-3.7%	11.4%	144/165=87.3%	141/169=83.4%	
>100_K_ABC/3TC	1.7%	-19.9%	23.4%	25/35=71.4%	23/33=69.7%	
>100_K_TDF/FTC	19.3%	5.8%	32.7%	64/76=84.2%	50/77=64.9%	
AGEGPCD						
<36	3.5%	-5.0%	11.9%	139/179=77.7%	158/213=74.2%	0.62
>=36	4.7%	-2.2%	11.6%	193/221=87.3%	157/190=82.6%	
AGECAT						
<=30	3.4%	-7.6%	14.5%	86/113=76.1%	93/128=72.7%	0.91
30-36	4.0%	-8.4%	16.4%	64/81=79.0%	72/96=75.0%	
36-44	3.4%	-7.0%	13.8%	102/121=84.3%	72/89=80.9%	
>44	6.1%	-3.4%	15.6%	80/88=90.9%	78/92=84.8%	
SEX						
F	1.7%	-15.7%	19.1%	39/56=69.6%	36/53=67.9%	0.56
M	5.2%	-0.5%	10.9%	293/347=84.4%	279/352=79.3%	
RACE						
Black	-2.4%	-20.9%	16.2%	36/50=72.0%	29/39=74.4%	0.39
White	5.1%	-0.8%	11.0%	282/338=83.4%	271/346=78.3%	
ETHNICCD						
Hispanic	10.2%	-6.7%	27.2%	35/43=81.4%	37/52=71.2%	0.54
Not	3.7%	-2.1%	9.5%	297/360=82.5%	278/353=78.8%	

SINGLE_4467_%BLQ_WEEK_96						
SUBGROUP	MEAN	95% LIMITS		DTG	CONTROL	
	DIFF	LOWER	UPPER			
ALL	8.1%	2.4%	13.9%	333/414=80.4%	303/419=72.3%	
STRAT						
<100_K_<=200	-2.1%	-26.9%	22.7%	16/21=76.2%	18/23=78.3%	0.2
<100_K_>200	12.2%	5.3%	19.1%	223/262=85.1%	191/262=72.9%	
>100_K_<=200	-4.7%	-26.7%	17.3%	22/34=64.7%	25/36=69.4%	
>100_K_>200	3.9%	-8.5%	16.4%	72/95=75.8%	69/96=71.9%	
AGECAT						
<=29	10.7%	-0.5%	21.9%	97/125=77.6%	79/118=66.9%	0.85
29-36	4.9%	-5.9%	15.7%	83/101=82.2%	85/110=77.3%	
36-43	11.9%	-0.2%	24.0%	67/80=83.8%	69/96=71.9%	
>43	5.9%	-5.7%	17.6%	86/108=79.6%	70/95=73.7%	
SEX						
F	20.6%	4.6%	36.5%	51/67=76.1%	35/63=55.6%	0.17
M	6.0%	-0.1%	12.1%	282/347=81.3%	268/356=75.3%	
RACE						
Black	18.0%	5.7%	30.3%	79/98=80.6%	62/99=62.6%	0.012
White	2.1%	-4.7%	8.9%	225/284=79.2%	219/284=77.1%	
Other	30.6%	11.5%	49.7%	29/32=90.6%	21/35=60.0%	
ETHNICCD						
Hispanic	-1.8%	-18.4%	14.8%	40/56=71.4%	41/56=73.2%	0.17
Not	9.7%	3.6%	15.8%	293/358=81.8%	262/363=72.2%	
METHOD_INFECTED						
Homosexual	6.5%	-0.4%	13.3%	215/262=82.1%	217/287=75.6%	0.49
Other	12.5%	1.5%	23.5%	103/131=78.6%	80/121=66.1%	

FLAMINGO_WEEK_24_DRV\RTV_VS_DTG_50mg						
SUBGROUP	MEAN DIFF	95% LOWER	LIMITS UPPER	DTG	CONTROL	
ALL	9.5%	3.3%	15.8%	218/242=90.1%	195/242=80.6%	
AGEGPCD						
<36	7.4%	-0.9%	15.7%	117/130=90.0%	109/132=82.6%	0.64
>=36	10.6%	1.4%	19.8%	101/111=91.0%	86/107=80.4%	
AGEQ						
<=27	12.7%	-0.1%	25.6%	55/61=90.2%	48/62=77.4%	0.65
27-34	1.4%	-10.3%	13.2%	53/60=88.3%	53/61=86.9%	
34-44	8.4%	-3.2%	20.0%	64/70=91.4%	49/59=83.1%	
>44	13.1%	0.1%	26.0%	46/50=92.0%	45/57=78.9%	
GENDER						
Female	5.3%	-9.9%	20.5%	28/31=90.3%	34/40=85.0%	0.69
Male	9.6%	2.8%	16.3%	190/210=90.5%	161/199=80.9%	
RACE						
Black	5.1%	-7.9%	18.2%	52/59=88.1%	44/53=83.0%	0.53
White	9.8%	2.6%	17.1%	157/173=90.8%	140/173=80.9%	
ETHNICCD						
Hispanic	5.2%	-6.6%	17.1%	44/47=93.6%	38/43=88.4%	0.9
Not	9.6%	2.5%	16.6%	174/194=89.7%	157/196=80.1%	

FLAMINGO_WEEK_48_DRV\RTV_VS_DTG_50mg						
SUBGROUP	MEAN DIFF	95% LIMITS LOWER UPPER		DTG	CONTROL	
ALL	7.4%	1.4%	13.5%	218/242=90.1%	200/242=82.6%	
AGEGPCD						
<36	9.0%	0.7%	17.2%	118/130=90.8%	108/132=81.8%	0.51
>=36	4.1%	-4.5%	12.7%	100/111=90.1%	92/107=86.0%	
AGEQ						
<=27	11.1%	-1.5%	23.7%	55/61=90.2%	49/62=79.0%	0.9
27-34	8.0%	-4.2%	20.3%	54/60=90.0%	50/61=82.0%	
34-44	3.3%	-7.2%	13.8%	64/70=91.4%	52/59=88.1%	
>44	4.0%	-8.2%	16.3%	45/50=90.0%	49/57=86.0%	
GENDER						
Female	8.9%	-9.8%	27.5%	26/31=83.9%	30/40=75.0%	0.93
Male	6.0%	-0.2%	12.2%	192/210=91.4%	170/199=85.4%	
RACE						
Black	9.1%	-5.2%	23.3%	51/59=86.4%	41/53=77.4%	0.99
White	6.4%	-0.4%	13.1%	158/173=91.3%	147/173=85.0%	
ETHNICCD						
Hispanic	4.8%	-3.8%	13.5%	46/47=97.9%	40/43=93.0%	0.58
Not	7.0%	0.0%	14.0%	172/194=88.7%	160/196=81.6%	

### 4.1.2 Two Class Resistant INI Naive Trial

SAILING\_1762\_%BLQ\_WEEK\_48

SUBGROUP	MEAN DIFF	95% LIMITS LOWER UPPER		DTG	CONTROL	
ALL	7.2%	0.4%	14.0%	256/354=72.3%	235/361=65.1%	
STRAT						
<50_K_DRV/r_OBR=2	3.5%	-13.8%	20.8%	37/49=75.5%	36/50=72.0%	0.85
<50_K_No_DRV/r_OBR<2	3.9%	-11.3%	19.2%	45/57=78.9%	45/60=75.0%	
<50_K_No_DRV/r_OBR=2	5.1%	-4.9%	15.0%	107/133=80.5%	101/134=75.4%	
>50_K_No_DRV/r_OBR<2	18.2%	-9.2%	45.6%	13/24=54.2%	9/25=36.0%	
>50_K_No_DRV/r_OBR=2	16.1%	-0.8%	32.9%	40/65=61.5%	30/66=45.5%	
AGEGPCD						
<43	9.4%	-0.2%	19.0%	131/178=73.6%	113/176=64.2%	0.58
>=43	5.3%	-4.2%	14.8%	125/171=73.1%	122/180=67.8%	
AGEGP3CD						
<50	10.6%	2.9%	18.3%	199/265=75.1%	176/273=64.5%	0.089
>=50	-3.2%	-17.2%	10.7%	57/84=67.9%	59/83=71.1%	
AGECAT						
<=35	16.7%	2.6%	30.8%	64/92=69.6%	46/87=52.9%	0.26
35-42	4.3%	-8.3%	16.9%	67/86=77.9%	67/91=73.6%	
42-49	11.1%	-1.9%	24.1%	68/91=74.7%	63/99=63.6%	
>49	-3.2%	-17.2%	10.8%	57/85=67.1%	59/84=70.2%	
SEX						
F	14.7%	2.9%	26.6%	81/107=75.7%	75/123=61.0%	0.14
M	3.6%	-4.6%	11.9%	175/247=70.9%	160/238=67.2%	
RACE						
Black	11.2%	0.5%	21.9%	100/143=69.9%	94/160=58.8%	0.55
White	2.7%	-6.4%	11.8%	135/178=75.8%	128/175=73.1%	
Other	13.6%	-12.0%	39.2%	21/32=65.6%	13/25=52.0%	
ETHNICCD						
Hispanic	8.5%	-2.8%	19.8%	100/135=74.1%	78/119=65.5%	0.73
Not	6.4%	-2.1%	14.8%	156/219=71.2%	157/242=64.9%	

## **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

SPRING\_2\_WEEK\_96

SUBGROUP	MEAN DIFF	95% LIMITS		DTG	CONTROL	P-VALUE
		LOWER	UPPER			
METHOD_INFECTED						
Homosexual	3.5%	-2.7%	9.8%	229/265=86.4%	208/251=82.9%	0.55
Other	0.8%	-9.9%	11.4%	88/115=76.5%	100/132=75.8%	
NRTIGP						
ABC/3TC	-1.4%	-10.4%	7.6%	125/160=78.1%	124/156=79.5%	0.06
TDF/FTC	8.9%	2.1%	15.7%	207/240=86.3%	191/247=77.3%	
BLVLGPCD						
<=100 K	0.7%	-5.3%	6.6%	243/287=84.7%	241/287=84.0%	0.068
>100 K	15.0%	3.4%	26.5%	89/113=78.8%	74/116=63.8%	
BHIVCAT						
<=12753	-3.8%	-13.0%	5.4%	89/104=85.6%	84/94=89.4%	0.059
12753-35795	3.8%	-6.7%	14.4%	88/105=83.8%	80/100=80.0%	
35795-115492	-1.8%	-12.5%	9.0%	75/93=80.6%	89/108=82.4%	
>115492	19.0%	6.7%	31.3%	80/101=79.2%	62/103=60.2%	
BCD4GPCD						
<350	9.6%	1.0%	18.3%	155/195=79.5%	132/189=69.8%	0.23
>=350	0.8%	-5.8%	7.5%	177/205=86.3%	183/214=85.5%	
BCD4CAT						
<=274	13.9%	2.1%	25.8%	79/98=80.6%	72/108=66.7%	0.45
274-361	2.2%	-9.3%	13.6%	84/106=79.2%	74/96=77.1%	
361-470	0.0%	-10.4%	10.4%	80/96=83.3%	85/102=83.3%	
>470	2.4%	-6.7%	11.5%	89/100=89.0%	84/97=86.6%	
BCDCGPCD						
A	1.9%	-3.7%	7.5%	292/349=83.7%	278/340=81.8%	0.16
B	17.5%	-0.5%	35.4%	33/42=78.6%	33/54=61.1%	
ABCEXP						
No	8.9%	2.1%	15.7%	203/234=86.8%	190/244=77.9%	0.066
Yes	-0.9%	-9.9%	8.1%	129/166=77.7%	125/159=78.6%	

SINGLE\_4467\_%BLQ\_WEEK\_96

SUBGROUP	MEAN	95% LIMITS		DTG	CONTROL	
	DIFF	LOWER	UPPER			
BLVLGPCD						
<=100 K	12.4%	5.7%	19.0%	237/279=84.9%	209/288=72.6%	0.025
>100 K	-0.7%	-11.5%	10.1%	96/133=72.2%	94/129=72.9%	
BHIVCAT						
<=14650	14.7%	3.6%	25.7%	89/105=84.8%	75/107=70.1%	0.22
14650-48301	12.8%	1.6%	24.0%	90/107=84.1%	72/101=71.3%	
48301-143156	5.7%	-5.2%	16.6%	78/94=83.0%	85/110=77.3%	
>143156	0.1%	-12.3%	12.5%	76/108=70.4%	71/101=70.3%	
BCD4GPCD						
<=200	-1.7%	-18.0%	14.7%	39/55=70.9%	45/62=72.6%	0.16
>200	9.7%	3.6%	15.8%	294/357=82.4%	258/355=72.7%	
BCD4CAT						
<=246	5.7%	-6.0%	17.4%	77/99=77.8%	80/111=72.1%	0.37
246-339	13.0%	1.5%	24.4%	90/109=82.6%	71/102=69.6%	
339-438	1.0%	-10.5%	12.6%	83/107=77.6%	75/98=76.5%	
>438	12.9%	1.9%	23.9%	83/97=85.6%	77/106=72.6%	
CD4GP2CD						
50-200	-1.5%	-20.1%	17.1%	30/42=71.4%	35/48=72.9%	0.35
200-350	11.8%	2.6%	20.9%	135/163=82.8%	113/159=71.1%	
350-500	4.8%	-5.5%	15.1%	104/131=79.4%	94/126=74.6%	
>=500	14.4%	1.2%	27.7%	55/63=87.3%	51/70=72.9%	
BCDCGPCD						
A	8.8%	2.6%	14.9%	280/341=82.1%	256/349=73.4%	0.91
B	9.3%	-8.0%	26.5%	41/54=75.9%	34/51=66.7%	

FLAMINGO\_WEEK\_24\_DRV\RTV\_VS\_DTG\_50mg

SUBGROUP	MEAN	95% LIMITS		DTG	CONTROL	
	DIFF	LOWER	UPPER			
BCD4GPCD						
<=200	-4.3%	-27.2%	18.5%	18/23=78.3%	19/23=82.6%	0.3
200-350	13.9%	0.5%	27.4%	66/73=90.4%	39/51=76.5%	
>=350	9.4%	2.2%	16.6%	134/145=92.4%	137/165=83.0%	
CD4GP2CD						
50-200	5.3%	-19.3%	29.9%	16/19=84.2%	15/19=78.9%	0.77
200-350	13.9%	0.5%	27.4%	66/73=90.4%	39/51=76.5%	
350-500	6.7%	-3.1%	16.5%	72/79=91.1%	76/90=84.4%	
>=500	12.6%	2.1%	23.1%	62/66=93.9%	61/75=81.3%	
BCD4Q						
<=290	1.5%	-12.1%	15.0%	53/64=82.8%	48/59=81.4%	0.32
290-400	13.0%	2.6%	23.4%	57/59=96.6%	51/61=83.6%	
400-520	14.1%	0.8%	27.5%	60/67=89.6%	43/57=75.4%	
>520	8.6%	-2.3%	19.5%	48/51=94.1%	53/62=85.5%	
BLVLGPCD						
<=100_K	1.1%	-4.6%	6.8%	166/180=92.2%	164/180=91.1%	0.012
>100_K	32.7%	17.2%	48.2%	52/61=85.2%	31/59=52.5%	
BLVLG2CD						
1-10_K	3.8%	-4.5%	12.1%	56/58=96.6%	51/55=92.7%	0.063
10-50_K	-2.1%	-9.9%	5.6%	83/91=91.2%	84/90=93.3%	
50-100_K	8.4%	-9.1%	25.9%	26/29=89.7%	26/32=81.3%	
100-500_K	32.7%	17.2%	48.2%	52/61=85.2%	31/59=52.5%	
BHIVQ						
<=10_K	1.7%	-6.7%	10.0%	57/60=95.0%	56/60=93.3%	0.017
10-31_K	-6.6%	-16.3%	3.0%	54/61=88.5%	59/62=95.2%	
31-102_K	10.2%	-1.4%	21.7%	55/59=93.2%	49/59=83.1%	
>102_K	31.8%	16.2%	47.4%	52/61=85.2%	31/58=53.4%	
BCDCGPCD						
A	10.3%	3.7%	16.9%	185/202=91.6%	165/203=81.3%	0.56
B	6.0%	-12.5%	24.5%	26/30=86.7%	25/31=80.6%	
METHOD_INFECTED						
Homosexual	10.0%	2.6%	17.4%	151/165=91.5%	128/157=81.5%	0.5
Other	5.8%	-5.4%	17.1%	63/71=88.7%	63/76=82.9%	

FLAMINGO\_WEEK\_48\_DRV\RTV\_VS\_DTG\_50mg

SUBGROUP	MEAN	95% LIMITS		DTG	CONTROL	
	DIFF	LOWER	UPPER			
BCD4GPCD						
<=200	8.7%	-10.6%	28.0%	21/23=91.3%	19/23=82.6%	0.88
200-350	5.9%	-7.5%	19.4%	63/73=86.3%	41/51=80.4%	
>=350	7.6%	0.6%	14.5%	134/145=92.4%	140/165=84.8%	
CD4GP2CD						
50-200	15.8%	-5.1%	36.7%	18/19=94.7%	15/19=78.9%	0.85
200-350	5.9%	-7.5%	19.4%	63/73=86.3%	41/51=80.4%	
350-500	8.9%	-1.2%	19.0%	72/79=91.1%	74/90=82.2%	
>=500	5.9%	-3.4%	15.3%	62/66=93.9%	66/75=88.0%	
BCD4Q						
<=290	2.9%	-9.9%	15.7%	55/64=85.9%	49/59=83.1%	0.75
290-400	11.3%	-0.3%	22.8%	55/59=93.2%	50/61=82.0%	
400-520	8.9%	-3.7%	21.4%	60/67=89.6%	46/57=80.7%	
>520	5.4%	-4.8%	15.6%	48/51=94.1%	55/62=88.7%	
BLVLGPCD						
<=100_K	2.2%	-4.4%	8.9%	161/180=89.4%	157/180=87.2%	0.032
>100_K	20.6%	7.6%	33.5%	57/61=93.4%	43/59=72.9%	
BLVLG2CD						
1-10_K	9.3%	-0.7%	19.3%	56/58=96.6%	48/55=87.3%	0.029
10-50_K	3.5%	-6.6%	13.5%	80/91=87.9%	76/90=84.4%	
50-100_K	-11.0%	-27.1%	5.1%	24/29=82.8%	30/32=93.8%	
100-500_K	20.6%	7.6%	33.5%	57/61=93.4%	43/59=72.9%	
BHIVQ						
<=10_K	8.3%	-1.9%	18.6%	57/60=95.0%	52/60=86.7%	0.072
10-31_K	-0.2%	-12.7%	12.3%	52/61=85.2%	53/62=85.5%	
31-102_K	-1.7%	-13.0%	9.6%	52/59=88.1%	53/59=89.8%	
>102_K	21.0%	8.0%	34.1%	57/61=93.4%	42/58=72.4%	
BCDCGPCD						
A	8.8%	2.6%	15.1%	187/202=92.6%	170/203=83.7%	0.13
B	-3.9%	-23.2%	15.4%	24/30=80.0%	26/31=83.9%	
METHOD_INFECTED						
Homosexual	4.9%	-1.9%	11.7%	151/165=91.5%	136/157=86.6%	0.62
Other	11.1%	-0.8%	23.0%	63/71=88.7%	59/76=77.6%	

#### 4.2.2 Two Class Resistant INI Naive Trials

SAILING_%BLQ_WEEK_48						
SUBGROUP	MEAN DIFF	95% LIMITS		DTG	CONTROL	
METHOD_INFECTED		LOWER	UPPER			
Drug_use	8.3%	-16.1%	32.6%	17/23=73.9%	21/32=65.6%	0.14
Homosexual	-2.6%	-13.6%	8.3%	93/127=73.2%	88/116=75.9%	
Other	12.8%	3.7%	21.8%	146/199=73.4%	126/208=60.6%	
BLVLGPCD						
<=50 K	4.5%	-3.0%	12.1%	191/246=77.6%	185/253=73.1%	0.32
>50 K	14.6%	1.1%	28.0%	65/103=63.1%	50/103=48.5%	
BHIVCAT						
<=2801	-3.1%	-14.7%	8.5%	69/87=79.3%	75/91=82.4%	0.33
2801-15259	3.9%	-8.8%	16.6%	71/92=77.2%	63/86=73.3%	
15259-67283	14.6%	1.0%	28.1%	66/88=75.0%	55/91=60.4%	
>67283	12.3%	-2.2%	26.8%	50/87=57.5%	42/93=45.2%	
BVLGP2CD						
<1 K	3.8%	-12.4%	20.0%	36/44=81.8%	39/50=78.0%	0.77
1-10 K	-0.8%	-11.5%	10.0%	87/109=79.8%	83/103=80.6%	
10-50 K	10.1%	-2.9%	23.2%	68/93=73.1%	63/100=63.0%	
50-100 K	14.6%	-7.7%	37.0%	26/36=72.2%	19/33=57.6%	
100-500 K	9.7%	-9.1%	28.5%	32/52=61.5%	28/54=51.9%	
BCD4GPCD						
<=200	6.1%	-4.1%	16.2%	112/171=65.5%	107/180=59.4%	0.55
>200	8.2%	-0.6%	16.9%	144/178=80.9%	128/176=72.7%	
BCD4CAT						
<=95	6.6%	-7.9%	21.0%	55/90=61.1%	48/88=54.5%	0.98
95-201	7.3%	-6.6%	21.2%	58/82=70.7%	59/93=63.4%	
201-365	8.8%	-4.0%	21.6%	71/90=78.9%	61/87=70.1%	
>365	6.6%	-5.3%	18.6%	72/87=82.8%	67/88=76.1%	
CD4GP2CD						
<50	4.9%	-12.9%	22.7%	34/61=55.7%	30/59=50.8%	0.92
50-200	7.3%	-4.8%	19.3%	78/110=70.9%	77/121=63.6%	
200-350	8.4%	-4.9%	21.7%	65/82=79.3%	56/79=70.9%	
350-500	4.9%	-11.0%	20.8%	42/54=77.8%	43/59=72.9%	
>=500	11.8%	-4.9%	28.5%	37/42=88.1%	29/38=76.3%	

### 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

SPRING\_2\_WEEK\_96

SUBGROUP	MEAN DIFF	95% LIMITS		DTG	CONTROL	
COUNTRY		LOWER	UPPER			
Canada	1.0%	-14.0%	16.0%	29/32=90.6%	26/29=89.7%	0.9
France	-2.7%	-17.2%	11.8%	41/49=83.7%	38/44=86.4%	
Germany	5.1%	-9.0%	19.2%	37/42=88.1%	44/53=83.0%	
Italy	-1.4%	-22.5%	19.7%	19/23=82.6%	21/25=84.0%	
Russia	4.6%	-16.0%	25.1%	27/37=73.0%	26/38=68.4%	
Spain	9.6%	-0.6%	19.8%	105/125=84.0%	87/117=74.4%	
US	1.8%	-12.8%	16.5%	47/62=75.8%	54/73=74.0%	
HEIGHT_QUARTILE						
<=170	6.2%	-4.7%	17.1%	87/108=80.6%	87/117=74.4%	0.39
170-175	8.8%	-3.0%	20.5%	81/97=83.5%	65/87=74.7%	
175-180	-3.8%	-13.9%	6.4%	90/111=81.1%	84/99=84.8%	
>180	7.3%	-3.9%	18.4%	72/85=84.7%	79/102=77.5%	
WEIGHT_QUARTILE						
<=66	6.9%	-4.5%	18.3%	90/112=80.4%	72/98=73.5%	0.4
66-74.3	9.2%	-2.3%	20.7%	81/98=82.7%	72/98=73.5%	
74.3-84	-3.8%	-13.5%	5.9%	85/102=83.3%	88/101=87.1%	
>84	6.5%	-4.6%	17.6%	75/90=83.3%	83/108=76.9%	

SINGLE\_4467\_%BLQ\_WEEK\_96

SUBGROUP	MEAN DIFF	95% LIMITS		DTG	CONTROL	
COUNTRY		LOWER	UPPER			
Canada	34.4%	15.4%	53.3%	27/28=96.4%	18/29=62.1%	0.022
Germany	-7.3%	-22.2%	7.7%	28/33=84.8%	35/38=92.1%	
Spain	10.3%	-0.6%	21.3%	94/116=81.0%	82/116=70.7%	
US	3.6%	-5.7%	12.9%	126/161=78.3%	118/158=74.7%	
HEIGHT QUARTILE						
<=169	12.8%	0.9%	24.8%	84/111=75.7%	71/113=62.8%	0.29
169-175	-1.1%	-12.1%	9.8%	92/119=77.3%	80/102=78.4%	
175-181	12.2%	0.4%	24.0%	84/101=83.2%	66/93=71.0%	
>181	10.7%	0.2%	21.2%	73/83=88.0%	85/110=77.3%	
WEIGHT QUARTILE						
<=66.6	12.3%	-0.1%	24.8%	80/110=72.7%	64/106=60.4%	0.92
66.6-75	4.0%	-6.7%	14.6%	90/108=83.3%	77/97=79.4%	
75-85	8.5%	-3.2%	20.1%	79/100=79.0%	79/112=70.5%	
>85	7.9%	-2.3%	18.1%	84/96=87.5%	82/103=79.6%	

FLAMINGO\_WEEK\_24\_DRV\RTV\_VS\_DTG\_50mg

SUBGROUP	MEAN	95% LIMITS		DTG	CONTROL	
	DIFF	LOWER	UPPER			
ABCEXP						
No	13.2%	5.3%	21.0%	144/158=91.1%	124/159=78.0%	0.1
Yes	0.4%	-9.2%	10.0%	74/83=89.2%	71/80=88.8%	
COUNTRY						
France	34.8%	9.8%	59.9%	28/33=84.8%	10/20=50.0%	0.48
Italy	18.7%	0.5%	36.9%	22/23=95.7%	20/26=76.9%	
Spain	2.7%	-8.9%	14.3%	41/44=93.2%	38/42=90.5%	
USA	8.8%	0.1%	17.5%	98/106=92.5%	87/104=83.7%	
REGION						
America	8.4%	0.1%	16.6%	105/113=92.9%	93/110=84.5%	0.76
Europe	9.2%	0.2%	18.2%	113/128=88.3%	102/129=79.1%	
LDLGPCD						
<2.59	8.4%	-0.8%	17.7%	113/129=87.6%	95/120=79.2%	0.86
>=2.59	6.5%	-2.3%	15.4%	72/77=93.5%	80/92=87.0%	
HEIGHT_QUARTILE						
<=170	4.4%	-6.3%	15.2%	65/73=89.0%	66/78=84.6%	0.83
170-175	12.8%	-0.3%	26.0%	58/64=90.6%	42/54=77.8%	
175-180	8.5%	-4.5%	21.5%	45/49=91.8%	40/48=83.3%	
>180	11.2%	-1.5%	24.0%	50/55=90.9%	47/59=79.7%	
WEIGHT_QUARTILE						
<=66.8	8.9%	-3.9%	21.6%	56/63=88.9%	48/60=80.0%	0.99
66.8-73.5	12.3%	-1.2%	25.7%	57/64=89.1%	43/56=76.8%	
73.5-84	9.8%	-3.2%	22.9%	54/61=88.5%	48/61=78.7%	
>84	5.9%	-3.1%	14.9%	51/53=96.2%	56/62=90.3%	

FLAMINGO\_WEEK\_48\_DRV\RTV\_VS\_DTG\_50mg

SUBGROUP	MEAN	95% LIMITS		DTG	CONTROL	
	DIFF	LOWER	UPPER			
ABCEXP						
No	10.0%	2.8%	17.2%	146/158=92.4%	131/159=82.4%	0.13
Yes	0.5%	-10.0%	11.0%	72/83=86.7%	69/80=86.3%	
COUNTRY						
France	7.9%	-12.9%	28.6%	29/33=87.9%	16/20=80.0%	0.98
Italy	17.7%	-4.7%	40.2%	20/23=87.0%	18/26=69.2%	
Spain	2.5%	-5.3%	10.3%	43/44=97.7%	40/42=95.2%	
USA	10.8%	1.2%	20.3%	96/106=90.6%	83/104=79.8%	
REGION						
America	10.2%	1.2%	19.3%	103/113=91.2%	89/110=80.9%	0.36
Europe	3.8%	-4.1%	11.7%	115/128=89.8%	111/129=86.0%	
LDLGPCD						
<2.59	7.5%	-1.3%	16.2%	115/129=89.1%	98/120=81.7%	0.66
>=2.59	3.7%	-6.1%	13.6%	69/77=89.6%	79/92=85.9%	
HEIGHT_QUARTILE						
<=170	9.6%	-1.9%	21.0%	65/73=89.0%	62/78=79.5%	0.98
170-175	5.4%	-6.4%	17.3%	58/64=90.6%	46/54=85.2%	
175-180	2.2%	-8.1%	12.5%	46/49=93.9%	44/48=91.7%	
>180	7.7%	-5.2%	20.6%	49/55=89.1%	48/59=81.4%	
WEIGHT_QUARTILE						
<=66.8	7.1%	-4.8%	19.0%	57/63=90.5%	50/60=83.3%	0.39
66.8-73.5	-0.2%	-11.4%	10.9%	57/64=89.1%	50/56=89.3%	
73.5-84	6.6%	-6.5%	19.6%	53/61=86.9%	49/61=80.3%	
>84	14.0%	3.2%	24.8%	51/53=96.2%	51/62=82.3%	

### 4.3.2 Two Class Resistant INI Naive Trial

SAILING\_1762\_%BLQ\_WEEK\_48

SUBGROUP	MEAN DIFF	95% LIMITS LOWER	UPPER	DTG	CONTROL	
REGION						
Europe	16.8%	1.7%	31.9%	42/47=89.4%	37/51=72.5%	0.31
N America	7.6%	-3.8%	19.1%	89/131=67.9%	82/136=60.3%	
Other	4.5%	-5.2%	14.1%	125/171=73.1%	116/169=68.6%	
COUNTRY						
Argentina	17.6%	-3.8%	39.0%	25/27=92.6%	15/20=75.0%	0.73
Brazil	2.3%	-13.7%	18.3%	44/61=72.1%	44/63=69.8%	
Mexico	4.8%	-24.4%	33.9%	15/21=71.4%	12/18=66.7%	
S Africa	4.2%	-14.7%	23.0%	34/51=66.7%	30/48=62.5%	
US	7.2%	-5.4%	19.8%	72/108=66.7%	69/116=59.5%	
HEIGHT_QUARTILE						
<=164	7.5%	-5.2%	20.3%	69/93=74.2%	68/102=66.7%	0.76
164-170	8.6%	-4.6%	21.7%	73/99=73.7%	58/89=65.2%	
170-177	11.1%	-2.7%	24.8%	65/88=73.9%	54/86=62.8%	
>177	0.7%	-14.1%	15.6%	49/74=66.2%	55/84=65.5%	
WEIGHT_QUARTILE						
<=62	7.6%	-6.2%	21.4%	69/101=68.3%	51/84=60.7%	0.21
62-72	4.0%	-9.2%	17.1%	67/91=73.6%	62/89=69.7%	
72-82.5	19.5%	6.0%	33.0%	68/87=78.2%	51/87=58.6%	
>82.5	-1.0%	-14.7%	12.8%	52/75=69.3%	71/101=70.3%	

#### 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\_48

SUBGROUP	MEAN	95% LIMITS		DTG	CONTROL	
	DIFF	LOWER	UPPER			
Baseline CDC Group						
A	12.7%	1.3%	24.2%	88/110=80.0%	76/113=67.3%	0.014
B	-11.8%	-26.6%	3.0%	42/68=61.8%	64/87=73.6%	
C	12.8%	2.7%	22.9%	126/171=73.7%	95/156=60.9%	
ABC EXPOSURE						
No	7.7%	0.6%	14.8%	235/320=73.4%	209/318=65.7%	0.76
Yes	4.0%	-18.0%	26.0%	21/29=72.4%	26/38=68.4%	
CLADE						
B	6.7%	-1.4%	14.8%	177/238=74.4%	163/241=67.6%	0.57
C	2.5%	-16.4%	21.4%	34/54=63.0%	29/48=60.4%	
Other	14.4%	-1.3%	30.1%	44/56=78.6%	43/67=64.2%	
Class resistance						
2	4.5%	-4.9%	13.8%	135/183=73.8%	122/176=69.3%	0.46
>=3	10.1%	0.3%	19.9%	121/166=72.9%	113/180=62.8%	

SAILING\_1762\_%BLQ\_WEEK\_48

SUBGROUP	MEAN		95% LIMITS		DTG	CONTROL	
	DIFF	LOWER	UPPER				
DRV use and no primary PI mutation?							
No	8.6%	1.0%	16.3%		203/277=73.3%	181/280=64.6%	0.5
Yes	2.6%	-11.8%	17.0%		53/72=73.6%	54/76=71.1%	
Recent approved ART in background reg.							
N	5.9%	-3.7%	15.6%		127/185=68.6%	116/185=62.7%	0.53
Y	9.1%	-0.3%	18.4%		129/164=78.7%	119/171=69.6%	
Use of DRV in background regimen							
N	6.3%	-2.8%	15.4%		145/209=69.4%	130/206=63.1%	0.54
Y	9.3%	-0.7%	19.2%		111/140=79.3%	105/150=70.0%	
Use of ETR in background regimen							
N	6.0%	-1.3%	13.3%		220/305=72.1%	205/310=66.1%	0.26
Y	16.6%	-1.3%	34.5%		36/44=81.8%	30/46=65.2%	
Use of inducer in background regimen							
N	8.2%	1.2%	15.3%		238/323=73.7%	216/330=65.5%	0.36
Y	-3.8%	-28.5%	20.8%		18/26=69.2%	19/26=73.1%	
Use of MVC in background regimen							
N	7.6%	0.4%	14.7%		226/310=72.9%	211/323=65.3%	0.82
Y	4.2%	-15.9%	24.3%		30/39=76.9%	24/33=72.7%	

## 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_48						
SUBGROUP	MEAN DIFF	95% LIMITS		DTG	CONTROL	
		LOWER	UPPER			
Baseline GSS to BR group						
2	7.9%	-2.6%	18.4%	98/138=71.0%	106/168=63.1%	0.89
<2	6.3%	-2.6%	15.1%	158/211=74.9%	129/188=68.6%	
Baseline GSS to BR group						
0_to_<1	12.4%	-16.9%	41.8%	17/25=68.0%	10/18=55.6%	0.93
1_to_<2	5.8%	-3.4%	15.0%	141/186=75.8%	119/170=70.0%	
2	8.4%	-2.1%	18.9%	98/137=71.5%	106/168=63.1%	
Baseline PSSp to BR group						
<2	6.8%	-6.3%	19.9%	71/99=71.7%	61/94=64.9%	0.9
>=2	7.6%	-0.3%	15.5%	185/250=74.0%	174/262=66.4%	
Baseline PSSf to BR group						
2	7.5%	-0.4%	15.4%	184/249=73.9%	174/262=66.4%	0.94
<2	7.1%	-6.0%	20.2%	72/100=72.0%	61/94=64.9%	
Baseline PSSp to BR group						
1	15.6%	-0.3%	31.6%	48/65=73.8%	39/67=58.2%	0.29
>1	5.4%	-2.0%	12.9%	208/284=73.2%	196/289=67.8%	
BL GSS to BR						
1.00	8.8%	-6.0%	23.6%	49/66=74.2%	53/81=65.4%	0.63
1.25	1.7%	-17.9%	21.4%	35/47=74.5%	24/33=72.7%	
1.50	-3.6%	-20.7%	13.6%	37/49=75.5%	34/43=79.1%	
1.75	21.8%	-8.6%	52.2%	20/24=83.3%	8/13=61.5%	
2.00	8.4%	-2.1%	18.9%	98/137=71.5%	106/168=63.1%	

SAILING\_1762\_%BLQ\_WEEK\_48

SUBGROUP	MEAN	95% LIMITS		DTG	CONTROL	
	DIFF	LOWER	UPPER			
BL PSS to BR full sensitivity group						
1	5.0%	-8.4%	18.4%	66/93=71.0%	60/91=65.9%	0.68
2	8.1%	0.2%	16.0%	184/247=74.5%	174/262=66.4%	
BL PSS to background ART partial sens.						
1	5.0%	-8.4%	18.4%	66/93=71.0%	60/91=65.9%	0.68
2	8.1%	0.2%	16.0%	184/247=74.5%	174/262=66.4%	
BL PSS to BR full sens. inc mis.						
1	7.0%	-6.6%	20.5%	66/92=71.7%	57/88=64.8%	0.88
2	7.8%	0.1%	15.6%	190/255=74.5%	178/267=66.7%	
BL PSSp to BR						
1.0	13.0%	-3.6%	29.7%	42/58=72.4%	38/64=59.4%	0.15
1.5	-13.8%	-35.3%	7.7%	23/34=67.6%	22/27=81.5%	
2.0	8.4%	0.5%	16.3%	184/246=74.8%	174/262=66.4%	
BL Max PSSf						
11	0.0%	-19.6%	19.6%	22/26=84.6%	22/26=84.6%	0.45
12	6.3%	-13.8%	26.4%	25/32=78.1%	28/39=71.8%	
13	-3.1%	-20.4%	14.2%	35/48=72.9%	38/50=76.0%	
14	10.7%	-8.9%	30.3%	41/53=77.4%	22/33=66.7%	
15	-3.2%	-21.2%	14.8%	31/48=64.6%	40/59=67.8%	
16	32.6%	5.8%	59.4%	19/23=82.6%	10/20=50.0%	
17	9.1%	-23.3%	41.6%	8/14=57.1%	12/25=48.0%	

## 5. Summary and Conclusions:

The applicant has conducted nine 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. Seven of these trials have been discussed in a previous review. The current review gives longer term data on three of the large, randomized, controlled trials and also 24 week data on a new, large randomized controlled trial.

In treatment naïve patients, the applicant conducted five trials: one short term dose ranging study (1521), one long term dose ranging study (Spring 1), two long term pivotal trials (Spring 2 and Single), and one long term, open label, phase 3b trial (Flamingo).

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 previous review. The current data shows that this statistically significant superiority is maintained to 96 weeks.

In the second pivotal trial, trial Spring 2, DTG at 50mg QD was statistically non-inferior to raltegravir (RAL) at week 48 in the previous review. Again, the current review shows that the DTG regimen remains no more than 5% worse than RAL out to 96 weeks.

The third large, randomized, open-label, phase 3B trial, trial Flamingo, has been presented for the first time in this review. At 24 weeks, this trial showed DTG at 50mg QD was statistically significantly superior to DAR/rtv.

The applicant conducted one pivotal trial (Sailing) 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 at week 24. The new data in this NDA show that by week 48, the DTG regimen was statistically significantly superior to RAL.

The general pattern of convincing efficacy was also confirmed when one focused exclusively on subjects who received the ABC/3TC

background proposed in this NDA.

In the previous review, the applicant had 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. In the current review, the efficacy of DTG 50mg QD has been confirmed to 96 weeks in treatment naïve patients and to 48 weeks in two class resistant, INI naïve patients.

Finally, the pattern of CD4 count over time also confirms the conclusion of efficacy of DTG in general and specifically with ABC/3TC background.

Thomas Hammerstrom, Ph.D.  
Mathematical Statistician

Concur: Dr. Soon

-----  
**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  
07/17/2014

GUOXING SOON  
07/17/2014

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number: 205551**

**Applicant: ViiV Healthcare**

**Stamp Date: 10/22/2013**

**Drug Name: Dolutegravir  
FDC**

**NDA/BLA Type: NDA**

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

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

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?   Yes**

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

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

<b>Content Parameter (possible review concerns for 74-day letter)</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

File name: 5\_Statistics Filing Checklist for a New NDA\_BLA110207

**STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA**

Thomas Hammerstrom 12/16/13  
\_\_\_\_\_  
Reviewing Statistician Date

Greg Soon  
\_\_\_\_\_  
Supervisor/Team Leader Date

-----  
**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  
12/16/2013

GUOXING SOON  
12/20/2013