550

Consistency of Dolutegravir Treatment Difference in HIV+ Treatment Naives at Week 96

Catherine Granier,[1] Robert Cuffe,[2] Louise Martin-Carpenter,[3] Kimberly Smith,[3] Clare Brennan,[4] Keith Pappa,[4] Brian Wynne,[5] Steve Almond,[6] Naomi Givens,[1] Michael Aboud[2]

[1]GlaxoSmithKline, Stockley Park, UK; [2]ViiV Healthcare, London, UK; [3]ViiV Healthcare, Research Triangle Park, NC, USA; [4]GlaxoSmithKline, Research Triangle Park, NC, USA; [5]GlaxoSmithKline, Upper Providence, PA, USA; [6]GlaxoSmithKline, Mississauga, ON, Canada

Catherine Granier
1-3 Ironbridge Road
Uxbridge, Middlesex UB11 1BU UK
44 20 89904239
catherine.z.granier@gsk.com

Introduction

- Dolutegravir (DTG, GSK1349572), an INSTI not requiring boosting, is approved in 29 countries for HIV-1 infected patients. It has shown good efficacy and safety in treatment-naive patients.[1-3]
- We present subgroup results from the efficacy analyses of the phase III/IV studies ING113086 (SPRING-2), ING114467 (SINGLE) and ING114915 (FLAMINGO) up to Week 96 (and Week 144 for SINGLE) in antiretroviral-naive adults with HIV-1 infection.[1-3]

Methods

- Studies:
  - SPRING-2: DTG 50 mg QD vs raltegravir (RAL) 400 mg BID, stratified by investigator-selected NRTIs (coformulated tenofovir/emtricitabine [TDF/FTC] or abacavir/lamivudine [ABC/3TC]) and baseline viral load (VL) levels
  - SINGLE: DTG 50 mg QD + fixed-dose combination tablet ABC/3TC vs efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC), stratified by baseline VL and CD4 levels
  - FLAMINGO: DTG 50 mg QD vs darunavir (DRV/r) 800/100 mg QD, stratified by investigator-selected NRTIs (TDF/FTC or ABC/3TC) and baseline VL levels
- In the Snapshot analysis (1° endpoint in each study), a switch or discontinuation for any reason was treated as a treatment failure. The adjusted difference in the proportions was based on a stratified analysis using Cochran-Mantel-Haenszel weights.
- In the efficacy-related discontinuations = failure (ERDF) analysis, only virologic failure or withdrawal due to lack of efficacy were counted as failure. Participants who discontinued for other reasons were censored.
- Time to ERDF was analysed using the Kaplan-Meier method to allow for censoring.

Results

- Snapshot responders (<50 c/mL HIV-1 RNA):
  - In SPRING-2, DTG was non-inferior to RAL based on the Snapshot algorithm at Week 96 (adjusted difference in proportion [95% CI; DTG-RAL] 4.5 [-1.1, 10.0]).
  - In FLAMINGO, DTG was superior to DRV/r at Week 96 (adjusted difference in proportion [95% CI; DTG-DRV/r] 12.4 [4.7, 20.2], *P*=0.002).
  - In SINGLE, DTG + ABC/3TC was superior to EFV/TDF/FTC at Week 96 (adjusted difference in proportion [95% CI; DTG-EFV/TDF/FTC] 8.0 [2.3, 13.8], *P*=0.006) and at Week 144 (71% vs 63%, adjusted difference: 8.3 [2.0, 14.6], *P*=0.01).
  - In the >100K BL VL stratum in SINGLE, the Week 144 response rates were 69% for DTG + ABC/3TC and 61% for EFV/TDF/FTC (difference DTG-EFV/TDF/FTC: 7.6; 95% CI: -3.9, 19.1).

Figure 1. ERDF by Baseline (BL) VL and Randomised Treatment

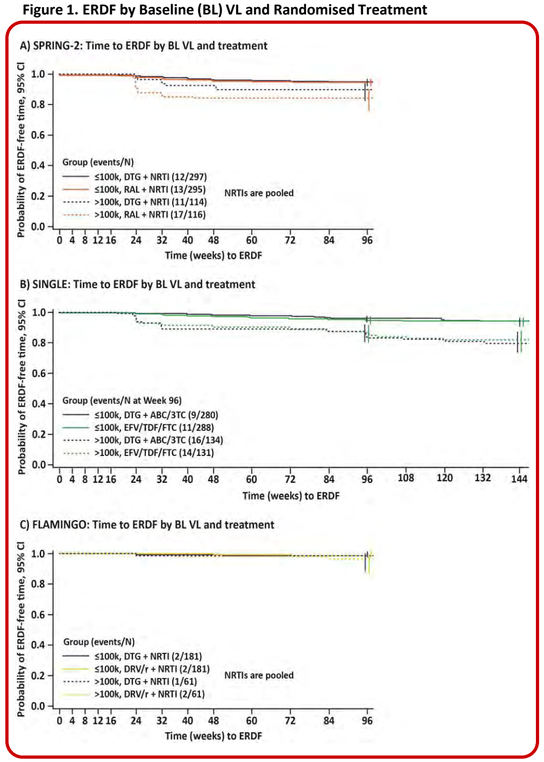
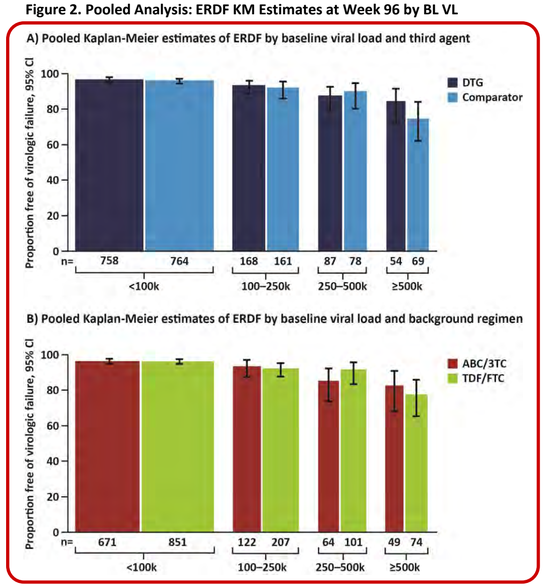


Table 1. Snapshot Responders at Week 96

	SPRING-2		SINGLE		FLAMINGO	
	DTG	RAL	DTG	EFV/FTC/TDF	DTG	DRV/r
OVERALL	332/411 (81%)	314/411 (76%)	332/414 (80%)	303/419 (72%)	194/242 (80%)	164/242 (68%)
INDIVIDUALS WITH HIGH BASELINE VL BY BACKGROUND REGIMEN						
>100,000 c/mL						
ABC/3TC	27/37 (73%)	26/39 (67%)	95/134 (71%)	—	11/13 (85%)	7/12 (58%)
TDF/FTC	62/77 (81%)	47/77 (61%)	—	94/131 (72%)	39/48 (81%)	25/49 (51%)
INDIVIDUALS WITH LOW BASELINE CD4						
<200 c/mm³	39/55 (71%)	28/50 (56%)	39/57 (68%)	45/62 (73%)	18/23 (78%)	14/24 (58%)
200 to <350 c/mm³	116/144 (81%)	103/139 (74%)	135/163 (83%)	113/159 (71%)	60/73 (82%)	36/51 (71%)

Figure 2. Pooled Analysis: ERDF KM Estimates at Week 96 by BL VL



Discussion

- DTG administered once daily with 2 NRTIs showed non-inferiority to RAL and superiority to DRV/r and EFV/TDF/FTC up to Week 96, as well as up to Week 144 vs EFV/TDF/FTC.
- Snapshot treatment differences were not always consistent at high VL.
  - In SPRING-2 and FLAMINGO, there was a bigger difference between arms above 100k c/mL at Week 96.
  - In SINGLE (Week 96), there was a smaller difference between arms above 100k c/mL.
- These potential interactions were not consistent across studies or time points.
  - At Weeks 48 and 144 in SINGLE, the difference between arms was consistent across baseline VL strata. Differences in efficacy were driven by withdrawal for adverse events.
  - At Week 48 in SPRING-2, the difference between arms was consistent across baseline VL strata.
- Analyses of efficacy-related failure did not show the same inconsistencies in treatment differences in small subgroups.
- Pooled analyses, allowing greater information for smaller subgroups defined by high VL, used the ERDF analysis.
- In pooled analysis, there was no evidence of a difference between DTG and pooled comparator in the rate of long-term efficacy-related failure at low, high or very high VL.
- In pooled analysis, there was no evidence of a difference between the NRTI backbones in the rate of efficacy-related failure at low, high or extreme VL.
  - NRTIs were chosen by investigators (not randomised) in SPRING-2 and FLAMINGO.

Conclusions

- By Snapshot analysis, DTG showed superiority over comparator in 2 of the 3 naive studies.
- Inconsistencies in Snapshot treatment differences were observed in smaller subgroups but not observed consistently across studies, endpoints or time points.
- The efficacy-related endpoint (ERDF) did not show the same inconsistencies, enabling pooled analyses.
- These pooled analyses suggested no evidence of a difference in long-term virologic efficacy between DTG and third agents or between ABC/3TC and TDF/FTC at low or high viral load.

Acknowledgments
This study was sponsored by ViiV Healthcare. The authors thank the following individuals: all subjects who participated in SPRING-2, SINGLE and FLAMINGO; all investigators and site staff; and the study teams and the numerous contributors from ViiV Healthcare and GSK.

References

1. Raffi F, Rachlis A, Stellbrink H-J, et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. *Lancet*. 2013;381(9868):735-743.
2. Walmsley S, Berenguer J, Khuong-Josses M, et al. Dolutegravir regimen statistically superior to efavirenz/tenofovir/emtricitabine: 96-week results from the SINGLE study (ING114467). Abstract 337. Presented at: 21st Conference on Retroviruses and Opportunistic Infections; March 3-6, 2014; Boston, MA.
3. Molina J-M, Clotet B, van Lunzen J, et al. Dolutegravir is superior to darunavir/ritonavir in treatment-naive HIV-1 infected individuals: 96 week results from FLAMINGO. Slides O153. Presented at: HIV Drug Therapy Glasgow; November 2-6, 2014; Glasgow, UK.

22nd Conference on Retroviruses and Opportunistic Infections; February 23-26, 2015; Seattle, WA