

## Consistency of Dolutegravir Treatment Difference in HIV Positive Treatment Naives at Week 96

Granier CM<sup>1</sup>, Bloch M<sup>2</sup>, Finlayson R<sup>3</sup>, Roth N<sup>4</sup>, Cuffe R<sup>5</sup>, Martin-Carpenter L<sup>6</sup>, Smith K<sup>6</sup>, Brennan C<sup>7</sup>, Pappa K<sup>7</sup>, Wynne B<sup>7</sup>, Almond S<sup>8</sup>, Givens N<sup>1</sup>, Aboud M<sup>5</sup>

<sup>1</sup>R&D, GlaxoSmithKline, Uxbridge, Middlesex, United Kingdom; <sup>2</sup>Holdsworth House Medical Practice, Sydney, Australia; <sup>3</sup>Taylor Square Private Clinic, Sydney, Australia; <sup>4</sup>Pratron Market Clinic, Melbourne, Australia; <sup>5</sup>ViiV Healthcare, London, United Kingdom; <sup>6</sup>ViiV Healthcare, RTP, NC, United States; <sup>7</sup>GlaxoSmithKline, RTP, NC, United States; <sup>8</sup>GlaxoSmithKline, Mississauga, ON, Canada.




Australasian HIV&AIDS Conference 2015;16-18 September 2015; Brisbane Australia

## Introduction

- Dolutegravir (DTG, GSK1349572), an INSTI not requiring boosting, is approved in 53 countries for HIV-1 infected patients. It has shown good efficacy and safety in treatment-naive patients<sup>1-3</sup>
- 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<sup>1-3</sup>

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## Methods: DTG treatment naive study designs

<b>SINGLE<sup>1</sup></b> Treatment-naive	<b>N=833</b>	Phase III non-inferiority, randomised, double-blind, double-dummy, multicentre study of: • DTG (50 mg QD) with ABC/3TC FDC plus EFV/TDF/FTC placebo • EFV/TDF/FTC (QD) plus DTG and ABC/3TC FDC placebos	
<b>SPRING-2<sup>2</sup></b> Treatment-naive	<b>N=822</b>	Phase III non-inferiority, randomised, double-blind, double-dummy, multicentre study of: • DTG (50 mg QD) plus RAL placebo (BID) + 2 NRTIs • RAL (400 mg BID) plus DTG placebo (QD) + 2 NRTIs	
<b>FLAMINGO<sup>3</sup></b> Treatment-naive	<b>N=484</b>	Phase IIIb non-inferiority, randomised, active-controlled, multicentre, open-label study of: • DTG (50 mg QD) + 2 NRTIs • DRV/r (600/100 mg QD) + 2 NRTIs	

- SINGLE study: stratified by baseline HIV-1 RNA (<100,000 or >100,000 copies/mL) and investigator selected CD4 cell count (<200 or ≥200 cells/mm<sup>3</sup>)
- SPRING-2 and FLAMINGO studies: stratified by baseline HIV-1 RNA (<100,000 or ≥100,000 copies/mL) and investigator selected NRTI backbone (ABC/3TC or TDF/FTC)

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## Methods: Efficacy Analysis - Overall Response (Snapshot) and Virologic Response (ERDF)

- In the Snapshot analysis (1<sup>st</sup> 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

Outcome (Snapshot), n (%)	
Virologic success HIV-1 RNA <50 c/mL	
Virologic non response	
Discontinued for lack of efficacy	
Protocol Defined Virologic Failure (PDVF)	
Data in window not <50 c/mL	
Discontinued for other reason while not <50 c/mL	
No virologic data at Week 48	
Discontinued because of AE or death	
Discontinued for other reasons	
Missing data during window, but on study	

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## DTG Phase III Treatment-Naïve studies Snapshot Responders: <50 c/mL HIV-1 RNA (week 96)

Study	DTG (n/N)	Control (n/N)	Statistical Significance
SPRING-2	81 / 332/411	76 / 314/411	Non-inferior vs RAL + 2NRTIs
SINGLE	80 / 332/414	72 / 303/419	Statistically Superior vs EFV/TDF/FTC p = 0.006
FLAMINGO	80 / 194/242	68 / 164/242	Statistically Superior vs DRV/r + 2NRTIs p = 0.002

- 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])<sup>1</sup>
- 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<sup>2</sup>
- 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<sup>3</sup> and at Week 144 (71% vs 63%, adjusted difference: 8.3 [2.0, 14.6], P=0.01)<sup>3</sup>

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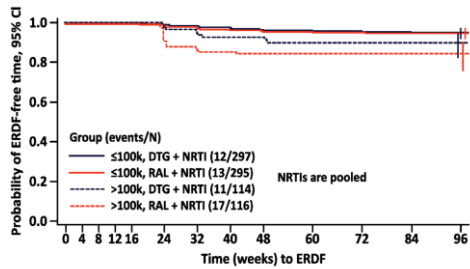
## FDA SNAPSHOT 96-Week Subgroup Response RATES

	SPRING-2		SINGLE		FLAMINGO	
	DTG	RAL	DTG	EFV/FTC/TDF	DTG	DRV/r
<b>OVERALL</b>	332/411 (81%)	314/411 (76%)	332/414 (80%)	303/419 (72%)	194/242 (80%)	164/242 (68%)
<b>INDIVIDUALS WITH HIGH BASELINE VL BY BACKGROUND REGIMEN</b>						
<b>&gt;100,000 c/mL</b>						
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%)
<b>INDIVIDUALS WITH LOW BASELINE CD4</b>						
<b>&lt;200 c/mm<sup>3</sup></b>						
	39/55 (71%)	28/50 (56%)	39/57 (68%)	45/62 (73%)	18/23 (78%)	14/24 (58%)
<b>200 to &lt;350 c/mm<sup>3</sup></b>	116/144 (81%)	103/139 (74%)	135/163 (83%)	113/159 (71%)	60/73 (82%)	36/51 (71%)

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### ERDF by Baseline (BL) VL and Randomised Treatment : SPRING-2

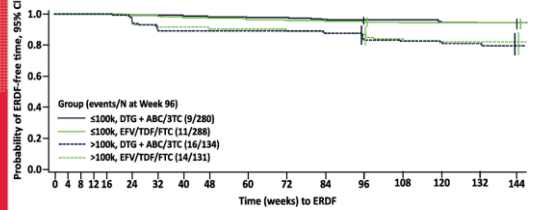
A) SPRING-2: Time to ERDF by BL VL and treatment



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### ERDF by Baseline (BL) VL and Randomised Treatment : SINGLE

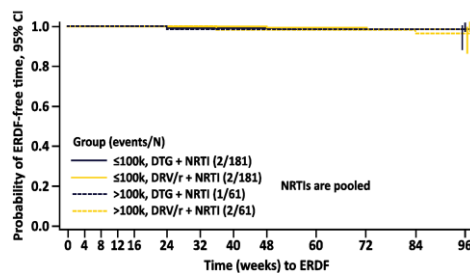
B) SINGLE: Time to ERDF by BL VL and treatment



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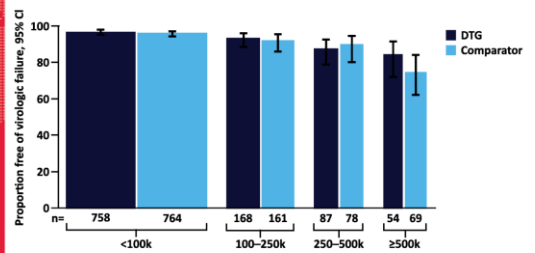
### ERDF by Baseline (BL) VL and Randomised Treatment : FLAMINGO

C) FLAMINGO: Time to ERDF by BL VL and treatment



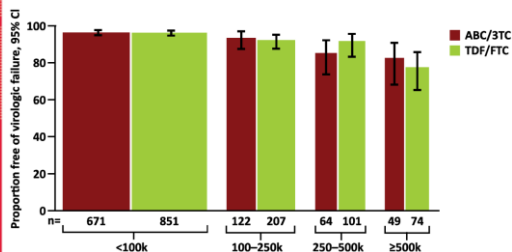
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### Pooled Analysis: ERDF Kaplan-Meier Estimates at Week 96 by BL VL and Third Agent



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### Pooled Analysis: ERDF Kaplan-Meier Estimates at Week 96 by BL VL and Background Regimen



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### 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

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## Acknowledgements

- 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;
  - The study teams and the numerous contributors from ViiV Healthcare and GSK



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