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Dolutegravir Regimen Statistically Superior to Efavirenz/Tenofovir/Emtricitabine: 96-Week Results From the SINGLE Study (ING114467)

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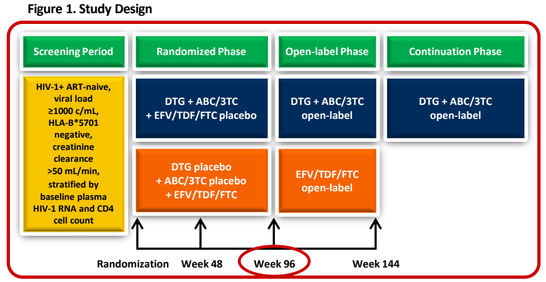
Introduction

- At the primary 48-week analysis, dolutegravir (DTG) 50 mg + abacavir (ABC)/lamivudine (3TC) once daily was superior to efavirenz (EFV)/tenofovir (TDF)/emtricitabine (FTC) in treatment-naive HIV-1 patients.[1]
  - 88% vs 81% were suppressed virologically (plasma HIV <50 c/mL by snapshot algorithm [*P*=0.003]); safety/tolerability was favorable for DTG + ABC/3TC.
- We now present 96-week results.

Methods

- SINGLE (ING114467) is an ongoing, phase III, randomized, multicenter, double-blind, double-dummy study comparing the efficacy and safety of DTG 50 mg plus ABC/3TC fixed-dose combination (FDC) vs EFV/TDF/FTC FDC in treatment-naive HIV patients (Figure 1).
- Randomization was stratified by baseline plasma HIV-1 RNA (≤ vs >100,000 c/mL) and CD4 cell count (≤ vs >200 cells/mm^3; Figure 1).

Figure 1. Study Design

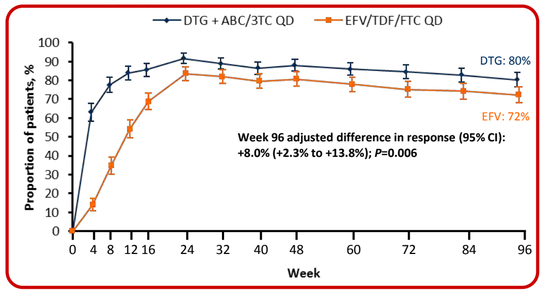


Results

Baseline Patient Characteristics

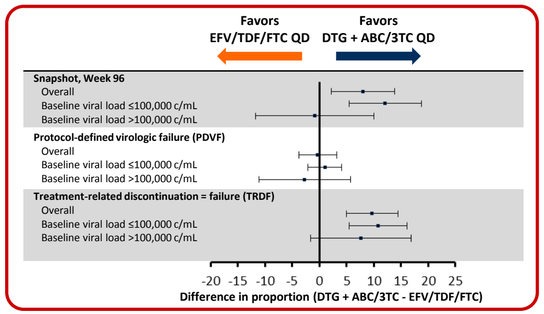
- Baseline patient characteristics were similar between treatment arms and were characteristic of a treatment-naive population.[1]
- Median patient age was 35 years; 16% of patients were female; 32% were non-white; 7% had hepatitis C co-infection; and 4% were CDC class C.
- In each arm, 14% of patients had a CD4 cell count <200 cells/mm^3.
- 31% and 32% of patients with viral load >100,000 copies/mL were enrolled in the DTG + ABC/3TC arm and the EFV/TDF/FTC arm, respectively.

Figure 2. Virologic Suppression (HIV-1 RNA <50 c/mL; FDA Snapshot)



- Overall, the statistically higher responses on DTG + ABC/3TC vs EFV/TDF/FTC were driven by withdrawals due to AEs (3% vs 11%, respectively), irrespective of viral load strata.
- Differences in time to viral suppression favored DTG + ABC/3TC (28 vs 84 days, *P*<0.0001).

Figure 3. Proportion With HIV-1 RNA <50 c/mL by Baseline Viral Load: Snapshot, PDVF, TRDF



- Less-pronounced differences by snapshot in the high viral load subgroup due to withdrawals for reasons unrelated to treatment (DTG + ABC/3TC = 14, EFV/TDF/FTC = 8) (eg, lost to follow-up, withdrawn consent, protocol deviation)
- No significant differences were observed in protocol-defined virologic failure (PDVF) between the high and low viral load subgroups.
- Difference in treatment-related discontinuation = failure (TRDF) analysis, which considers only withdrawals for safety or efficacy, was consistently in favor of DTG + ABC/3TC between the high and low viral load subgroups.

Table 1. Week 96 Adjusted Mean Change From Baseline in CD4 Cell Count (cells/mm^3)

Treatment	Adjusted mean	SE	Difference in response (95% CI)
DTG + ABC/3TC QD (n=414)	325.3	10.5	44.0 (14.3, 73.6) *P*=0.004
EFV/TDF/FTC QD (n=419)	281.4	10.9	

Table 2. Protocol-Defined Virologic Failure

Time point	DTG + ABC/3TC QD (n=414)	EFV/TDF/FTC QD (n=419)
Up to Week 48	18 (4%)	17 (4%)
Week 60	1 (<1%)	3 (<1%)
Week 72	1 (<1%)	3 (<1%)
Week 84	5 (1%)	2 (<1%)
Up to Week 96	25 (6%)	25 (6%)

- PDVF was defined as confirmed HIV-1 RNA ≥50 c/mL at or after Week 24.
  - After 2 years of therapy, the majority of subjects who met PDVF at confirmed failure had low-level viremia (<200 c/mL HIV-1 RNA):
    - 20/25 (80%) subjects on DTG + ABC/3TC and 17/25 (68%) subjects on EFV/TDF/FTC

Table 3. Resistance Mutations in Individuals Who Met PDVF Criteria

Mutation	DTG + ABC/3TC QD (n=414)	EFV/TDF/FTC QD (n=419)
NRTI TE major mutations	0	1 (K65R)
NNRTI TE major mutations	0	6 (K101E, K103N, G190A)*
INI-r TE major substitution	0**	0

TE = treatment emergent
*n=1 with K101E, n=1 with K103N, n=2 with K103K/N, n=1 with G190A and n=1 with K103N + G190A
**E157Q/P polymorphism detected with no significant change in IN phenotypic susceptibility

Table 4. Summary of Treatment-Related Adverse Events

Adverse event	DTG + ABC/3TC QD (n=414)	EFV/TDF/FTC QD (n=419)
Treatment-related	**184 (44%)**	**282 (67%)**
Preferred term ≥10% in either arm		
Dizziness	29 (7%)	139 (33%)
Abnormal dreams	27 (7%)	66 (16%)
Nausea	44 (11%)	49 (12%)
Insomnia	41 (10%)	25 (6%)
Treatment-related Grades 2-4 (≥5% in either arm)	**58 (14%)**	**116 (28%)**
Dizziness	2 (<1%)	21 (5%)

- Treatment-related rash was reported significantly more commonly in the EFV/TDF/FTC arm (34/419, 8%) than in the DTG + ABC/3TC arm (4/414, <1%).

Table 5. Summary of Adverse Events Leading to Discontinuation

Parameter	DTG + ABC/3TC QD (n=414)	EFV/TDF/FTC QD (n=419)
Body system (at least 2% in either arm)		
Psychiatric disorders	4 (<1%)	23 (5%)
Nervous system disorders	1 (<1%)	17 (4%)
Skin and subcutaneous tissue disorders	2 (<1%)	9 (2%)
General disorders and administration site conditions	0	10 (2%)
Gastrointestinal disorders	0	8 (2%)

Table 6. Laboratory Analyses: Change From Baseline in Renal Parameters

	DTG + ABC/3TC QD		EFV/TDF/FTC QD	
Parameter	Week 48	Week 96	Week 48	Week 96
Urine albumin/creatinine ratio (mg/mmoL) Median change (IQR)	0 (-0.3, 0.3)	0 (-0.3, 0.2)	0.05 (-0.2, 0.3)	0.05 (-0.2, 0.3)
Serum creatinine (mg/dL) Median change (IQR)	0.11 (0.05, 0.18)	0.14 (0.07, 0.20)	-0.01 (-0.06, 0.04)	0.02 (-0.04, 0.07)

- Small, non-progressive changes in serum creatinine were observed in the DTG + ABC/3TC arm, due to known inhibition of tubular creatinine secretion by DTG.[2]
- Grade 2 or higher ALT elevations were observed more commonly in the EFV/TDF/FTC arm (24/419; 6%) than in the DTG + ABC/3TC arm (12/414; 3%).

Conclusions

- Overall, DTG + ABC/3TC was superior to EFV/TDF/FTC with respect to snapshot (<50 c/mL).
  - 80% of subjects on DTG + ABC/3TC achieved <50 c/mL vs 72% on EFV/TDF/FTC (*P*=0.006).
  - Differences in efficacy were driven by a lower rate of discontinuation due to AEs for the DTG + ABC/3TC arm, which was independent of baseline viral load.
  - In the high viral load subgroup, tolerability advantages were attenuated by reasons unrelated to treatment.
  - DTG + ABC/3TC was statistically superior to EFV/TDF/FTC in CD4 cell count change from baseline.
- DTG + ABC/3TC safety and tolerability were generally more favorable when compared to EFV/TDF/FTC.
  - Lower rates of CNS and rash events; fewer discontinuations due to AEs
  - Lower rate of liver chemistry elevations
- No major treatment-emergent INI or NRTI resistance mutations were detected through 96 weeks with DTG + ABC/3TC.

Acknowledgment

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References

1. Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med.* 2013;369(19):1807-1818.
2. Koteff J, Borland J, Chen S, et al. A phase 1 study to evaluate the effect of dolutegravir on renal function via measurement of iohexol and para-aminohippurate clearance in healthy subjects. *Br J Clin Pharmacol.* 2013;75(4):990-996.

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