Safety and Efficacy of DTG+RPV in the Phase III SWORD-1 and SWORD-2 Studies: 48 Week Subgroup Analysis by Baseline Third Agent Class and Geographic Location

BPD1/5

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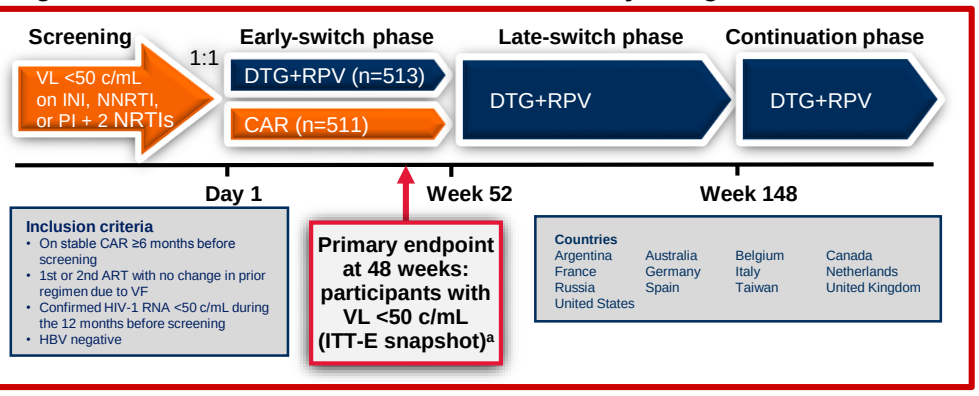
Introduction

- The efficacy and safety of switching to a 2-drug regimen (2DR) of dolutegravir (DTG) 50 mg and rilpivirine (RPV) 25 mg administered once daily with a meal in 2 phase III trials (SWORD-1 and SWORD-2) recently showed noninferiority to continuing a suppressive 3-drug comparator[1]
- A prespecified secondary endpoint was a subgroup analysis comparing the efficacy and safety of switching from current antiretroviral regimen (CAR) to DTG+RPV by background third agent
  - An exploratory objective was to evaluate the effect of geographic location on responses to DTG+RPV compared with CAR

Methods

- SWORD-1 and SWORD-2 were identically designed, randomized, open-label, parallel-group, phase III, noninferiority studies (Figure 1)

Figure 1. SWORD-1 and SWORD-2 Phase III Study Design



[a]Noninferiority margin of −8% for pooled data. Noninferiority margin of −10% for individual studies.

- Primary endpoint was proportion of participants with HIV-1 viral load <50 c/mL at Week 48 using FDA snapshot
  - Additional analyses were performed to summarize efficacy based on geographic region and baseline third-agent class subgroups for each individual study and pooled data from both studies
- Acceptable stable antiretroviral therapy (ART) regimens prior to screening included 2 NRTIs plus an INSTI, NNRTI, or boosted PI (or ATV unboosted)
- Efficacy analyses were conducted based on the intent-to-treat exposed (ITT-E) population, which consisted of all randomly assigned participants who received at least 1 dose of study drug
- Safety analyses included monitoring of adverse events (AEs), laboratory values, physical exams, and concomitant medications received in all participants who received at least 1 dose of study drug. Suicidality checks were done periodically

Results

- 1024 participants (DTG+RPV, n=513; CAR, n=511) were randomly assigned and exposed across both studies
- Baseline characteristics were well matched across treatment groups (Table 1)

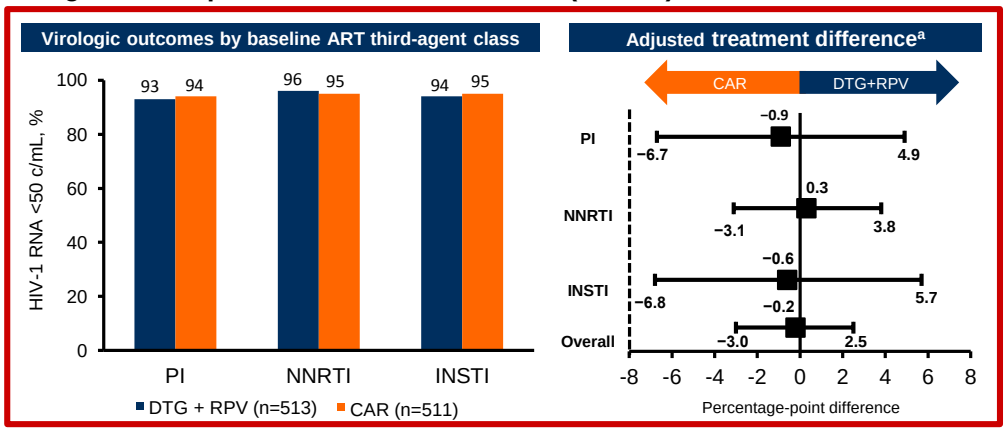
Table 1. Baseline Demographics From SWORD-1 and SWORD-2 for the ITT-E Population

	DTG+RPV (n=513)	CAR (n=511)
Median age (range), y	43.0 (21-79)	43.0 (22-76)
Age: ≥50 years, n (%)	147 (29)	142 (28)
Female, n (%)	120 (23)	108 (21)
Hispanic/Latino, n (%)	67 (13)	82 (16)
Non-white, n (%)	92 (18)	113 (22)
Baseline ART third-agent class, n (%)		
NNRTI	275 (54)	278 (54)
PI	133 (26)	136 (27)
INSTI	105 (20)	97 (19)

Efficacy Results by Baseline Third-Agent Class

- At Week 48, the percentage of participants who maintained VL <50 c/mL was 95% in both groups of the pooled SWORD-1 and SWORD-2 analysis (adjusted treatment difference, –0.2%; 95% CI, –3.0 to 2.5; Figure 1)
- Subgroup analyses by baseline third-agent class gave consistent virologic efficacy results to support overall findings with no marked differences (test of homogeneity for treatment difference, *P*=0.930; Figure 1)

Figure 1. Snapshot Outcomes at Week 48 (Pooled)



[a]Error bars show the 95% confidence interval. Treatment difference for the overall population is adjusted for age and baseline third-agent class. Treatment difference between each class is unadjusted.

- Subgroup analyses of virologic outcomes were consistent across various regions
  - North America: DTG+RPV, 91/99 (92%); CAR, 86/93 (92%)
  - Europe: DTG+RPV, 298/314 (95%); CAR, 295/310 (95%)
  - Other regions: DTG+RPV, 97/100 (97%); CAR, 100/108 (93%)

Safety Results

Table 3. Summary of All Adverse Events Reported (>5%) by Baseline ART Third-Agent Class

	NNRTI		PI		INSTI	
n (%)	DTG+RPV (n=275)	CAR (n=278)	DTG+RPV (n=133)	CAR (n=136)	DTG+RPV (n=105)	CAR (n=97)
Any AE	208 (76)	194 (70)	102 (77)	100 (74)	85 (81)	85 (81)
Infections and infestations	118 (43)	120 (43)	59 (44)	67 (49)	46 (44)	47 (48)
Gastrointestinal disorders	66 (24)	37 (13)	33 (25)	27 (20)	30 (29)	18 (19)
Musculoskeletal disorders	42 (15)	46 (17)	22 (17)	23 (17)	14 (13)	13 (13)
Nervous system disorders	45 (16)	22 (8)	15 (11)	15 (11)	17 (16)	5 (5)
Psychiatric disorders	32 (12)	15 (5)	14 (11)	7 (5)	15 (14)	10 (10)
Skin/Subcutaneous tissue disorders	33 (12)	22 (8)	19 (14)	10 (7)	16 (15)	13 (13)
General/Admin. site conditions	20 (7)	20 (7)	19 (14)	20 (15)	10 (10)	11 (11)
Injury, poisoning, and procedural complications	24 (9)	28 (10)	8 (6)	12 (9)	9 (9)	9 (9)
Respiratory, thoracic, and mediastinal disorders	23 (8)	13 (5)	11 (8)	5 (4)	11 (10)	6 (6)
Reproductive system and breast disorders	9 (3)	12 (4)	6 (5)	11 (8)	6 (6)	3 (3)
Benign, malignant, and unspecified neoplasms	8 (3)	7 (3)	5 (4)	3 (2)	5 (5)	7 (7)

- The majority of AEs, regardless of third-agent class, were grade 1 or 2 (NNRTI, 93%; INSTI, 91%; PI, 90%)

Table 4. Frequently Reported Psychiatric Disorder Adverse Events by Baseline ART Third-Agent Class

	NNRTI		PI		INSTI	
n (%)	DTG+RPV (n=275)	CAR (n=278)	DTG+RPV (n=133)	CAR (n=136)	DTG+RPV (n=105)	CAR (n=97)
Insomnia	12 (4)	4 (1)	1 (<1)	2 (1)	4 (4)	4 (4)
Anxiety	5 (2)	7 (3)	4 (3)	0	2 (2)	1 (1)
Depression	4 (1)	2 (<1)	7 (5)	2 (1)	6 (6)	2 (2)

- 2% (n=9) of participants withdrew from the DTG+RPV group because of psychiatric AEs (CAR, <1% [n=1]; Table 5)

Table 5. Summary of AEs Leading to Withdrawal or Permanent Discontinuation of Study Drug by Baseline ART Third-Agent Class

	NNRTI		PI		INSTI	
n (%)	DTG+RPV (n=275)	CAR (n=278)	DTG+RPV (n=133)	CAR (n=136)	DTG+RPV (n=105)	CAR (n=97)
Any AE	8 (3)	1 (<1)	7 (5)	2 (1)	6 (6)	0
Gastrointestinal disorders	2 (<1)	0	3 (2)	0	2 (2)	0
Nervous system disorders	1 (<1)	0	0	0	1 (<1)	0
Psychiatric disorders	4 (1)	1 (<1)	3 (2)	0	2 (2)	0
Neoplasms	0	0	2 (2)	2 (1)	1 (<1)	0
Respiratory/Thoracic/Mediastinal disorders	0	0	1 (<1)	0	1 (<1)	0
Hepatobiliary disorders	1 (<1)	0	0	0	0	0

Discussion

- Switching to DTG+RPV was noninferior to CAR at 48 weeks, and response rate patterns were consistent regardless of third-agent class and across geographic location
- The safety profile of DTG+RPV demonstrated in the SWORD studies was consistent with previous studies
- 92% of psychiatric disorder AEs reported in patients who switched to DTG+RPV were grade 1 or 2
- Rates of psychiatric–related discontinuations were very low in both arms
  - The higher frequency of AEs reported in the DTG+RPV treatment group is likely attributable to introduction of a new regimen in an open-label study, whereas participants in the CAR group were expected to tolerate continuation of their regimen with no additional side effects. Similar observations have been made in previous switch studies[2,3]
- Limitations of the SWORD studies include the open-label design and the subsequent likelihood of introducing bias to both physicians and participants

Conclusion

- Switch to a novel, once-daily 2DR of DTG+RPV in participants with suppressed viral load showed high efficacy and low rates of adverse event–related discontinuation regardless of baseline third-agent class or geographic region, consistent with the overall population results

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