# Assessment of the Acceptability and Swallowability of Darunavir-containing Fixed-dose Combination (FDC) Tablets in Adolescents Living with HIV-1, Using Matched Placebo Tablets

P034

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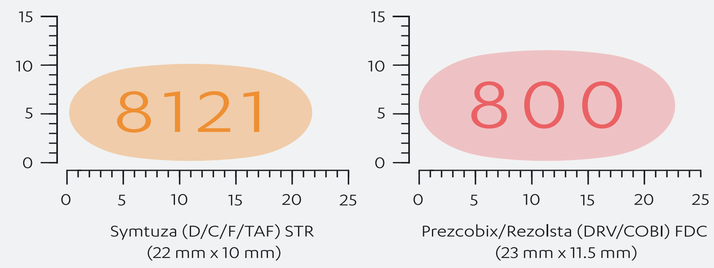
## INTRODUCTION

- Boosted darunavir (DRV, with ritonavir or cobicistat [COBI]) has demonstrated a high, durable virologic response, a high genetic barrier to resistance, and long-term safety in a broad range of patients,[1–8] and is included in international HIV-1 treatment guidelines.[9,10]
- DRV/COBI 800/150 mg once daily, available as a fixed-dose combination (FDC) tablet, combined with other antiretroviral therapy (ART) and the darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) 800/150/200/10 mg single-tablet regimen (STR) are approved in the EU, US and Canada for adults living with HIV-1.
- Two Phase III randomised trials demonstrated that D/C/F/TAF had non-inferior efficacy with no primary PI, DRV or tenofovir resistance and favourable renal and bone safety
  - Versus D/C + F/TDF (Week 48 viral load [VL] <50 copies/mL: 91% vs 88%, respectively[5]; 85% at Week 96 in the D/C/F/TAF arm[6]; FDA Snapshot) in ART-naïve adults (AMBER; NCT02431247)
  - Versus boosted protease inhibitor + F/TDF (confirmed VL ≥50 copies/mL cumulative through Week 48: 2.5% vs 2.1%[7] and 3.1% through Week 96 in the D/C/F/TAF arm[8]; Week 48 VL <50 copies/mL: 95% vs 94%[7] and 91% at Week 96 in the D/C/F/TAF arm[8]; FDA Snapshot) in ART-experienced, virologically suppressed adults (EMERALD; NCT02269917).
- D/C/F/TAF had a high virologic response with 91% patients continuing treatment through 24 weeks and demonstrated high satisfaction scores in the first known Phase III trial of an STR in a rapid initiation model (DIAMOND).[11–12]
- The availability of FDCs for once-daily dosing reduces pill burden, which could potentially improve adherence to ART, an important consideration for adolescents.[13–15]
- Based on data for the individual agents, the respective FDCs with adult doses are also suitable for adolescents, and the D/C/F/TAF STR is currently also approved for adolescents weighing ≥40 kg in some regions.
- The objective of the current study was to assess the acceptability/swallowability of the DRV/COBI FDC tablet and D/C/F/TAF STR (**Figure 1**), each administered as matching placebo tablets, in treatment-experienced adolescents.

**Figure 1. Dimensions (mm) of D/C/F/TAF STR and DRV/COBI FDC tablets.**




The D/C/F/TAF STR is approximately 20% smaller than the DRV/COBI FDC.

## METHODS

### Study Design

- TMC114FD2HTX1003 (NCT02993237): a Phase I, open-label, randomised, single-dose, 2x2 crossover study in adolescents living with HIV-1 aged ≥12–<18 years and weighing ≥40 kg. All participants were virologically suppressed on a stable ART regimen for ≥3 months.
- The study was performed using only matching placebo tablets so as not to interfere with the participant's active ART.
- Written and informed consent was obtained from all participants/legal guardian before any study-related procedure. The study was performed in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki.
- The study consisted of a screening period (including an assessment of willingness and ability to swallow a reference placebo tablet equivalent in size to a PREZISTA 800 mg tablet) and a 1-day open-label administration phase.
- Patients were randomised on Day 1 using randomly permuted blocks and stratified by age category (≥12–<15, ≥15–<18 years) to one of two intake sequences in a 1:1 ratio
  - D/C/F/TAF FDC placebo then DRV/COBI FDC placebo (N=12)
  - DRV/COBI FDC placebo then D/C/F/TAF FDC placebo (N=15).
- On Day 1, patients took one of each FDC placebo tablet in the assigned sequence ≥30 minutes apart.
- The total study duration was maximum 22 days, since screening took place within 21 days prior to the Day 1 visit (or could also be combined with the Day 1 visit).

### Assessments

- Each patient completed a 7-point swallowability questionnaire immediately after intake of each FDC placebo tablet, as well as after the reference placebo tablet and the current ART
  - Ease of swallowability was graded according to the following scale: 1 = very difficult, 2 = moderately difficult; 3 = slightly difficult; 4 = neither difficult nor easy; 5 = slightly easy; 6 = moderately easy; 7 = very easy.
- The acceptability for long-term daily use of the FDC tablets was assessed by a 3-point questionnaire completed by each patient i.e. good to take; acceptable; not acceptable.
- Intake of the tablets was observed by an independent person, and an observer questionnaire was completed to comment on how the tablet was taken and if the patient had problems with each attempt to take the tablet.
- Safety assessments were limited (as only placebo tablets were used) and consisted of recording adverse events on Day 1.

### Data Analyses

- Sample size was calculated based on precision i.e. assuming that if ≥75% of patients determined swallowing to be 'neither difficult nor easy' or better, a sample size of 24–30 patients would provide an estimation of the acceptability proportion for 71–74% confidence level, with a margin of error of 5% (1-sided).
- The primary parameter was the acceptability proportion, obtained by a dichotomisation of the data from the 7-point questionnaire, i.e. *Easy* = very easy + moderately easy + slightly easy + neither difficult nor easy; *Difficult* = slightly difficult + moderately difficult + very difficult, and the corresponding 95% confidence interval, using the Clopper-Pearson exact confidence interval for binomial proportion.

## RESULTS

### Patient Demographics and Baseline Characteristics

- 28 patients were screened and one patient failed screening (because of intake of a disallowed drug, diphenhydramine, which causes dry mouth [xerostomia] and so may interfere with swallowing). There were no screening failures related to non-willingness or inability to swallow the reference tablet.
- All 27 patients completed the study as planned.
- Baseline characteristics are shown in **Table 1**.
- All patients received ≥1 FDC in their current ART regimen, most commonly
  - Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate: 12 (44%) patients
  - Rilpivirine/emtricitabine/tenofovir disoproxil fumarate, dolutegravir/abacavir/lamivudine and abacavir/lamivudine: 4 (15%) patients each.

**Table 1. Baseline characteristics.**

| Parameter | Overall N=27 |
|---|---|
| Median (range) age, years | 14 (12–17) |
| Age at screening, n (%) | |
| ≥12–<15 years | 14 (52) |
| ≥15–<18 years | 13 (48) |
| Sex, n (%) | |
| Male | 14 (52) |
| Female | 13 (48) |
| Median (range) body mass index, kg/m² | 21.1 (15.3–50.7) |
| Race, n (%) | |
| Black or African American | 17 (63) |
| White | 9 (33) |
| Black or African American + White | 1 (4) |
| Ethnicity, n (%) | |
| Not Hispanic or Latino | 23 (85) |
| Hispanic or Latino | 4 (15) |
| Current ART, n (%) | |
| FDC | 21 (78) |
| FDC and single ARV tablets | 6 (22) |

### Swallowability and Acceptability Assessments

- Intake was successful in all cases. All the DRV/COBI and D/C/F/TAF FDC placebo tablets were ingested at first attempt by all the patients, and there were no second attempts needed. The tablets were taken with either water (89%), semi-solid food (4%) or another personally preferred method (7%) (**Table 2**).

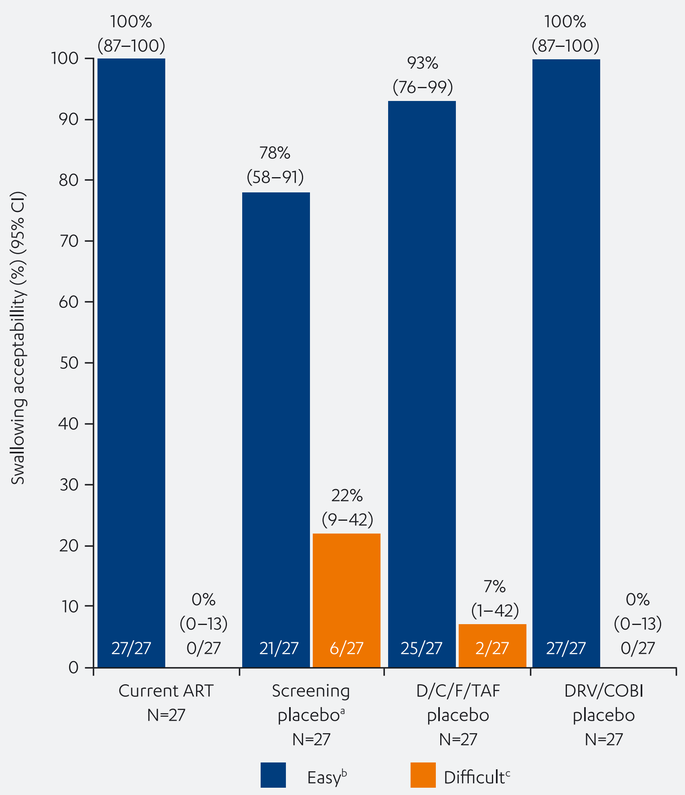
**Table 2. Intake Data (Based on Observer Questionnaire Outcomes).**

| Parameter, n (%) | D/C/F/TAF placebo (N=27) | DRV/COBI placebo (N=27) |
|---|---|---|
| How was the tablet taken? | | |
| Swallowed with water | 24 (89) | 24 (89) |
| Mixed with semi-solid food followed by water | 1 (4) | 1 (4) |
| Other personally preferred method | 2 (7) | 2 (7) |
| Attempt 1 | | |
| Did the patient have problems taking the tablet? | | |
| No | 27 (100) | 27 (100) |
| Yes | 0 | 0 |
| Spit it out | 0 | 0 |
| Multiple swallows* | 0 | 0 |

*Swallowed multiple times, cleared throat, swallowed multiple times after taking the tablet and asked for more water, to help the tablet move along the gastrointestinal tract

- When the responses to the seven swallowability questions were dichotomised, the FDC tablets were noted to be 'easy to swallow' by 25 patients (93%) for the D/C/F/TAF FDC placebo tablet, and all patients for the DRV/COBI FDC placebo tablet (**Figure 2**).

**Figure 2. Swallowing Acceptability of the Four Different Tablets - Dichotomisation.**




[a]Equivalent in size to a PREZISTA 800 mg tablet; [b]Easy = 'Very easy' + 'Moderately easy' + 'Slightly easy' + 'Neither difficult nor easy'; [c]Difficult = 'Slightly difficult' + 'Moderately difficult' + 'Very difficult'
95% CI: Clopper-Pearson exact confidence interval for binomial proportion

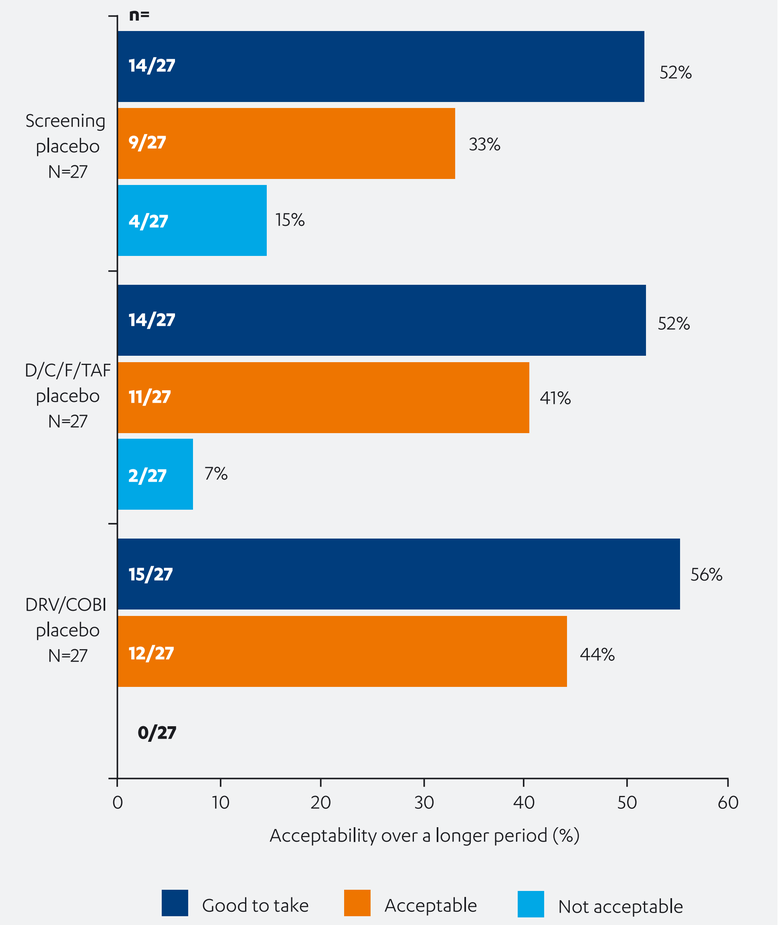
- Answers to the individual questions are shown in **Table 3**. Most patients rated the D/C/F/TAF placebo (63%) and the DRV/COBI placebo (59%) FDC tablets as 'very easy' to swallow.
- There were no relevant differences by age group (≥12–<15, ≥15–<18 years) in the administration of the D/C/F/TAF placebo and DRV/COBI placebo FDC tablets (data not shown).

**Table 3. Swallowability Questionnaire Outcomes.**

| Parameter | Current ART (N=27) | Screening placebo (N=27) | D/C/F/TAF placebo (N=27) | DRV/COBI placebo (N=27) |
|---|---|---|---|---|
| How difficult/easy to swallow tablet, n (%; cumulative %) | | | | |
| Very easy | 18 (67; 67) | 12 (44; 44) | 17 (63; 63) | 16 (59; 59) |
| Moderately easy | 5 (18; 85) | 6 (22; 67) | 3 (11; 74) | 4 (15; 74) |
| Slightly easy | 2 (7; 93) | 2 (7; 74) | 4 (15; 89) | 5 (19; 93) |
| Neither difficult nor easy | 2 (7; 100) | 1 (4; 78) | 1 (4; 93) | 2 (7; 100) |
| Slightly difficult | 0 | 4 (15; 93) | 1 (4; 96) | 0 |
| Moderately difficult | 0 | 0 | 0 | 0 |
| Very difficult | 0 | 2 (7; 100) | 1 (4;100) | 0 |

- Almost all patients considered each tablet to be at least acceptable (acceptable or good to take) for use over a longer period of time: 25/27 (93%; D/C/F/TAF placebo) and 100% (DRV/COBI placebo) (**Figure 3**).

**Figure 3. Acceptability if the Tablets were to be Taken Once Daily Over a Longer Period.**




### Safety

- No adverse events were reported during this study.

## CONCLUSION

- Both the D/C/F/TAF and the DRV/COBI FDC tablets are suitable to be administered to adolescents. Both tablets were considered to be acceptable to swallow and acceptable for use over a longer period of time by almost all of the adolescent patients participating in this study.

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