LBPE15

Subgroup analysis and predictors of virological response in treatment-experienced, HIV-1-infected patients in the ODIN trial

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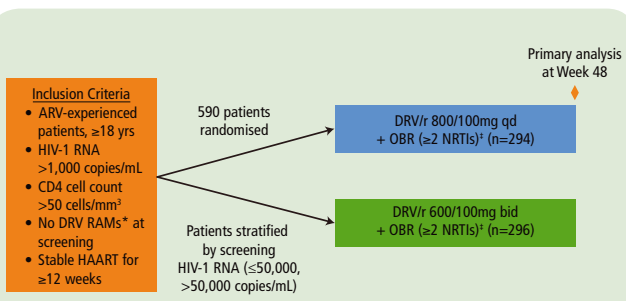
Introduction

- The protease inhibitor (PI) darunavir (DRV) with low-dose ritonavir (DRV/r) at a dose of 800/100mg qd in combination with other antiretrovirals (ARVs) is approved for the treatment of ARV-naïve, HIV-1-infected adults in the USA,[1] Europe[2] and other countries
  - DRV/r is approved for the treatment of ARV-experienced, HIV-1-infected patients at a dose of 600/100mg bid.[1,2]
- In the Phase III, randomised, open-label ODIN trial (TMC114-C229: **O**nce-daily **D**arunavir **I**n treatment-experie**N**ced patients), the efficacy, safety and tolerability of once-daily DRV/r 800/100mg was compared with twice-daily DRV/r 600/100mg both with an optimised background regimen (OBR) in treatment-experienced, HIV-1-infected adults with no DRV resistance-associated mutations (RAMs)[3] at screening.
- In ODIN, the primary objective of non-inferiority in virological response of once-daily to twice-daily DRV/r was established at Week 48
  - response rates (HIV-1 RNA <50 copies/mL) were 72.1% in once-daily vs 70.9% in twice-daily arms (intent-to-treat/time-to-loss of virological response [ITT-TLOVR]; difference in response = 1.2%; 95% confidence interval [CI]: −6.1 to 8.5%; p<0.001).[4]
- This analysis reports Week 48 virological response rates of once- versus twice-daily DRV/r by subgroups and also evaluates which subgroup factors were the strongest predictors of virological response in ODIN.

Methods

Study design

- ODIN was a Phase III, randomised, open-label study (Figure 1).



*DRV RAMs include the following mutations: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V and L89V[3]; ‡Investigator-selected OBR based on ARV history and resistance testing, HAART=highly active ARV therapy

Figure 1. ODIN study design.

- Primary objective of ODIN: to assess non-inferiority of DRV/r 800/100mg qd to DRV/r 600/100mg bid in virological response (HIV-1 RNA <50 copies/mL, ITT-TLOVR) over 48 weeks, with a predetermined non-inferiority margin (delta) of 12%.
- The study protocol was reviewed and approved by the appropriate review boards or institutional ethics committees and health authorities, and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all study participants.

Efficacy assessments

- Efficacy in terms of virological response (HIV-1 RNA <50 copies/mL, ITT-TLOVR) was assessed at each visit (Weeks 4, 8, 12, 24, 36 and 48 or withdrawal).
- In the present analysis, virological response was assessed at Week 48 according to stratification factor (screening HIV-1 RNA ≤ or >50,000 copies/mL), baseline CD4 cell count, presence of International AIDS Society-USA (IAS-USA)[5] primary (major) PI mutations, PI RAMs or M184V/I mutation at baseline, number of previously used PIs, number of active NRTIs in the OBR, and adherence
  - adherence was assessed by the Modified Medication Adherence Self-Report Inventory (M-MASRI) questionnaire, where mean adherence was converted to a binary variable to determine adherence (>95%) or suboptimal adherence (≤95%).
- Two-sided 95% CIs were derived for the difference in virological response at Week 48 between treatment arms.

Multiple logistic regression analysis

- A multiple logistic regression analysis was conducted to investigate factors predictive of virological response by means of a backward elimination procedure. A p value of greater than 0.05 was used to select variables for removal from the model.
- Regardless of level of statistical significance, treatment arm (DRV/r 800/100mg qd or DRV/r 600/100mg bid) was kept in the model for all analyses.
- The following candidate predictors were examined
  - baseline CD4 cell count
  - baseline $\log_{10}$ plasma HIV-1 RNA
  - number of IAS-USA[5] primary (major) PI mutations at baseline (0, 1 or ≥2)
  - number of IAS-USA[5] PI RAMs at baseline (0, 1 or ≥2)
  - presence of NRTI (FTC/3TC) RAM M184V/I[3] at baseline (present or absent)
    - M184V/I was included as a candidate predictor as it is the most prevalent NRTI mutation (harboured by 66.1% of ODIN patients at [pre] baseline) and also based on findings from King, et al[6]
  - adherence (based on M-MASRI; adherent or suboptimally adherent)
  - number of sensitive NRTIs in the OBR (0, 1 or ≥2)
  - number of previously used PIs (0, 1 or ≥2).
- Associations between candidate predictors of virological response were examined using contingency table analysis (Chi square tests).

Results

Patient disposition and baseline characteristics

- A total of 590 treatment-experienced patients were randomised and treated with once-daily DRV/r 800/100mg (n=294) or twice-daily DRV/r 600/100mg (n=296).
- Baseline demographics and disease characteristics were generally well balanced between treatment arms (Table 1).
- Overall, 15.1% of patients prematurely discontinued the trial: 13.9% in the once-daily DRV/r arm and 16.2% in the twice-daily DRV/r arm
  - the two most common reasons for discontinuation were: adverse events (3.4% in the once-daily and 4.1% in the twice-daily arm) and lost to follow-up (3.1% once-daily and 4.4% twice-daily).

Virological responses in once-daily and twice-daily arms by screening HIV-1 RNA (stratification factor) and baseline CD4 cell count

- Virological responses were similar in the once- and twice-daily DRV/r arms both for patients with HIV-1 RNA ≤50,000 and >50,000 copies/mL (Figure 2)
  - overall a numerically higher response rate was observed in patients who had lower baseline HIV-1 RNA counts, regardless of treatment arm.
- Across the three CD4 cell count subgroups examined, virological responses were similar between the once- and twice-daily DRV/r arms (Figure 3)
  - overall, virological response rates improved with increasing CD4 cell count, regardless of treatment arm.

Table 1. Baseline demographics and disease characteristics.

	Once-daily DRV/r 800/100mg (n=294)	Twice-daily DRV/r 600/100mg (n=296)
Baseline demographics		
Female, n (%)	115 (39.1)	98 (33.1)
Mean age, years (SE)	40.2 (0.53)	40.7 (0.55)
Race, n (%)		
Caucasian	102 (34.7)	110 (37.2)
Black	83 (28.2)	72 (24.3)
Hispanic	47 (16.0)	59 (19.9)
Asian	48 (16.3)	41 (13.9)
Other	14 (4.8)	14 (4.7)
Baseline disease characteristics		
Mean $\log_{10}$ HIV-1 RNA (SE)	4.19 (0.05)	4.13 (0.05)
Median CD4 cells/mm³ (range)	219 (24–1,306)	236 (44–864)
Stratification factor at screening		
HIV-1 RNA ≤50,000 copies/mL, n (%)	222 (75.5)	224 (75.7)
Previous ARV experience, n (%)		
PIs: 0	135 (45.9)	137 (46.3)
PIs: 1	74 (25.2)	77 (26.0)
PIs: ≥2	85 (28.9)	82 (27.7)
NRTIs: ≥3	174 (59.1)	164 (55.4)
NNRTIs: ≥1	258 (87.8)	258 (87.2)
Median (range) DRV fold-change at baseline	**0.5 (0.1–1.8)**	**0.5 (0.1–1.9)**
Sensitivity to eight PIs* at baseline	**248 (85.2)**	**247 (86.1)**
Optimised background therapy, n (%)		
Number of active‡ NRTIs used[§]		
0	19 (6.6)	15 (5.3)
1	53 (18.3)	75 (26.4)
≥2	218 (75.2)	194 (68.3)
Median (range) IAS-USA mutations at baseline[5]		
PI RAMs	3 (0–13)	4 (0–14)
Primary (major) PI mutations	0 (0–5)	0 (0–4)
NRTI RAMs	1 (0–7)	1 (0–8)
NNRTI RAMs	2 (0–5)	1 (0–5)

*All eight currently available PIs, excluding ritonavir: (fos)amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, saquinavir, tipranavir and DRV; †Phenotypes were determined by Antivirogram®; §Data available for 290 patients in the once-daily DRV/r arm and 284 in the twice-daily DRV/r arm; An ARV was considered susceptible if the fold-change was below or equal to the clinical or biological cut-off; SE = standard error

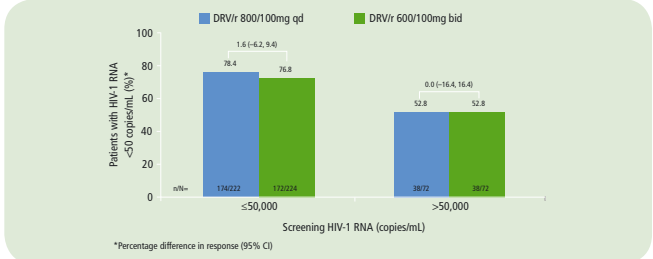


Figure 2. Virological response rates at Week 48 by stratification factor (screening HIV-1 RNA).

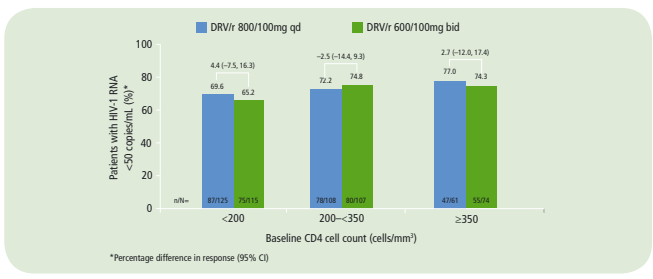


Figure 3. Virological response rates by baseline CD4 cell count.

Virological responses in once-daily and twice-daily arms by baseline mutations

- Response rates in the once- and twice-daily DRV/r arms are shown according to number of IAS-USA[5] primary PI mutations at baseline (Figure 4), number of IAS-USA[5] PI RAMs at baseline (Figure 5) and the presence or absence of M184V/I mutation at baseline (Figure 6).
- Response rates were similar across treatment arms for patients with 0 or ≥1 primary PI mutations at baseline
  - for those patients with 1 or ≥2 baseline primary PI mutations, subgroups were too small to make any conclusions regarding a difference between the groups.
- Similar response rates were observed with both once- and twice-daily DRV/r across all three subgroups of IAS-USA[5] PI RAMs.
- A numerically higher response rate was observed in patients who had the M184V/I mutation detected at baseline than those who did not, irrespective of whether they received once- or twice-daily DRV/r (Figure 6).

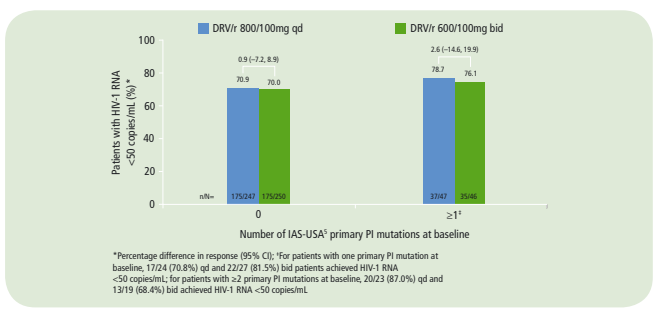


Figure 4. Virological response rates at Week 48 by number of IAS-USA[5] primary PI mutations at baseline.

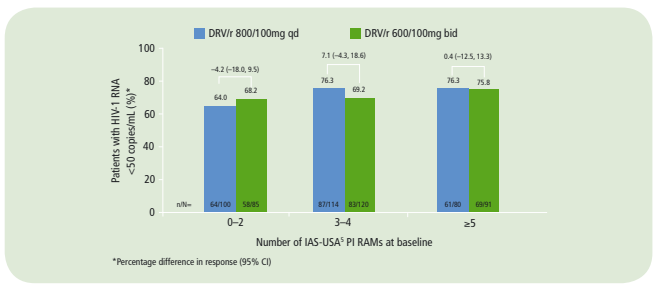


Figure 5. Impact of number of IAS-USA[5] PI RAMs at baseline on virological response rates at Week 48.

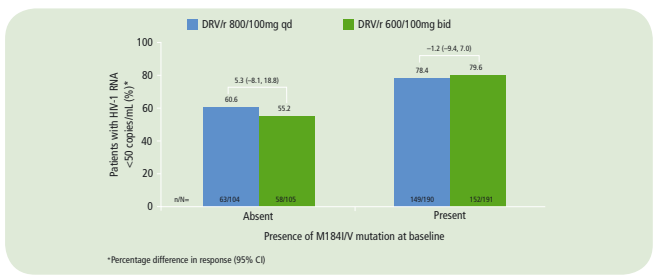


Figure 6. Virological response rates at Week 48 by presence of M184V/I mutation at baseline.

Virological responses in once-daily and twice-daily arms by prior PI experience and number of active NRTIs in the OBR

- No relevant differences in response were observed between once- and twice-daily DRV/r arms by number of PIs previously used or number of active NRTIs in the OBR
  - however, a trend towards lower response rates was observed in patients who had previously used ≥1 PI (Figure 7); this was not accounted for by baseline PI resistance.
- While response rates were unexpectedly highest in patients with no active NRTIs in the OBR than for those with 1 or ≥2 active NRTIs in the OBR, the sample size was small, making meaningful interpretation difficult (Figure 8).

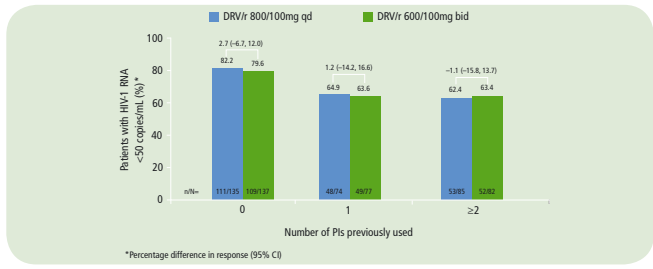


Figure 7. Virological response rates at Week 48 by previous use of PIs.

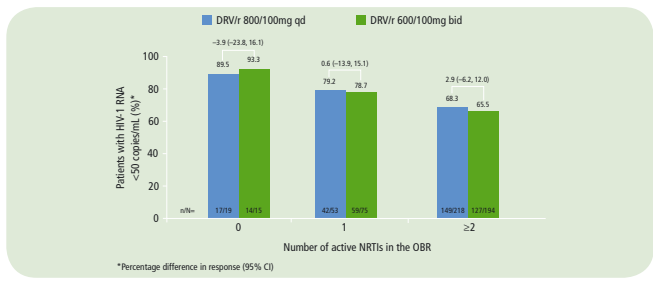


Figure 8. Virological response rates at Week 48 by number of active NRTIs in the OBR.

Influence of adherence on virological response

- Similar response rates were observed with both once- and twice-daily DRV/r arms for patients who were adherent, though there were small differences between arms for patients who were suboptimally adherent based on the M-MASRI questionnaire (Figure 9)
  - overall, patients who were adherent had higher virological response rates than those who were suboptimally adherent
  - for more details on the effect of adherence, please see poster TUPE0184.[7]

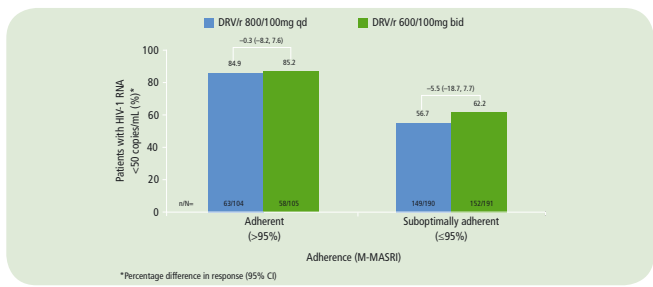


Figure 9. Impact of adherence (M-MASRI) on virological response at Week 48.

Factors predictive of virological response

- Since the above analyses provided some unexpected associations between subgroups and virological response, a multivariate analysis was performed to evaluate predictors of virological response. The analysis revealed that the following had no significant effect on virological response (p>0.05)
  - baseline CD4 cell count
  - number of prior PIs
  - number of active NRTIs in the OBR
  - the presence of IAS-USA[5] primary PI mutations at baseline
  - the presence of IAS-USA[5] PI RAMs at baseline.
- Significant predictors of response in the model were
  - baseline HIV-1 RNA $\log_{10}$ copies/mL (p=0.0014)
  - adherence as measured by the M-MASRI questionnaire (p<0.0001)
  - presence of mutation M184V/I at baseline (p<0.0001).
- The association between virological response and a) previous PI use and b) number of active NRTIs in the OBR appears to be driven by the presence of M184V/I mutation at baseline
  - the presence of the M184V/I mutation was a marker for fewer active NRTIs in the OBR (p<0.0001), and a lower number of previously used PIs (p<0.0001).

Conclusions

- Once-daily DRV/r 800/100mg was non-inferior in virological response (HIV-1 RNA <50 copies/mL) to twice-daily DRV/r 600/100mg at 48 weeks in ODIN.
- No meaningful differences in virological responses were observed between once- and twice-daily DRV/r arms across various subgroups at Week 48
  - as the trial was not designed for treatment comparisons in subgroups and numbers were small in some subgroups, these exploratory findings should be interpreted with caution.
- In a multiple logistic regression model, baseline HIV-1 RNA, adherence as measured by the M-MASRI questionnaire and the presence of M184V/I at baseline were significantly associated with virological response.
- Overall, these results suggest that once-daily DRV/r 800/100mg is a suitable treatment option in treatment-experienced patients with no DRV RAMs, regardless of baseline characteristics.

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XVIII International AIDS Conference, Vienna, Austria, 18–23 July 2010.
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