Address correspondence to: Avy Violari, MD, Chris Hani Baragwanath Hospital, Johannesburg, South Africa;
E-mail: violari@mweb.co.za

ARIEL: 24-week safety and efficacy of darunavir/ritonavir in treatment-experienced pediatric patients aged 3 to <6 years

Avy Violari,[1] Rosa Bologna,[2] Robert Kimutai,[3] Nagalingeswaran Kumarasamy,[4] Jose Henrique Pilotto,[5] Annemie Hendrickx,[6] Greet Kauwenberghs,[6] Erkki Lathouwers,[6] Tom Van de Casteele,[6] Sabrina Spinosa-Guzman[6]

[1]Chris Hani Baragwanath Hospital, Johannesburg, South Africa; [2]Helios Salud, Buenos Aires, Argentina; [3]KEMRI Wellcome Trust Research Programme, Kilifi, Kenya; [4]YRGCARE Medical Centre, VHS, Chennai, India; [5]Hospital Geral De Nova Iguacu, Rio de Janeiro, Brazil; [6]Tibotec BVBA, Beerse, Belgium

Introduction

- The protease inhibitor (PI) darunavir (DRV) in combination with low-dose ritonavir (DRV/r) is approved for the treatment of HIV-1-infected adults and treatment-experienced pediatric patients aged 6 to <18 years in the USA,[1] Europe[2] and other countries.
- The safety and efficacy of DRV/r was assessed in treatment-experienced pediatric patients aged 6 to <18 years weighing 20 to <50kg in the DELPHI trial (TMC114-C212; **D**arunavir **EvaL**uation in **P**ediatric **HI**V-1-**I**nfected treatment-experienced patients).[3] Over 24 weeks of treatment
  - DRV (375–600mg twice daily [bid]) plus ritonavir (50–100mg bid) (weight-based dose) demonstrated favorable safety and tolerability in this patient population
  - sixty-four percent of patients achieved HIV-1 RNA <400 copies/mL, and 50% achieved HIV-1 RNA <50 copies/mL (intent-to-treat/time-to-loss of virologic response [ITT-TLOVR] algorithm).
- ARIEL (TMC114-C228; d**A**runavir in t**R**eatment exper**I**enced p**E**diatric popu**L**ation) is a 48-week, open-label, single-arm, Phase II trial assessing DRV/r plus an optimized background regimen (OBR) in HIV-1-infected, treatment-experienced children aged 3 to <6 years weighing 10 to <20kg
  - the primary objectives of the trial were to assess the pharmacokinetics and short-term safety and efficacy of DRV/r with ≥2 active NRTIs to support dose recommendations of DRV/r by bodyweight.
- In this poster, 24-week safety and efficacy outcomes from ARIEL are reported.

Methods

Study design

- Patients were HIV-1-infected children aged 3 to <6 years who had been on highly active antiretroviral therapy for at least 12 weeks.
- Inclusion criteria are shown in Figure 1.

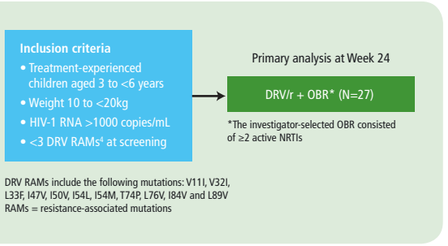

Figure 1. Study design.

- The initial dose was DRV 20mg/kg plus ritonavir 2.6–3.2mg/kg bid
  - DRV was given as a high concentrate oral suspension (100mg/mL).
- After the Week 2 pharmacokinetic analysis, DRV dose was amended to 25mg/kg bid for patients weighing 10 to <15kg and 375mg bid fixed for patients weighing 15 to <20kg (following Data Safety Monitoring Board [DSMB] recommendations)
  - this would reduce any potential risk of underdosing for children weighing 10 to <15kg, ensure continuous change in exposure for children weighing 15 to <20kg, and have the added advantage of facilitating the change from oral suspension to tablet formulation
  - the ritonavir dose remained unchanged for the lower weight group and was changed to 50mg fixed for the upper weight group.
- The study protocol was reviewed and approved by independent ethics committees and appropriate health authorities, and was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All parents or legally appointed representatives gave written informed consent and children were informed about the trial.

Safety and efficacy assessments

- Safety and efficacy were evaluated at baseline and Weeks 2, 4, 8, 16, 24, 32, 40 and 48.
- Safety was assessed using an ITT analysis, which included all patients who took at least one dose of study medication, regardless of compliance with protocol
  - the incidence and severity of adverse events (AEs) and laboratory abnormalities were recorded and causality assessed by the investigator.
- Growth parameters (height, weight and body mass index [BMI]) were recorded.
- Efficacy was assessed using the ITT-TLOVR algorithm
  - the primary efficacy endpoint was the proportion of patients achieving HIV-1 RNA <50 copies/mL (ITT-TLOVR) at Week 24.
- Changes in CD4 cell count and percentage from baseline to Week 24 were determined; missing values were imputed as a change of 0 (using the non-completer=failure [NC=F] analysis).

Resistance determinations

- Virologic failure (VF) was defined as patients who lost (rebounders) or never achieved (never suppressed) HIV-1 RNA <50 copies/mL using a TLOVR non-VF censored analysis, in which responses after discontinuation were not imputed for patients who discontinued for reasons other than VF.
- Standard genotypes and phenotypes were determined on samples with HIV-1 RNA ≥1000 copies/mL by means of Virco® TYPE HIV-1 and Antivirogram®, respectively, at screening, baseline, Weeks 24 and 48, or early withdrawal (before Week 48)
  - where possible, additional resistance determinations were performed on samples from VFs with HIV-1 RNA ≥50 copies/mL.

Results

Patient disposition and baseline characteristics

- Of 42 patients screened, 27 were enrolled and treated with DRV/r plus an OBR.
- The OBR consisted of only NRTIs; 25 (92.6%) patients used two NRTIs and two (7.4%) patients used three NRTIs
  - the most commonly used NRTIs were abacavir (52%), lamivudine (52%) and zidovudine (52%).
- One (3.7%) patient discontinued treatment (due to an AE).
- Baseline demographics and disease characteristics are shown in Table 1.

Safety

- Twenty-three (85.2%) patients experienced ≥1 AE (Table 2).
- The most commonly reported AEs are presented in Figure 2.
- Five (18.5%) patients had a grade 3 or 4 AE
  - these included: neutropenia (n=1), pneumonia (n=1), acidosis (n=2), alkalosis (n=2), hypokalemia (n=1), hyponatremia (n=1), trigger finger (n=1), asthmatic crisis (n=1) and neurodermatitis (n=1)
  - of these, only trigger finger was grade 4 in severity
  - it should be noted that acidosis and alkalosis were assessed through venous sampling; results from these tests are considered less reliable than through arterial sampling.
- Three (11.1%) patients had a serious AE (SAE) (pneumonia, trigger finger and asthmatic crisis; each occurred in one patient).
- One patient discontinued treatment due to an AE (grade 2 vomiting), which was considered related to ritonavir treatment.
- No deaths occurred during the treatment period.

Treatment-related AEs

- The most frequently reported AE considered at least possibly related to treatment was diarrhea, reported in two patients
  - treatment-related AEs were: increased blood cholesterol, papular rash, increased aspartate aminotransferase (AST), pustular rash and prolonged electrocardiogram QT (value uncorrected); each occurred in one patient.
- Two (7.4%) patients experienced a grade 2 AE considered at least possibly related to treatment (increased AST and increased blood cholesterol, each in one patient)
  - no grade 3 or 4 AEs or SAEs were considered to be treatment related.

Table 1. Baseline demographics and disease characteristics.

	N=27
Demographics	
Male, n (%)	15 (55.6)
Mean age, years	4.6
Race, n (%)	
White	6 (22.2)
Black or African-American	18 (66.7)
Asian	1 (3.7)
Multiple	2 (7.4)
Ethnicity, n (%)	
Hispanic or Latino	10 (37.0)
Not Hispanic or Latino	17 (63.0)
Growth and development parameters, mean (SE)	
Height, cm	101.2 (1.43)
Age-adjusted z-score	–1.4 (0.20)
Weight, kg	15.3 (0.40)
Age-adjusted z-score	–1.1 (0.18)
BMI, kg/m^2	14.9 (0.29)
Age-adjusted z-score	–0.4 (0.24)
Disease characteristics	
Mean baseline $\log_{10}$ HIV-1 RNA, copies/mL	4.43
Median CD4 cell count, cells/mm^3	927
Median CD4 percentage	27.7
Median (range) number of baseline IAS-USA[4] mutations	
Primary PI mutations	0 (0–3)
PI RAMs	4 (1–13)
DRV RAMs	0 (0–2)
NRTI RAMs*	1 (0–5)
NNRTI RAMs	1 (0–4)
Median (range) fold-change in EC_{50} for DRV	0.5 (0.2–2.3)

*Twenty-two patients harbored the M184V mutation; SE = standard error; IAS-USA = International AIDS Society-USA; EC_{50} = 50% effective concentration

Table 2. Frequency of AEs, n (%).

	N=27
Mean exposure, weeks	**30.5**
≥1 AE	23 (85.2)
≥1 AE at least possibly related to treatment	5 (18.5)
≥1 AE leading to permanent discontinuation	1 (3.7)
≥1 grade 3 or 4 AE	5 (18.5)
≥1 grade 3 or 4 AE at least possibly related to treatment	0
≥1 SAE	3 (11.1)
≥1 SAE at least possibly related to treatment	0

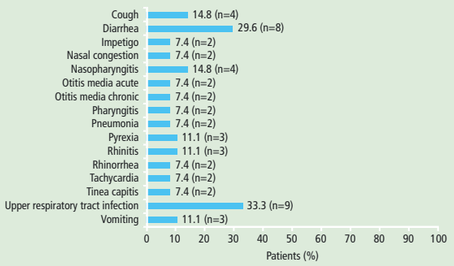

Figure 2. Most commonly reported AEs (occurring in ≥2 patients, regardless of severity or causality, excluding laboratory abnormalities reported as AEs).

Laboratory safety

- There were no clinically relevant mean changes from baseline for any laboratory parameter.
- All laboratory abnormalities were grade 1 or 2 in severity, with the exception of grade 3 neutropenia reported by one patient
  - this abnormality had been present since baseline and was not considered treatment related.

Growth parameters

- Mean changes from baseline to Week 24 showed small increases in height (2.6cm) and weight (0.8kg); there was no mean change in BMI.
- Mean age-adjusted z-scores at baseline showed that patients were below normal population values with respect to height, weight and BMI
  - small changes in mean values for all parameters were seen at Week 24; none were statistically significant.

Efficacy

- Response rates increased steadily from Week 2 to Week 24 (Figure 3)
  - at Week 24, 55.6% of patients achieved the primary efficacy endpoint of HIV-1 RNA <50 copies/mL (ITT-TLOVR)
  - the percentage of patients achieving HIV-1 RNA <50 copies/mL was similar (59.3%) when applying the Food and Drug Administration (FDA) Snapshot algorithm (Figure 4).
- Virologic response rates for secondary efficacy endpoints (HIV-1 RNA <400 copies/mL and ≥1 $\log_{10}$ reduction in HIV-1 RNA from baseline) are shown in Figure 4.

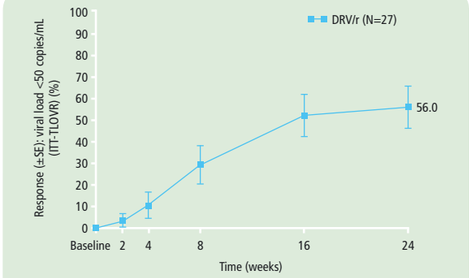

Figure 3. Proportion of patients achieving HIV-1 RNA <50 copies/mL over 24 weeks of treatment (ITT-TLOVR).

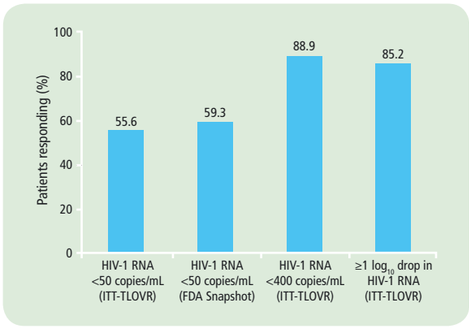

Figure 4. Proportion of patients achieving virologic response at Week 24.

- The mean increase in CD4 cell count from baseline to Week 24 was 109 cells/mm^3.
- Over 24 weeks, mean CD4 cell count percentage increased by 3.8% (Figure 5).

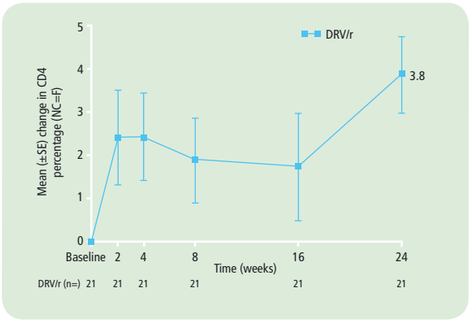

Figure 5. Mean change in CD4 cell count percentage from baseline to Week 24 (NC=F).

Resistance

- Two patients had DRV RAMs detected at baseline (L33F + L76V [n=1] and L76V [n=1])
  - both patients were virologically suppressed (HIV-1 RNA <50 copies/mL) at Week 24.
- Eleven (40.7%) patients were considered VFs at Week 24
  - all 11 patients were non-responders; eight of these 11 patients had achieved an unconfirmed HIV-1 RNA <50 copies/mL
  - no patients were rebounders.
- None of the six patients with paired baseline/endpoint genotypes (Week 24 samples) developed IAS-USA[4] PI or NRTI RAMs.
- All six patients with paired baseline/endpoint phenotypes (Week 24 samples) remained susceptible to all PIs and NRTIs in the OBR post baseline.

Conclusions

- Over 24 weeks of treatment, DRV/r and an OBR was effective and well tolerated in HIV-1-infected, treatment-experienced patients aged 3 to <6 years.
- No new safety concerns were reported compared with the known safety profile of DRV/r.
- No development of resistance (development of RAMs or loss of susceptibility to PIs or NRTIs in the OBR) was observed in VFs.
- These findings support the use of DRV/r and an OBR in treatment-experienced, HIV-1-infected patients aged 3 to <6 years at the following doses
  - DRV/r 25/3mg/kg bid for patients weighing 10 to <15kg
  - DRV/r 375/50mg bid for patients weighing 15 to <20kg.

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