PREZISTA® (darunavir)
Use of PREZISTA in Pediatric and Adolescent Patients

SUMMARY

- The DIONE (TMC114-C230) study was a phase 2, open-label, 48-week trial assessing the efficacy, safety, tolerability, and pharmacokinetics (PK) of PREZISTA/ritonavir (r) 800/100 mg once daily (QD) plus zidovudine (AZT)/lamivudine (3TC) or abacavir (ABC)/3TC in 12 treatment-naïve, HIV-1-infected adolescents aged 12 to <18 years.[1]
  - At week 48, 83.3% (intent-to-treat population, time-to-loss of virologic response [ITT-TLOVR]) and 92% (FDA snapshot) of patients had achieved viral load (VL) <50 copies/mL.
- The ARIEL study (TMC114-C228) assessed the short-term safety and efficacy of PREZISTA/r plus an optimized background regimen (OBR) in HIV-1 infected, treatment-experienced children aged 3 to <6 years (N=21).[2]
  - At week 48, 81% (ITT-TLOVR) and 71.4% (FDA snapshot) of patients achieved VL <50 copies/mL, while the mean CD4+ cell count increased by 187 cells/mm.
- The DELPHI study (TMC114-C212) evaluated the efficacy, safety, and tolerability of PREZISTA/r plus an OBR in treatment-experienced, HIV-1-infected children aged 6-17 years.[3]
  - Virologic response to PREZISTA at week 48 was reduced in those patients with ≥3 darunavir (DRV) resistance-associated mutations (RAMs) at baseline.
  - At week 48, the proportion of patients that achieved VL <50 copies/mL and <400 copies/mL was 48% and 59%, respectively.
- The DIANA study (TMC114-TiDP29-C232) was an open-label, single arm study that evaluated long-term safety in patients receiving continued access to PREZISTA/r plus an OBR in patients aged 3 to <18 years who participated in the DELPHI, DIONE, or ARIEL studies.[4]
  - The overall median duration of PREZISTA/r intake was 4.2 years (0.1 – 7.1), with majority of patients aged ≥12 to <18 (54%, 25/46).
  - The most common AEs, any grade in ≥2 patients, were pneumonia (7%, 3/46), asthma (4%, 2/46), gastroenteritis (4%, 2/46), and lipoatrophy (4%, 2/46).
  - No deaths were reported and none of the serious adverse events (SAEs) were considered related to PREZISTA/r treatment or led to study discontinuation.

CLINICAL STUDIES

TREATMENT-NAIVE PEDIATRIC PATIENTS

DIONE Study

The DIONE Study (TMC114-C230) was a phase 2, open-label, 48-week trial assessing the efficacy, safety, tolerability, and PK of PREZISTA/r 800/100 mg QD plus AZT/3TC or ABC/3TC in treatment-naïve, HIV-1-infected adolescents aged 12 to <18 years.[1]

Study Design/Methods

- Treatment-naïve adolescents weighing ≥40 kg with VL levels ≥1,000 copies/mL were admitted to the study.
- Primary efficacy parameter: proportion of patients with VL <50 copies/ml at week 24 (IIT-TLOVR).
- Secondary outcome measures included VL <50 copies/mL at week 48 (ITT-TLOVR, noncompleter=failure [NC=F]), virologic response at weeks 24 and 48 via FDA snapshot analysis, VL <400 copies/mL, ≥1 $\log_{10}$ decrease in VL compared to baseline (NC=F), and change in CD4+ count.

- Phenotypic and genotypic analyses were performed at baseline, week 24, week 48, or at time of study withdrawal for samples with VL ≥1000 copies/ML.
- DRV PK concentrations were determined using rich sampling (6 samples) over a 24-hour period after 2 weeks and sparse sampling (2 samples) after 4, 24, and 48 weeks of treatment.
- Safety was evaluated in the ITT population.

Results

Patient Characteristics

- All 12 patients enrolled in the study completed 48 weeks of treatment (median age [range]: 14.4 years [12.6 - 17.3]; 67% female; 58% Caucasian).
  - PREZISTA /r plus AZT/3TC (n=6)
  - PREZISTA/r plus ABC/3TC (n=6)
- Mean (SE) baseline VL was 4.72 (0.172) copies/mL; median CD4+ cell count was 282 cells/mm^3 (range 204-515).

Efficacy

- In the primary analysis at week 24, 11/12 (92%) patients achieved VL <50 copies/mL (ITT-TLOVR).
- At week 48, 10/12 patients (83%; ITT-TLOVR) and 11/12 (92%; FDA snapshot) had VL <50 copies/mL.
- Eleven patients (ITT-TLOVR) had VL <400 copies/mL at week 48.
- All 12 patients achieved ≥1 log_{10} decrease in VL by week 24, which was maintained at week 48.
- Mean CD4+ count increased by 221 cells/mm^3 from baseline.

Resistance

- One patient was considered a VF.
  - The patient had an unconfirmed VL <50 copies/mL at week 24, but subsequent VL measurements were >50 copies/mL.
  - The primary PI mutation M46I had emerged, but the patient's virus remained susceptible to all PIs and NRTIs.
  - This patient was nonadherent from week 24 onward according to both the Study Adherence Questionnaire and pill count.
- One patient experienced rebound at week 40 but was resuppressed at week 48.
  - The patient had a treatment-emergent NRTI RAM (K219Q) but remained susceptible to the background regimen of AZT/3TC and all PIs.
- The only patient with a baseline DRV RAM (V11I) achieved virologic response at week 16, which was maintained through week 48 (ITT-TLOVR).

PK

- At week 2, the median (range) DRV area under the plasma concentration-time curve over the 24-hour dosing interval (AUC_T) and trough concentrations (C_{0h}) were 87.9 µg•h/mL (34.6-128) and 2196 ng/mL (510-3975), respectively.[5]
- At week 48, the mean (SD) DRV AUC_{24h} and C_{0h} were 80.7 (23.6) µg•h/mL and 1.93 (0.87) µg•h/mL, respectively.[1]
- Overall DRV exposure was comparable to that observed in HIV-1-infected, treatment-naïve adults receiving PREZISTA/r 800/100 mg QD in the ARTEMIS study (mean AUC_{24h} 89.7 µg•h/mL).[1]
- No relevant relationships were observed between DRV PK and virologic response, change in VL from baseline, or AEs of clinical interest.

Safety

- AEs were reported in 11/12 patients (Table: Incidence of AEs at Week 48).

Incidence of AEs at Week 48[1]

Parameter, n (%)	Any Causality	Possibly related to PREZISTA/r
≥1 AE	11 (92)	2 (17)
≥1 grade 3-4 AE	3 (25)	0
≥1 SAE	4 (33)[a]	1 (8)
≥1 AE leading to discontinuation	0	0

Abbreviations: AE, adverse event; r, ritonavir; SAE, serious adverse event.
[a]Anemia (n=2); neutropenia (n=1); cervical dysplasia (n=1); traumatic brain injury (n=1).

- AEs (regardless of causality or severity) reported in ≥2 patients included vomiting (n=4), anemia (n=3), nausea (n=3), cough (n=2), diarrhea (n=2), furuncle (n=2), pyrexia (n=2), and sinusitis (n=2).
- Five SAEs were reported in 4 patients; 4 were considered unrelated to PREZISTA and 1 (anemia) was considered doubtfully related to PREZISTA.
- No patients discontinued treatment due to an AE.
- Grade 2-4 treatment-emergent lipid- and glucose-related laboratory-related abnormalities are presented in Table: Lipid and Glucose-Related Laboratory Abnormalities at Week 48.

Lipid and Glucose-Related Laboratory Abnormalities at Week 48[1]

Grade 2-4 Treatment-Emergent Laboratory Abnormalities[a], n (%)	N=12
TC (≥200 mg/dL)	4 (33)
LDL-Cholesterol (≥130 mg/dL)	3 (25)
TG (≥500 mg/dL)	0
High serum glucose (≥125 mg/dL)	1 (8)

Abbreviations: LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides.
[a]Based on the Division of AIDS table for grading the severity of adult and pediatric adverse events, which does not have a grade 1 classification for TG or grade 4 for TC and LDL-cholesterol.

TREATMENT-EXPERIENCED PEDIATRIC PATIENTS

ARIEL Study

The ARIEL study (TMC114-C228) assessed the short-term safety and efficacy of PREZISTA/r plus an OBR in HIV-1 infected, treatment-experienced children aged 3 to <6 years (N=21) to support PREZISTA/r bodyweight dosage recommendations.[2]

Study Design/Methods

- Forty-eight week, open-label, single-arm, phase 2 trial.
- Inclusion criteria: HIV-1 infected children (3 to <6 years) receiving highly active antiretroviral therapy (HAART) for ≥ 12 weeks; weight 10 to <20 kg; VL >1000 copies/mL; ≤2 DRV RAMs at screening.
- The initial dose of PREZISTA/r was 20 mg/kg (oral suspension 100 mg/mL) and 3.0 mg/kg, respectively, administered BID.
  - Following PK analysis at week 2, the PREZISTA dose was amended to 25 mg/kg twice daily for patients weighing 10 to <15 kg and 375 mg twice daily (fixed) for patients weighing 15 to <20 kg.
  - The RTV dose remained the same for the lower weight group but was changed to 50 mg (fixed) for the upper weight group.
- Patients also received an investigator-selected OBR consisting of ≥2 ARVs.
- The primary efficacy analysis occurred at week 24, with final analysis at week 48.

- Primary efficacy endpoint: proportion of patients achieving VL <50 copies/mL (ITT-TLOVR).
- Secondary analyses included VL <50 copies/mL via FDA snapshot, VL <400 copies/mL, ≥1 $\log_{10}$ decrease in VL compared to baseline, change in CD4+ cell count and CD4+ percentage from baseline.
- Resistance was evaluated at screening (genotyping only), and at baseline, week 24, week 48, and in the event of early withdrawal (both genotyping and phenotyping) in patients with VL ≥1000 copies/mL.
- Resistance determinations were attempted on samples from VFs if VL ≥50 copies/mL.

Results

Patient Characteristics

- Twenty-one patients were treated with PREZISTA/r plus an OBR.
  - Demographics: male 10/21 (47.6%), median age 4.4 years, black (12/21), white (6/21), Asian (1/21), multiple races (2/21).
  - Mean (SE) baseline VL was 4.34 (0.18) copies/mL, with a median CD4+ count of 927 (range 209-2429) and median CD4+ percentage of 27.7.
  - Sixteen patients (76%) had previously received lopinavir (LPV)/r.
- Nineteen patients (90%) received 2 NRTIs while 2 patients (10%) received 3 NRTIs in the OBR.
  - 3TC and AZT (62% each) were the most commonly used NRTIs.
- Baseline resistance data are provided in Table: Baseline Resistance Data for Patients Enrolled in ARIEL.

Baseline Resistance Data for Patients Enrolled in ARIEL[2]

Median (range) Number of Baseline IAS-USA Mutations	PREZISTA/r (N=21)
Primary PI mutations	0 (0-3)
Secondary PI RAMs	4 (1-14)
DRV RAMs[a]	0 (0-2)
NRTI RAMs[b]	1 (0-5)
NRTI RAMs	1 (0-4)
Abbreviations: DRV, darunavir; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; r, ritonavir; RAMs, resistance associated mutations. [a]2 patients had DRV RAMs: L76V and L33F (n=1); L76V (n=1) [b]17 patients harbored the M184V mutation.	

Efficacy

- In the primary analysis at week 24, 12/21 (57.1%) patients achieved VL <50 copies/mL (ITT-TLOVR).
- At week 48, VL <50 copies was achieved in 17/21 (81%) and 15/21 (71.4%) patients via ITT-TLOVR and snapshot analysis, respectively.
  - Secondary endpoints, VL <400 copies/mL and ≥1 $\log_{10}$ reduction in VL from baseline, were achieved by 85.7% and 90.5% of patients, respectively.
- Mean increase in CD4+ cell count was 187 cells/mm^3, and CD4+ percentage increased by 4% from baseline to week 48.

Safety

- Twenty patients (95%) experienced ≥1 AE (Table: Frequency of AEs at Week 48).

Frequency of AEs at Week 48[2]

Parameter	PREZISTA/r (N=21)
Mean exposure, weeks	48.6
≥1 AE, n (%)	20 (95)

≥1 AE at least possibly related to treatment, n (%)[a]	1 (5)
≥1 AE leading to permanent discontinuation, n (%)[b]	1 (5)
≥1 grade 3 or 4 AE, n (%)[c]	2 (10)
Death, n (%)	0
Abbreviations: AE, adverse event; r, ritonavir. [a]QT prolonged; [b]1 patient discontinued treatment due to grade 2 vomiting considered very likely related to ritonavir treatment; [c]2 patients had grade 4 AEs (stenosing tenosynovitis, asthmatic crisis).	

- The most common AEs were upper respiratory tract infection (n=6), cough (n=5), diarrhea (n=5), tinea capitis (n=5), nasopharyngitis (n=4), vomiting (n=4), impetigo (n=3), nasal congestion (n=3), pyrexia (n=3), rash (n=3), rhinitis (n=3), and rhinorrhea (n=3).
- There were no clinically relevant changes in laboratory parameters from baseline to endpoint.
- All laboratory abnormalities were grade 1-2 except one case of grade 3 neutropenia, which was present since baseline and not considered treatment-related.
- Baseline median age-adjusted z-scores for height, weight and body mass index (BMI) revealed that patients were below normal population values with respect to height and weight, but not BMI.
    - At week 48, mean increases from baseline in height (5 cm), weight (1.7 kg), and BMI (0.1 kg/m^2) were observed.

Resistance

- The 2 patients with DRV RAMs (L33F + L76V, n=1; L76V, n=1) at baseline were virologically suppressed at weeks 24 and 48.
- At week 48, 3 patients were considered VFs (2 never suppressed, 1 rebounder).
- Of 2 VF patients with paired baseline/endpoint genotypes, none developed new PI or NRTI RAMs.
    - Both patients remained susceptible to DRV and NRTIs in the OBR.

DELPHI Study

The DELPHI study (TMC114-C212) evaluated the efficacy, safety, and tolerability of PREZISTA/r plus an OBR through 48 weeks in treatment-experienced, HIV-1-infected children aged 6-17 years.[3]

Study Design/Methods

- Randomized, 2-part, open-label, phase 2, 48-week study.
    - Part 1: dose-finding study based on body weight (n=44).[6]
        - Patients received 1 of 2 PREZISTA/r weight-based dosing regimens (group A: PREZISTA 9-15 mg/kg and RTV 1.5–2.5 mg/kg BID or group B: PREZISTA 11–19 mg/kg and RTV 1.5-2.5 mg/kg BID) in combination with ≥2 antiretrovirals (ARVs) for 14 days.
            - Group A: PREZISTA/r PK parameters (C_{0h}, AUC_{24h}, C_{max}) were 9%, 19%, and 12% lower than the reference adult exposure (PREZISTA/r 600/100 mg dose).
            - Group B: PREZISTA/r PK parameters in group B were 14%, 2%, and 12% greater than the reference adult exposure.
    - Part 2 of the study included all 44 patients from part 1, 24 additional patients with body weight 20-50 kg, plus 12 patients with body weight ≥50 kg (who received the adult dosage).[3]
    - Based on PK, safety, and efficacy data from part 1, PREZISTA 11–19 mg/kg and RTV 1.5–2.5 mg/kg BID was selected as an appropriate dose for administration in part 2 of the DELPHI study.[3,6]

Weight-Based Dosing for PREZISTA/r (used in Part 2)[3]

Body Weight	PREZISTA/r Dose (N=80)
20-<30 kg	375/50 mg BID (n=20)
30-<40 kg	450/60 mg BID (n=24)
≥40 kg	600/100 mg BID (n=36)
Abbreviations: BID, twice daily; r, ritonavir.	

- Inclusion criteria: 6-17 years; body weight ≥20 kg; VL ≥1,000 copies/mL; stable CD4+ percentage; on HAART ≥12 weeks; able to swallow the PREZISTA 75 mg or 300 mg tablets.[3,7]
- PK and pharmacodynamic (PD) analyses:
  - Steady-state DRV AUC_{12h} and C_{0h} at week 48.
  - Effect of DRV PK on efficacy or safety at week 24.[6]

Results

Patient Characteristics

Select Baseline Characteristics for Patients Enrolled in DELPHI[3]

Demographics	PREZISTA/r (N=80)
Age at screening	
6–<12 yrs, n (%)	24 (30)
12–17 yrs, n (%)	56 (70)
Perinatal infection, n (%)	62 (78)
CDC class C	40 (50)
Disease Characteristics	
Mean (±SD) VL log_{10} copies/mL	4.64±0.80
Median (range) CD4+ cell count, cells/mm^3	330 (6-1505)
Abbreviations: r, ritonavir; SD, standard deviation; VL, viral load.	

- Previous ARV exposure: ≥1 NRTI (100%); ≥1 PI (96%); ≥1 NNRTI (79%); enfuvirtide (ENF; 10%).[3]
- ARVs in the OBR: NRTIs (98%); NNRTIs (6%); ENF (30%).[3]
  - NRTIs in the OBR: 3TC (48%), tenofovir disoproxil fumarate (TDF; 45%), AZT (40%), didanosine (DDI; 30%).
- Median (range) number of IAS-USA mutations at baseline: PI RAMs 11 (0–19); primary PI RAMS 3 (0-6); NNRTI RAMs 2 (0–4); NRTI RAMs 4 (0–8).[7]

Pharmacokinetics

- DRV exposure in pediatric patients was comparable to that of treatment-experienced, HIV-infected adults from a 24-week analysis of POWER 1 and 2 studies (Table: DRV PK Comparison Between Pediatric and Adult Patients).[3]
- Trough concentrations (C_{0h}) were well above the protein-binding corrected EC_{50} value (550 ng/mL) for PI-resistant virus.[3]

DRV PK Comparison Between Pediatric and Adult Patients[3]

PK Parameter, median (range)[a]	Pediatric patients (N=76)	Adult[b] (N=119)
AUC_{24h}, ng•h/mL	123,276 (71,850–201,520)	123,336 (67,714–212,980)
C_{0h}, ng/mL	3693 (1842–7191)	3539 (1255–7368)
Abbreviations: AUC_{24h}, area under the plasma concentration curve over 24 hours; C_{0h}, pre-dose concentration; DRV, darunavir; PK, pharmacokinetic. [a]Estimated using population PK analysis [b]Reference adult exposure from primary 24–week analysis of integrated data from POWER 1 and 2 studies.		

- No relationship was observed between PREZISTA/r AUC_{12h} or C_{0h} and virologic response or AEs.[6]

Efficacy

Virologic and Immunologic Results from the DELPHI Study at Week 48[3]

Parameter	PREZISTA/r (N=80)
VL <50 copies/mL (ITT-TLOVR)	48%
VL <400 copies/mL (ITT-TLOVR)	59%
≥1 log VL reduction (ITT-TLOVR)	65%
Median increase in CD4+ cell count from baseline, cells/mm^3 (ITT-NC=F)	110
Abbreviations: ITT, intent to treat; NC=F, noncompleter equals failure; r, ritonavir; TLOVR, time to loss of virologic response; VL, viral load.	

- Fifty-eight patients (73%) were adherent to treatment (had not missed any doses of PREZISTA/r) based on responses to an adherence questionnaire. In the 6 to less than 12 years age group, 16 patients (67%) were adherent, whereas in the 12-17 years age group, there were 42 adherent patients (75%).

Factors associated with virologic success[3]

- A logistic regression model on virologic response (<50 copies/mL) at week 48 was performed and included the covariates: baseline VL, sex, age, number of DRV mutations, number of sensitive NRTIs in the OBR, ENF use and treatment compliance.
- Compliance and the number of DRV mutations were found to significantly affect response (P<0.0001); no other factors were significant.

Changes in Height and Weight

- Patients that received PREZISTA/r experienced statistically significant increases in height (+4.1 cm; P<0.001) and weight (+4.3 kg, P<0.003) from baseline at week 48.[3]

Resistance

- Thirty percent of patients (24/80) experienced VF: 21% (17/80) were rebounders, and 9% (7/80) were never suppressed.[3]
- Virologic response to PREZISTA at week 48 was reduced in those patients with ≥3 DRV RAMs at baseline (Table: Effect of DRV RAMs on Virologic Response).[7]
- PI mutations developing in at least 10% of rebounders (n ≥2) were 154L (n=5), V32I (n=4), I50V (n=3), I13V (n=2), M36L (n=2), V77I (n=2), and L89M (n=2). V32I, I50V, and I54L are DRV RAMs.[3]

Effect of DRV RAMs on Virologic Response at Week 48[7]

Number of DRV RAMs	PREZISTA/r (N=80)			
	0	**1**	2	**>**3
≥1 log VL reduction	74% (29/39)	71% (12/17)	60% (9/15)	22% (2/9)
VL <50 copies/mL	59% (23/39)	47% (8/17)	47% (7/15)	0
Abbreviations: DRV, darunavir; r, ritonavir; RAM, resistance associated mutation; VL, viral load.				

Safety

Summary of AEs (Regardless of Causality) at Week 48[3]

Parameter	PREZISTA/r (N=80)
Mean exposure, weeks	60
≥1 AE, n (%)	74 (93)
≥1 grade 3 or 4 AE, n (%)	21 (26)
≥1 SAE, n (%)	11 (14)
≥1 AE leading to treatment discontinuation, n (%)	1 (1)[a]
Death, n (%)	0
Abbreviations: AE, adverse event; r, ritonavir; SAE, serious adverse event. [a]Grade 3 anxiety considered unrelated to PREZISTA/r.	

- Incidence of both grade 2-4 treatment-related diarrhea and rash was 1%.
- The most common grade 2-4 lipid laboratory abnormalities at week 48 were increased total cholesterol (TC) and increased LDL (Table: Selected Grade 2-4 Laboratory Abnormalities through Week 48).

Selected Grade 2–4 Laboratory Abnormalities (≥1% Incidence) through Week 48[a3,8]

Parameter	PREZISTA/r (N=80)
ANC decreased, n (%)	10 (13)
Pancreatic amylase, n (%)	9 (11)
ALT increased, n (%)	5 (6)
AST increased, n (%)	4 (5)
Lipase, n (%)	3 (4)
TG increased, n (%)	1 (1.3)
TC increased, n (%)	11 (13.8)
LDL increased, n (%)	11 (13.8)
Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; LDL, low-density lipoprotein; r, ritonavir; TC, total cholesterol; TG, triglycerides. [a]Based on the Division of AIDS table for grading the severity of adult and pediatric adverse events, which does not have a grade 1 classification for TG or grade 4 for TC and LDL-cholesterol.	

- No significant increases were noted in mean blood glucose levels in patients who received PREZISTA/r through week 48 (P=0.77).

LONG-TERM SAFETY DATA

DIANA STUDY

The DIANA study (TMC114-TiDP29-C232) was an open-label, single arm study that evaluated long-term safety in patients receiving continued access to PREZISTA/r plus an OBR in patients aged 3 to <18 years who participated in the DELPHI, DIONE, or ARIEL studies.[4]

Study Design/Methods

- Treatment-experienced pediatric patients aged ≥3 years who completed the phase 2, open-label DELPHI, ARIEL, or DIONE studies and, per investigators, benefitted from PREZISTA use in countries where PREZISTA was unavailable or not accessible free of charge, were included in the study.
  - Safety was evaluated in the ITT population.
  - The patients continued to receive the same PREZISTA/r dosage regimen based on the original study protocols that they participated in (or on a body weight adjusted dose for patients from the DELPHI or ARIEL studies). Patients also received an OBR that was composed by the investigators.
  - Treatment with PREZISTA/r would be discontinued if the following criteria was met, whichever occurred first: virologic failure; treatment-limiting toxicity; loss to follow-up; withdrawal of consent/assent by the patient or withdrawal of consent by the parent(s)/legal representative(s); pregnancy; or termination of the study by the sponsor.
  - Treatment was also discontinued if PREZISTA became commercially available or could be accessed through another source.

Results

Patient Characteristics

- Forty-six patients were enrolled and received at least 1 dose of PREZISTA (ITT population).
- Median age (range) and number of patients from each study:
  - DELPHI: 15.0 years (11–17); n=16

- ARIEL: 5.0 years (4–6); n=20
- DIONE: 14.5 years (13–17); n=10

- The overall median (range) duration of PREZISTA/r intake was 4.2 years (0.1–7.1).
- Lamivudine was the most frequently used NRTI in the ITT population (74%; 34/46).

Safety

- AEs were reported in 33% (15/46) of patients (Table: Incidence of AEs).
- SAEs were reported in 26% (12/46) of patients.
- The most common AEs, any grade in ≥2 patients, were pneumonia (7%, 3/46), asthma (4%, 2/46), gastroenteritis (4%, 2/46), and lipoatrophy (4%, 2/46).

Incidence of AEs

Parameter, AE	PREZISTA/r BID (DELPHI) n=16	PREZISTA/r BID (ARIEL) n=20	PREZISTA/r QD (DIONE) n=10
≥ 1 AE	6 (38)	5 (25)	4 (40)
Possibly related to PREZISTA	0	0	1 (10)
≥1 grade 1 or 2 AEs, n (%)	1 (6)	2 (10	1 (10)
≥1 grade 3 or 4 AEs, n (%)	4 (25)	3 (15)	3 (30)
≥1 SAE, n (%)	5 (31)	4 (20)	3 (30)
≥ 1 AE leading to discontinuation	1 (6)[a]	0	1 (10)[a]

Abbreviations: AE, adverse event; BID, twice daily; r, ritonavir; QD, once daily; SAE, serious adverse event.
[a]Both of the AEs that led to DC were pregnancies.

- No deaths were reported, and none of the grade 3 or 4 AEs or SAEs were considered related to PREZISTA/r treatment or led to study discontinuation.
- Only one AE was considered related to PREZISTA/r treatment (grade 1 lipoatrophy).
- There were 3 pregnancies amongst the patients and 2 of them were reported as an AE. All the pregnancies that were reported led to study discontinuation.
  - Follow-up data was available for 2 patients; one patient gave birth to an infant with no abnormalities and the other patient reported grade 3 SAEs (blighted ovum and spontaneous abortion).

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 03 January 2025.

REFERENCES

1. Flynn P, Komar S, Blanche S, et al. Efficacy and safety of darunavir/ritonavir at 48 weeks in treatment-naïve, HIV-1-infected adolescents: results from a phase 2 open-label trial (DIONE). *Pediatr Infect Dis J*. 2014;33(9):940-945.

2. Violari A, Bologna R, Kumarasamy N, et al. Safety and efficacy of darunavir/ritonavir in treatment-experienced pediatric patients: week 48 results of the ARIEL trial. *Pediatri Infect Dis J*. 2015;34(5):e132-137.

3. Blanche S, Bologna R, Cahn P, et al. Pharmacokinetics, safety and efficacyof darunavir/ritonavir in treatment-experienced children and adolescents. *AIDS*. 2009;23(15):2005-2013.

4. Violari A, Masenya M, Blanche S, et al. The DIANA study: continued access to darunavir/ritonavir (DRV/r) and long-term safety follow-up in HIV-1-infected pediatric patients aged 3 to < 18 years. *Drug Saf*. 2021;44(4):439-446.

5. Flynn P, Blanche S, Giaquinto C, et al. 24-week efficacy, safety, tolerability, and pharmacokinetics (PK) of darunavir/ritonavir (DRV/r) once daily (qd) in treatment-naive adolescents aged 12 to < 18 years in DIONE. Abstract presented at: 6th International AIDS Society Conference (IAS); July 17-20,2011; Rome, Italy.

6. Sekar V, de Casteele TV, Baelen BV, et al. Dose selection and pharmacokinetics-pharmacodynamics of darunavir coadministered with low-dose ritonavir in the DELPHI (TMC-114-C212) trial in treatment-experienced, HIV-1-infected children and adolescents. Poster presented at: 17th International AIDS Conference (IAC); August 3-8, 2008; Mexico City, Mexico.

7. Blanche S, Bologna R, Cahn P, et al. 48-Wk safety and efficacy of darunavir/ritonavir (DRV/r) in treatment-experienced children and adolescents in DELPHI. Oral presentation presented at: 48th Annual ICAAC / IDSA 46th Annual Meeting; October 25-28, 2008; Washington, DC.

8. Meyers T, Joao E, Pilotto JH, et al. 48 week lipid- and glucose-related safety profile of daruavir/ritonavir in treatment-experienced peadiatric patients in DELPHI. Presentation presented at: 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention; July 19-22, 2009; Cape Town, South Africa.