SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals Ltd. **Trade Name**: darunavir **Indication**: HIV-infection	**Drug Substance**: TMC114 **Trial no.**: TMC114-C212 **Clinical Phase**: II
Title: A Phase II, open-label trial, to investigate pharmacokinetics, safety, tolerability and antiviral activity of TMC114/rtv b.i.d. in treatment-experienced HIV-1 infected children and adolescents - Analysis with cut-off date of 10 April 2008, at which time all subjects had reached Week 48 or discontinued before	
Investigator: R. Bologna, M.D., Hospital de Pediatria J. P. Garrahan, Combate de Los Pozos 1881, Buenos Aires, Argentina.	**Country**: Argentina, Brazil, Canada, Spain, France, Italy, Romania, United States, South Africa
Trial Period: Start: Part I (20 - < 50 kg): 06 Sep 2006 Part II (20 - < 50 kg): 15 Jan 2007 Part II (≥ 50 kg): 13 Jul 2006 End: Ongoing (10-Apr-2008 Clinical cut-off for Week 48 analysis)	**No. of Investigators**: 27 **No. of Subjects**: Part I (20 - < 50 kg): N = 44; Part II (20 - < 50 kg): N = 24; Part II (≥ 50 kg): N = 12.

Objectives: The trial was structured in two parts with differing objectives for each part:

The objectives of Part I of the trial were:
- To evaluate the pharmacokinetic profile of two different doses of darunavir (DRV, also known as TMC114) in combination with low-dose ritonavir administered b.i.d. in the pediatric population at steady-state: AUC_{12h}, C_{max} and C_{min};
- To provide dose recommendation of DRV per body weight in pediatric subjects of ≥ 20 kg to < 50 kg;
- To evaluate short-term safety, tolerability and antiviral activity of two different doses of DRV/rtv administered b.i.d. in treatment-experienced pediatric subjects.

The primary objective of the second part of the trial was:
- To evaluate long-term safety, tolerability and efficacy of DRV in combination with low-dose ritonavir administered b.i.d. and other ARV agents over a 24-week treatment period at the recommended pediatric (≥ 20 kg to < 50 kg) and adult (≥ 50 kg) doses.

Secondary objectives were:
- To evaluate long-term safety, tolerability and efficacy of DRV in combination with low-dose ritonavir administered b.i.d. and other ARV agents over a 48-week treatment period at the recommended pediatric (≥ 20 kg to < 50 kg) and adult (≥ 50 kg) doses;
- To evaluate immunology, resistance characteristics, pharmacokinetic parameters and pharmacokinetic/pharmacodynamic (PD) relationships of DRV/rtv over 48 weeks of treatment.

The primary objectives of Part II of the trial based on Week 24 data have been described in a previous report. The present report describes the secondary objectives of the trial after all subjects had been treated for 48 weeks or had discontinued earlier.

Design: This was an open-label Phase II trial to evaluate pharmacokinetics, short-term safety, tolerability and antiviral activity to support dose recommendations of DRV administered in combination with low-dose ritonavir and other antiretroviral (ARV) agents in treatment-experienced, HIV-1 infected pediatric subjects aged from 6 - < 18 years. In addition, efficacy, long-term safety and tolerability of DRV/ritonavir (rtv) were to be evaluated in combination with other ARV drugs over a 48 week treatment period.
The trial was structured in 2 parts:
Part I was designed to provide dose recommendations of DRV/rtv in pediatric HIV-1 infected ARV experienced subjects weighing between 20 and 50 kg.

Design (Cont'd.)
A maximum of 48 subjects were to be included in Part I and were to be randomized in a 1:1 ratio to receive either the adult equivalent dose of DRV with low-dose ritonavir b.i.d.
(Dose Group A) or a 20 to 33% higher dose of DRV with low-dose ritonavir b.i.d. (Dose Group B) in combination with ARV agents. The recommended dose was selected based on short-term safety, tolerability, antiviral activity and pharmacokinetics on Day 14. Once selected, all Part I subjects who were not on the selected dose were switched to the selected dose at the next visit and all subjects were to continue the second part of the trial up to 48 weeks as per protocol.

The second part of the trial evaluated long-term safety, tolerability and efficacy of the selected dose and comprised:
1) all subjects participating in Part I who switched to the selected dose once it was determined
2) all subjects participating in Part I who were already receiving the selected dose
3) 20 additional subjects with body weight from ≥ 20 to < 50 kg who received the pediatric dose as selected from Part I
4) approximately 12 subjects ≥ 50 kg who received the adult dose of DRV/rtv 600/100 mg b.i.d. for treatment-experienced subjects. Recruitment of subjects weighing ≥ 50 kg was able to precede or run in parallel with recruitment of Part I subjects.

Subjects ≤ 18 years at the point of reaching the Week 48 visit, and who continued to benefit from treatment with DRV and who were living in a country where DRV pediatric use was not yet part of the label, had the opportunity to roll-over to the extension phase where they were to continue to receive DRV/rtv until the subject became 18 years and DRV was available through the local Health Care Systems or until DRV was indicated for use in pediatrics.

Subject Selection

Inclusion Criteria
1. Boys and girls, aged between 6 and 17 years inclusive.
2. Subjects with documented HIV-1 infection.
3. Body weight Part I: ≥ 20 to < 50 kg.
   Body weight Part II: ≥ 50 kg and from ≥ 20 to < 50 kg after pediatric dose selection.
4. Able to swallow the DRV tablet formulation(s) and the ritonavir capsule formulation, and to tolerate the ritonavir liquid formulation (liquid formulation only applicable for subjects < 40 kg).
5. Stable CD4+ percentage: no more than 5% decrease in CD4+ percentage between the screening visit and the last available CD4+ measurement (with a minimum of 4 weeks and a maximum of 24 weeks between screening visit and last measurement).
6. Subjects on a stable ART who needed to change their ARV regimen because it was failing (at least 12 weeks on therapy), with a viral load of > 1000 copies/mL.
7. Parents or legal representative and trial subjects (where appropriate, depending on age and local regulation) willing and able to give consent. Children were informed about the trial and asked to give assent.
8. Subjects able to comply with the protocol requirements.
9. General medical condition, in the investigator's opinion, did not interfere with the assessments and the completion of the trial.
10. Female subjects who were sexually active and able to become pregnant had to use a safe and effective birth control method, such as sexual abstinence or medically accepted barrier methods of contraception (e.g., diaphragm, and condom) during the study. Hormonal birth control alone was not considered adequate, as the interaction between study drug and hormonal birth control was not available.

Exclusion Criteria
1. Part I: Use of the NNRTI efavirenz as part of the current regimen was not allowed.
   Part II: Use of efavirenz as part of the current regimen was allowed.

Exclusion Criteria (Cont'd)

2. Presence of any currently active AIDS defining illness [Category C conditions according to the CDC Classification System for HIV Infection 1993 or according to the 1994 revised CDC Classification System for HIV infection in children less than 13 years of age].
   Note: An AIDS defining illness not clinically stabilized for at least 30 days was considered as currently active.
   Note: Primary and secondary prophylaxis for an AIDS defining illness was allowed in cases where the medication administered is not part of the disallowed medications.
3. Active substance use as determined by the investigator during anamnesis that included but was not limited to daily or frequent alcohol intake, use of solvents, barbiturate, amphetamine, and recreational or narcotic drugs.
   Note: Prescribed use of methadone was allowed.
4. Use of disallowed concomitant therapy.
5. Use of any antiretroviral and non-antiretroviral investigational agents within 30 days prior to screening, except for tenofovir, tipranavir, atazanavir and fosamprenavir.
   ***Note*:** DRV was not to be used within 14 days following the use of tipranavir. A minimal 14-day washout period was required in which tipranavir had to be either interrupted or substituted to an investigator selected PI regimen until the baseline visit (Day 1).
6. Life expectancy of less than 6 months.
7. Co-enrollment in other clinical and/or cohort trials without written permission of the sponsor.
8. Pregnancy or breastfeeding
9. Any active clinically significant disease (e.g., TB, cardiac dysfunction, pancreatitis, acute viral infections) or findings during screening of medical history or physical examination that, in the investigator's opinion, would have compromised the subject's safety or outcome of the trial.
10. Previously demonstrated clinically significant allergy or hypersensitivity to any of the excipients of the investigational medication (DRV) or ritonavir.
    Note: DRV is a sulfonamide derivative. Subjects who previously experienced a sulfonamide allergy were allowed to enter the trial. To date, no potential for cross sensitivity between drugs in the sulfonamide class and DRV has been identified in subjects participating in phase II trials.
11. Subjects with documented hepatic impairment.
    Note: subjects co-infected with chronic hepatitis B or C (determined by hepatitis B surface antigen, anti core-hepatitis B IgG antibody and hepatitis C antibody) were allowed to enter the trial if their condition was clinically stable, and they were not expected to require treatment during the study period and have ALT or AST levels < 3 x ULN. Subjects diagnosed with acute viral hepatitis at screening were not allowed to enter the trial (e.g., hepatitis A IgM antibody).
12. Subjects with the following laboratory abnormalities as defined by the DAIDS grading scheme:
    - any grade 3 or 4 toxicity with the following exceptions unless clinical assessment foresaw an immediate health risk to the subject:
      - subjects with pre-existing diabetes or asymptomatic glucose elevations of grade 3 or grade 4
      - subjects with asymptomatic triglyceride or cholesterol elevations of grade 3 or 4.

Treatment	**DRV**		**Ritonavir**	
Concentration Formulation (TF No.) Usage	75 mg tablet F027 Oral	300 mg tablet F016 Oral	100 mg capsule n/a Oral	80 mg/mL liquid n/a Oral
Batch Number	PD1774; PD2169	PD1599; 7JG3081-X; PD1778		
Dose Regimen	Part I **Group A**: 1) ≥ 20 – < 30 kg: 300 mg DRV/50 mg ritonavir b.i.d. [(4 tablets of 75 mg **or** 1 tablet of 300 mg DRV) + (0.625 mL ritonavir)] 2) ≥ 30 – < 40 kg: 375 mg DRV/60 mg ritonavir b.i.d. [(5 tablets of 75 mg **or** 1 tablet of 300 mg + 1 tablet of 75 mg DRV) + (0.75 mL ritonavir)] 3) ≥ 40 – < 50 kg: 450 mg DRV/100 mg ritonavir b.i.d. [(6 tablets of 75 mg **or** 1 tablet of 300 mg + 2 tablets of 75 mg DRV + (one 100 mg capsule ritonavir)] **Group B**: 1) ≥ 20 – < 30 kg: 375 mg DRV/50 mg ritonavir b.i.d. [(5 tablets of 75 mg **or** 1 tablet of 300 mg + 1 tablet of 75 mg DRV) + (0.625 mL ritonavir] 2) ≥ 30 – < 40 kg: 450 mg DRV/60 mg ritonavir b.i.d. [(6 tablets of 75 mg **or** 1 tablet of 300 mg + 2 tablets of 75 mg DRV) + (0.75 mL ritonavir)] 3) ≥ 40 – < 50 kg: 600 mg DRV/100 mg ritonavir b.i.d. [(8 tablets of 75 mg **or** 2 tablets of 300 mg DRV) + (one 100 mg capsule ritonavir)] Part II 1) Subjects ≥ 50 kg received the adult dose of 600 mg (2 tablets of 300 mg) DRV/100 mg ritonavir b.i.d. 2) Subjects < 50 kg treated as per Part I Group B (recommended dose)			
Duration of Treatment	max. 48 weeks (plus optional extension phase)			
Duration of Trial	Screening period: maximum 4 weeks; treatment period: maximum 48 weeks; follow-up period: 4 weeks (plus optional extension phase)			
Disallowed Medication	***Disallowed for all subjects from screening until the end of the treatment period:*** ➢ Investigational agents (from 30 days before screening onwards); ➢ Experimental vaccines. ***Note:*** Approved vaccines are allowed if they are given at least 4 weeks before a viral load measurement. ➢ Herbal supplements: all products containing *Hypericum perforatum* (St John's Wort) ; ➢ Anticonvulsants: phenobarbital, phenytoin, carbamazepine ➢ Antibiotics: rifampin, rifapentine; ➢ Steroids: systemic dexamethasone. ***Note:*** Topical formulations are allowed.			

	Disallowed from baseline until the end of the treatment period: ➢ Antiarrhythmics: bepridil, flecainide, propafenone, systemic lidocaine, quinidine, mexilitine, disopyramide, amiodarone; ➢ Antibiotics: telithromycin; ➢ Antifungals: systemic use of ketoconazole, or itraconazole at > 200 mg/day; ➢ Antihistamines: astemizole, terfenadine; ➢ Antipsychotics: pimozide; ➢ Benzodiazepines: midazolam, triazolam; ➢ Ergot derivatives: dihydroergotamine, ergonovine, ergometrine, ergotamine, methylergonovine; ➢ Immunosuppressants: cyclosporin, rapamycin, tacrolimus, sirolimus; ➢ Lipid lowering agents & HMG-CoA reductase inhibitors: pravastatin, lovastatin, simvastatin, rosuvastatin; ➢ Narcotic analgesics: meperidine (pethidine). ***Note:*** In case surgery is needed, the sponsor should be contacted to discuss the use of anesthetics and/or narcotic analgesics. ➢ Gastroprokinetics: cisapride; ➢ Stimulants: amphetamines, amphetamine derivatives.
Assessments	
Pharmacokinetics	Pharmacokinetic samples for DRV/rtv: - Weeks 2, 4, 24, 48 (or early withdrawal); For subjects in Part I at Week 2 pharmacokinetic sampling occurred at 5 different timepoints. In the second part of the trial, sparse blood sampling (2 samples per subject) was performed for assessment of DRV population pharmacokinetics. The first blood sample was drawn prior to the morning dose intake at the clinic, and the second sample was drawn at least one hour after the first blood sample is drawn.
Efficacy Plasma Viral Load	Samples for plasma viral load determinations: - screening, baseline; - Weeks 2, 4, 8, 12, 16, 24, 32, 40 and 48 (or early withdrawal); - follow-up visit.
Immunology	Samples for immunology assessment: - screening, baseline; - Weeks 2, 4, 8, 12, 16, 24, 32, 40 and 48 (or early withdrawal); - follow-up visit.
Resistance Determinations	Samples for pheno- and genotype determinations: - screening, baseline; - Weeks 24 and 48 (or early withdrawal).

Safety Adverse Events	AEs and HIV-related events were checked at every visit and reported from screening onwards until the last trial-related activity.
Clinical Laboratory	Samples for hematology, biochemistry and urinalysis: - screening, baseline; - Weeks 1, 2, 4, 8, 12, 16, 20, 24, 32, 40 and 48 (or early withdrawal); - follow-up visit. Coagulation testing: - screening; - at other visits if needed. Pregnancy test for female subjects having had first menses: - serum test: screening; - urine test: baseline, Weeks 4, 8, 12, 16, 20, 24, 32, 40 and 48 (or early withdrawal) - follow-up visit. Urine drug screen (alcohol, barbiturates, opiates and amphetamines) - screening Hepatitis A, B and C test: - screening; - other visits: only if diagnosis was suspected
Cardiovascular Safety	Vital signs (pulse, blood pressure, temperature): - screening, baseline; - Weeks 1, 2, 4, 8, 12, 16, 20, 24, 32, 40 and 48 (or early withdrawal). ECG readings (Part I only): - baseline; - Week 2.
Physical Examination	Physical examination: - screening, baseline; - Weeks 2, 8, 12, 16, 20, 24, 32, 40 and 48 (or early withdrawal).
Statistical Methods	Descriptive statistics, frequency tabulations Intent-to-Treat analysis, Wilcoxon matched-pairs signed-ranks test

Main Features of the Subject Sample and Summary of the Results – Part I

Baseline Characteristics for Subjects in Part I			
Demographics	**Group A**	**Group B**	**All Subjects**
Number of Subjects (M/F)	22 (15/7)	22 (18/4)	44 (33/11)
Age (years), median (range)	12.0 (6; 17)	13.0 (7; 17)	12.5 (6; 17)
Age category (years), n (%)			
< 10	4 (18.2)	3 (13.6)	7 (15.9)
10 - 15	15 (68.2)	13 (59.1)	28 (63.6)
> 15	3 (13.6)	6 (27.3)	9 (20.5)
Weight band as stratified (kg), n (%)			
20 - 29	7 (31.8)	7 (31.8)	14 (31.8)
30 - 39	8 (36.4)	7 (31.8)	15 (34.1)
40 - 49	7 (31.8)	8 (36.4)	15 (34.1)
Race, n (%)			
Caucasian	11 (50.0)	15 (68.2)	26 (59.1)
Black	9 (40.9)	3 (13.6)	12 (27.3)
Hispanic	2 (9.1)	3 (13.6)	5 (11.4)
Other	0	1 (4.5)	1 (2.3)
Baseline Disease Characteristics			
Log_{10} viral load: median (range), copies/mL	4.87 (3.5; 6.0)	4.54 (2.7; 6.6)	4.77 (2.7; 6.6)
CD4+ cell count: median (range), x 10^6/L	335 (9; 1480)	351 (6; 1140)	345 (6; 1480)
CD4 (%), median (range)	16.8 (0.7; 39)	14.9 (1; 37)	16.4 (0.7; 39)
Duration of known HIV infection: median (range), years	10.0 (5; 15)	11.1 (3; 17)	10.6 (3; 17)
Clinical stage of HIV infection, n (%),			
CDC Category N	1 (4.5)	2 (9.1)	3 (6.8)
CDC Category A	2 (9.1)	3 (13.6)	5 (11.4)
CDC Category B	7 (31.8)	7 (31.8)	14 (31.8)
CDC Category C	12 (54.5)	10 (45.5)	22 (50.0)
Subject Disposition			
Discontinuations	0	0	0

Pharmacokinetics for Subjects in Part I (Week 2)		
Pharmacokinetics of DRV, median (range)	**Group A**	**Group B**
AUC_{24h}[a], ng.h/mL	N = 21 94610 (51360; 191640)	N = 19 112780 (26792; 332900)
C_{0h}, ng/mL	N = 20 2905 (1940; 6060)	N = 20 3985 (147; 10300)
C_{max}, ng/mL	N = 21 5690 (2950; 14000)	N = 20 7090 (1350; 17600)

[a] calculated as 2 x AUC_{12h} , N = number of subjects with data.

Overall, the mean DRV exposure from HIV infected children in Group A was lower than the exposure in HIV-infected adults whereas in Group B, exposure was higher than the exposure in adults. Mean values of DRV AUC_{24h}, C_{0h} and C_{max} in Group A were found to be 81%, 91% and 88%, respectively, of the corresponding mean adult pharmacokinetic parameter whereas in Group B, mean values of DRV AUC_{24h}, C_{0h} and C_{max} were 102%, 114% and 112%, respectively, of the corresponding mean adult pharmacokinetic parameters. Thus, both dose groups met the protocol specified criteria for PK evaluations in that the mean values of the pharmacokinetic parameters in this pediatric population fell within 80 to 130% of the corresponding treatment-experienced adult pharmacokinetic parameters.

Group A had lower ritonavir plasma concentrations than those observed in HIV-infected adults at the recommended 600/100 mg b.i.d. dose of DRV/rtv, whereas Group B had ritonavir plasma concentrations which were comparable to those observed in HIV-infected adults in phase IIb studies.

Efficacy Results for Subjects in Part I (Week 2)

Parameter at Week 2	Group A		Group B		Difference [95% CI] in Response
Primary Efficacy Variable ***Virologic Response***[a]	**N**		**N**		
≥ 0.5 $\log_{10}$ decrease from baseline in viral load, n (%)	22	20 (90.9)	20	20 (100.0)	-9.1 [-22.1; 3.9]
Secondary Efficacy Variables	**N**		**N**		
Viral load < 400 copies/mL, n (%)	22	6 (27.3)	20	8 (40.0)	-12.7 [-41.9; 16.4]
Viral load – Mean (SE) change from baseline ($\log_{10}$ copies/mL)	22	-1.61 (0.13)	20	-1.77 (0.14)	0.16 [-0.21; 0.54]
CD4+ cell count - Mean (SE) change from baseline ($x10^6$ cells/L)	19	59 (22.8)	21	17 (30.1)	42 [-32; 116]

N = number of subjects; n = number of observations; CI = confidence interval
[a] Observed data

Results of the Part I efficacy analysis showed that observed virologic response rates defined as the percentage of subjects with a decrease from baseline of at least 0.5 $\log_{10}$ in plasma viral load were 90.9% in Group A and 100.0% in Group B. The results for the primary efficacy parameter were supported by those for the secondary virologic parameters. The percentage of subjects with a plasma viral load < 400 copies/mL at Week 2 was 27.3% in Group A and 40.0% in Group B.

Safety Results for Subjects in Part I (Week 2)

Adverse Events, n (%)	Group A N = 22	Group B N = 22
≥ 1 AE	8 (36.4)	8 (36.4)
Most frequently reported AEs[a]		
Pyrexia	2 (9.1)	1 (4.5)
Cough	2 (9.1)	1 (4.5)
Diarrhea	2 (9.1)	0
Headache	2 (9.1)	0
Rash	0	2 (9.1)
International normalized ratio increased	0	2 (9.1)
Deaths	0	0
≥ 1 SAE	0	0
≥ 1 AE at least possibly related[b]	0	4 (18.2)
≥ 1 AE leading to permanent stop	0	0
≥ 1 grade 3 or 4 AE	1 (4.5)	3 (13.6)
≥ 1 grade 3 or 4 AE at least possibly related to DRV[b]	0	2 (9.1)

N = number of subjects; n = number of subjects with observations.
[a] In > 1 subject in either group.
[b] In the opinion of the investigator

During the 2-week treatment period there was no substantial difference between the dose groups with respect to the incidence of adverse events. At least one AE was reported in 36.4% of subjects, with the most common AEs (at least 2 subjects) being pyrexia, cough, diarrhea, headache, rash and INR increased. Most AEs were grade 1 or 2 in severity. Four grade 3 or 4 AEs were seen. No subjects died and no subjects reported SAEs. No subject permanently discontinued trial treatment due to an AE

Clinical Laboratory	The majority of graded laboratory abnormalities were grade 1 or 2 in severity. Grade 3 abnormalities were observed in 2 (9.1%) of Group A subjects and 4 (18.2%) Group B subjects. One Group A subject had a grade 4 laboratory abnormality (amylase). There were no consistent or relevant differences between the treatment groups with respect to the incidence of laboratory abnormalities.

Cardiovascular Safety	Small median changes from baseline were observed for vital signs and ECG parameters in both groups. None of the observed mean changes from baseline were considered clinically relevant.
Other Safety Parameters	There were no clinically relevant changes over time in physical examination findings.

Conclusions on Part I and Pediatric Dose Selection

Both groups met the protocol specified criteria for pharmacokinetics based on the overall mean results, however, based on the individual pharmacokinetic data as well as the favorable efficacy, safety and tolerability profile seen with the higher dose (Group B), the following dosages for treatment-experienced pediatric subjects weighing between 20 and 50 kg were recommended:

For subjects ≥ 20 – < 30 kg: 375/50 mg b.i.d. DRV/rtv

For subjects ≥ 30 – < 40 kg: 450/60 mg b.i.d. DRV/rtv

For subjects ≥ 40 – < 50 kg: 600/100 mg b.i.d. DRV/rtv

These recommended dosages were communicated to all participating sites and Part I Group A subjects who were not receiving this dose were switched to the selected dose at the next visit. All subjects were then to continue the overall planned schedule of assessments.

Main Features of the Subject Sample and Summary of the Week 48 Results (Part I and Part II)

Subject Disposition for the Overall Trial Population Discontinuations and Treatment Duration	**DRV/rtv N = 80**
Discontinuations – Reason, n (%)	***10 (12.5)***
At Week 48 or earlier – any reason	***5 (6.3)***
Subject noncompliant	3 (3.8)
Adverse event/HIV related event	1 (1.3)
Other[a]	1 (1.3)
After Week 48 – any reason	***5 (6.3)***
Subject reached a virologic endpoint	3 (3.8)
Subject noncompliant	1 (1.3)
Other[b]	1 (1.3)
Duration of Treatment	
Median (range), weeks	68.0 (2 – 79)
Total patient-years of exposure	92.8

N = number of subjects, n = number of subjects with observations
[a] Subject moved away.
[b] Subject reached 18 years of age and switched to DRV/rtv available to adults in the Public Health System

Baseline Characteristics for the Overall Trial Population	**DRV/rtv N = 80**
Demographic Data	
Gender, n (%)	
Female	23 (28.8)
Male	57 (71.3)
Age (years), median (range)	14 (6 – 17)
Age category (years), n (%)	
6 - < 12	24 (30.0)
12 - < 18	56 (70.0)
Weight band as stratified (kg)	
20 - 29	19 (23.8)
30 - 39	21 (26.3)
40 - 49	28 (35.0)
≥ 50	12 (15.0)
Race, n (%)	
White	50 (62.5)
Black or African American	24 (30.0)
Asian	1 (1.3)
Multiple	5 (6.3)
Ethnicity, n (%)	
Hispanic or Latino	43 (53.8)
Not Hispanic or Latino	33 (41.3)
Unknown	4 (5.0)

N = number of subjects; n = number of subjects with observations

Baseline Disease Characteristics	**Age Group 6 - < 12 years N = 24**	**Age Group 12 - < 18 years N = 56**	**DRV/rtv N = 80**
Log_{10} viral load: median (range), copies/mL	4.28 (2.7; 5.4)	4.90 (2.8; 6.6)	4.82 (2.7; 6.6)
CD4+ cell count: median (range), x 10^6 cells/L	531 (116; 1480)	239 (6; 1505)	330 (6; 1505)
CD4%, median (range)	24.0 (4; 47)	15.2 (1; 37)	16.8 (0.7; 47)
Duration of known HIV infection: median (range), years	8.5 (3; 11)	12.0 (5; 17)	11.0 (3; 17)
Clinical stage of HIV infection, n (%)			
CDC Category N	5 (20.8)	0	5 (6.3)
CDC Category A	4 (16.7)	6 (10.7)	10 (12.5)
CDC Category B	7 (29.2)	18 (32.1)	25 (31.3)
CDC Category C	8 (33.3)	32 (57.1)	40 (50.0)
Hepatitis B or C co-infection status[a]			
Negative	24 (100)	53 (94.6)	77 (96.3)
Positive	0	2 (3.6)	2 (2.5)
Missing	0	1 (1.8)	1 (1.3)

N = number of subjects; n = number of subjects with observations
[a]Hepatitis test results were not available for 1 subject

Baseline Resistance Data for the Overall Trial Population	**Age Group 6 - < 12 years**	**Age Group 12 - < 18 years**	**Total DRV/rtv**
Baseline PI Mutations, median (range)	***N =24***	***N = 56***	***N = 80***
PI RAMs[a]	10 (1; 16)	11 (0; 19)	11 (0; 19)
Primary PI mutations[a]	2 (0; 5)	3 (0; 6)	3 (0; 6)
FDA defined PI mutations	4 (0; 6)	5 (0; 8)	4 (0; 8)
DRV RAMs[b]	0 (0; 3)	1 (0; 4)	1 (0; 4)

N = number of subjects.
[a] Based on the 2007 IAS-USA list of mutations
[b] DRV RAMs list 2007

Underlying ART for the Overall Treatment Period	**Age Group 6 - < 12 years N = 24**	**Age Group 12 - < 18 years N = 56**	**Total DRV/rtv N = 80**
Number of ARVs in Underlying ART, n (%)			
NRTI			
0	1 (4.2)	1 (1.8)	2 (2.5)
1	0	6 (10.7)	6 (7.5)
2	13 (54.2)	29 (51.8)	42 (52.5)
3	10 (41.7)	18 (32.1)	28 (35.0)
4	0	2 (3.6)	2 (2.5)
NNRTI			
0	23 (95.8)	52 (92.9)	75 (93.8)
1	1 (4.2)	4 (7.1)	5 (6.3)
Fusion Inhibitor (Enfuvirtide)			
0	20 (83.3)	36 (64.3)	56 (70.0)
1	4 (16.7)	20 (35.7)	24 (30.0)
Individual ARVs in Underlying ART, n (%)			
NNRTI			
Efavirenz (EFV)	1 (4.2)	3 (5.4)	4 (5.0)
Nevirapine (NVP)	0	1 (1.8)	1 (1.3)

Underlying ART for the Overall Treatment Period (Cont'd.)	**Age Group 6 - < 12 years N = 24**	**Age Group 12 - < 18 years N = 56**	**Total DRV/rtv N = 80**
Number of ARVs in Underlying ART, n (%)			
NRTI			
Lamivudine (3TC)	14 (58.3)	24 (42.9)	38 (47.5)
Tenofovir (TDF)	7 (29.2)	29 (51.8)	36 (45.0)
Zidovudine (ZDV)	9 (37.5)	22 (39.3)	32 (40.0)
Didanosine (ddI)	8 (33.3)	16 (28.6)	24 (30.0)
Stavudine (d4T)	8 (33.3)	13 (23.2)	21 (26.3)
Abacavir (ABC)	9 (37.5)	11 (19.6)	20 (25.0)
Emtricitabine (FTC)	1 (4.2)	11 (19.6)	12 (15.0)
Fusion Inhibitor			
Enfuvirtide (ENF)	4 (16.7)	20 (35.7)	24 (30.0)

N = number of subjects; n = number of subjects with observations
Only the initial therapies (i.e., as determined on Day 7) were considered

Susceptibility of Underlying ARVs used During the Overall Treatment Period[a,b]	**Age Group 6 – < 12 years N = 24**	**Age Group 12 – < 18 years N = 56**	**Total DRV/rtv N = 80**
Number of Susceptible ARVs (Antivirogram®) in Underlying ART, n (%)			
Any ARV* (Total PSS[c])	22	51	73
0	3 (13.6)	8 (15.7)	11 (15.1)
1	8 (36.4)	17 (33.3)	25 (34.2)
2	7 (31.8)	23 (45.1)	30 (41.1)
3	4 (18.2)	3 (5.9)	7 (9.6)
NRTI	21	50	71
0	6 (28.6)	15 (30.0)	21 (29.6)
1	4 (19.0)	17 (34.0)	21 (29.6)
2	7 (33.3)	17 (34.0)	24 (33.8)
3	4 (19.0)	1 (2.0)	5 (7.0)
NNRTI	1	4	5
1	1 (100.0)	4 (100.0)	5 (100.0)
FI	3	17	20
0	0	3 (17.6)	3 (15.0)
1	3 (100.0)	14 (82.4)	17 (85.0)

N = number of subjects; n = number of subjects with available data
[a] Only subjects with available Antivirogram® data were used for the determination of susceptibility. ENF was counted as susceptible if it had not been used previously.
[b] Only the initial therapies (i.e., as determined on Day 7) in the underlying ART were considered.
[c] PSS = phenotypic susceptibility score
* delavirdine, ritonavir, zalcitabine and DRV are excluded from this table

Safety Results for the Treatment Period to Week 48	
Treatment-Emergent AEs (Treatment Period)	**DRV/rtv N = 80**
≥ 1 AE	74 (92.5)
Most frequently reported AEs[a], n (%)	
Pyrexia	16 (20.0)
Cough	15 (18.8)
Upper respiratory tract infection	13 (16.3)
Diarrhea	12 (15.0)
Vomiting	11 (13.8)
Lymphadenopathy	11 (13.8)
Herpes simplex	11 (13.8)
Abdominal pain	9 (11.3)
Pneumonia	9 (11.3)
Sinusitis	9 (11.3)
Tonsillitis	8 (10.0)
Conjunctivitis	8 (10.0)
Headache	8 (10.0)
Deaths	0
≥ 1 SAE of any causality	11 (13.8)
≥ 1 SAE at least possibly related to DRV[b]	1 (1.3)
≥ 1 AE leading to permanent stop	1 (1.3)
≥ 1 grade 3 or 4 AE	21 (26.3)
Treatment-Emergent AEs of Interest	
≥ 1 rash-related AE	11 (13.8)
≥ 1 GI-related AE	27 (33.8)
≥ 1 hematology-related AE	9 (11.3)
≥ 1 liver-related AE	5 (6.3)
≥ 1 lipid-related AE	3 (3.8)
≥ 1 pancreas-related AE	2 (2.5)
≥ 1 cardiac-related AE	2 (2.5)
≥ 1 glucose metabolism-related AE	0

N = number of subjects; n = number of subjects with observations.
[a] In at least 10% (rounded %) of subjects
[b] In the opinion of the investigator.

During the 48-week treatment period, 92.5% of subjects reported at least 1 AE, with the most common AEs (at least 10.0%) being pyrexia, cough, upper respiratory tract infection, diarrhea, vomiting, lymphadenopathy, herpes simplex, abdominal pain, pneumonia, sinusitis, tonsillitis, conjunctivitis and headache. Most AEs were grade 1 or 2 in severity. Twenty-one subjects experienced a grade 3 or 4 AE, of which 5 were grade 4 and none was related to treatment. No subjects died during the treatment period. SAEs were reported in 11 subjects (13.8%) during treatment. All SAEs occurred in no more than 1 subject each. One SAE (increased ALT) was considered at least possibly related to investigational medication. One subject permanently discontinued trial treatment due to an AE (anxiety) considered not related to investigational medication by the investigator. Rash-related events were reported in 11 subjects (13.8%). Rash-related events considered at least possibly related to treatment were reported in 2 subjects (2.5%). No grade 3 or 4 rashes occurred. The overall incidence of GI-related events was 33.8% with grade 2 as the worst severity rating. GI-related events considered at least possibly related to treatment were reported in 7.5% of subjects. Hematology-related AEs in 9 subjects (11.3%). Liver-, cardiac-, lipid-, and pancreas-related events were generally low in incidence (< 10%). The safety results in the 48 week analysis are comparable to the Week 24 results and no new safety findings were observed.

Clinical Laboratory Tests				
Laboratory Parameter of Interest at Week 48	**DRV/rtv N = 80**			
Worst Grade, n (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Liver-related abnormalities				
AST	14 (17.5)	3 (3.8)	1 (1.3)	0
ALT	10 (12.5)	2 (2.5)	2 (2.5)	1 (1.3)
Hyperbilirubinemia	1 (1.3)	0	0	0
Lipid and glucose-related abnormalities				
Total cholesterol	11 (13.9)	10 (2.7)	1 (1.3)	n/a
LDL	8 (10.3)	9 (11.5)	2 (2.6)	n/a
Hyperglycemia	11 (13.8)	9 (11.3)	0	0
Triglycerides	n/a	1 (1.3)	0	0
General biochemistry-related abnormalities				
Amylase	9 (11.3)	3 (3.8)	5 (6.3)	1 (1.3)
Lipase	0	2 (2.5)	1 (1.3)	0
Creatinine	1 (1.3)	1 (1.3)	0	0
Hematology-related abnormalities				
Increased PT	3 (3.8)	4 (5.0)	2 (2.5)	1 (1.3)
Increased PTT	10 (12.5)	0	0	1 (1.3)
Decreased hemoglobin	3 (3.8)	2 (2.5)	1 (1.3)	0
Decreased WBC count	3 (3.8)	0	0	0
Decreased platelet count	1 (1.3)	0	1 (1.3)	1 (1.3)
Decreased neutrophil count	13 (16.3)	4 (5.0)	4 (5.0)	2 (2.5)
No clinically relevant mean changes from baseline were observed for any laboratory test parameter. The majority of graded laboratory abnormalities were grade 1 or 2 in severity.				

Cardiovascular Safety
Small mean changes from baseline were observed for vital signs parameters. None of the changes over time or treatment-emergent individual abnormalities were considered clinically relevant.
Other Safety Parameters
There were no clinically relevant changes over time in physical examination findings. For anthropometric measurements, at baseline, z-score values indicated that subjects were 0.7 to 1.4 standard deviations below the normal population median value with respect to BMI, height and weight. Following initiation of treatment, a rapid and significant response was seen as early as Week 4 in the age-adjusted z-scores for weight, Week 8 for age-adjusted BMI z-scores and Week 16 for age-adjusted height z-scores. At Week 48, within-group comparison for the changes from baseline revealed statistically significant differences with respect to age adjusted weight z-scores and age adjusted BMI z-scores but not for age adjusted height z-score.

Efficacy Results at Week 48	
Parameter at Week 48	**DRV/rtv N = 80**
Confirmed Virologic Response (TLOVR), n (%)	
≥ 1.0 log_{10} decrease from baseline in viral load	52 (65.0)
Viral load < 50 copies/mL	38 (47.5)
Viral load < 400 copies/mL	47 (58.8)
Viral load – Mean (SE) change from baseline (log_{10} copies/mL)	-1.81 (0.151)
CD4+ cell count – Mean (SE) change from baseline ($x10^6$ cells/L)	147 (27.2)

N = number of subjects; n = number of observations; SE = standard error

Efficacy results in these experienced pediatric subjects showed that confirmed virologic response defined as the percentage of subjects with a decrease from baseline of at least 1.0 log_{10} in plasma viral load at Week 48 was 65.0%. Confirmed virologic response (plasma viral load < 50 copies/mL, TLOVR) at Week 48 was seen in 47.5% of subjects. Virologic response defined as the percentage of subjects with a confirmed plasma viral load < 400 copies/mL (TLOVR) was 58.8%. Virologic response was sustained over time. For subjects with a confirmed virologic response of at least 1 log_{10} decrease in viral load at Week 24, 88.1% of subjects retained at least 1 log decrease from baseline at Week 48 while of those subjects with a confirmed virologic response < 50 copies/mL at Week 24 (undetectable), 87.5% remained undetectable at Week 48. Subgroup analyses by age showed higher response rates in subjects aged 6 - < 12 years compared with subjects in the 12 - < 18 years subgroup. These differences in response rates with respect to age are very likely influenced by the greater ARV treatment experience and higher degree of resistance in adolescent subjects aged 12 - < 18 years compared with children in the 6 - < 12 years age group. Additionally, treatment adherence issues associated with ARV therapy are frequent in adolescents and may potentially have played a role in the outcomes of this age group. The mean change in log_{10} viral load from baseline (ITT – NC = F) at Week 48 was -1.81 log_{10} copies/mL. A mean increase in CD4+ cell count from baseline was observed at all time points. The mean change in CD4+ cell count from baseline (ITT - NC = F) at Week 48 was 147 x 10^6/L. At baseline, 32 (40.0%) subjects had a CD4% of < 15% (CDC category: severe suppression) and 18 (22.5%) subjects had a CD4% of ≥ 25% (CDC category: no suppression). By Week 48, only 12 (16.9%) subjects were severely immunosuppressed and 37 (52.1%) subjects had no evidence of immunosuppression.

Resistance Determinations

The predictive value of baseline phenotype and genotype on response, as observed in adults, was confirmed in this pediatric population. Virologic failures, rebounders and subjects who were never suppressed were defined using the TLOVR (non-VF censored) algorithm. Of the 80 subjects on DRV/rtv, 24 (30.0%) experienced virologic failure. In this group, 17 (21.3%) subjects were rebounders and 7 (8.8%) subjects were never suppressed, defined as loss of or never achieving a viral load decrease ≥ 1 log_{10} from baseline, respectively. Development of resistance was assessed in the rebounders for which matching baseline/endpoint genotypic profiles were available (n = 16). Protease mutations emerging in ≥ 10% of rebounders (n ≥ 2) were I54L (n = 5), V32I (n = 4), I50V (n = 3), I13V (n = 2), M36L (n = 2), V77I (n = 2) and L89M (n = 2). The development of resistance in this treatment-experienced pediatric population was similar to that observed in treatment–experienced adults.

Pharmacokinetic and Pharmacodynamic Results at Week 48	
Pharmacokinetics of DRV, median (range)	**DRV/rtv N = 76**
AUC_{12h}, ng.h/mL	61638 (35925; 100760)
C_{0h}, ng/mL	3692.6 (1841.6; 7191.3)
CL/F, L/hr	8.1 (4.0; 16.7)
The target treatment-experienced adult DRV exposures were achieved in children across weight bands and age groups. Trough concentrations in all subjects were well above the protein binding corrected EC_{50} value of 550 ng/mL. Subgroup pharmacokinetic analyses assessing the effect of race, sex, region and effects of coadministered EFV or TDF showed no clinically relevant effect of these covariates on DRV exposure, consistent with findings in adults. No relevant relationships were observed between the DRV pharmacokinetics and efficacy response parameters at Week 48. No clinically relevant relationships were observed between DRV pharmacokinetics and safety.	

Overall Conclusions

The safety results from the 48 week data of the TMC114-C212 trial are comparable to the 24 week results and support the use of the selected pediatric dose of DRV/rtv in combination with other ARVs in treatment-experienced HIV-1 infected subjects aged between 6 and < 18 years:

- For subjects ≥ 20 – < 30 kg: DRV/rtv 375/50 mg b.i.d.

- For subjects ≥ 30 – < 40 kg: DRV/rtv 450/60 mg b.i.d.

- For subjects ≥ 40 kg: DRV/rtv 600/100 mg b.i.d.

The target treatment-experienced adult DRV exposures were achieved in treatment-experienced children aged 6 - < 18 years, confirming that doses selected were appropriate across the weight and age range evaluated. The safety profile was consistent with that observed in adults. In addition, no new safety findings were observed with significant improvements in age-adjusted weight and BMI z-scores over the course of the trial. The efficacy data observed at Week 48 in subjects receiving DRV/rtv b.i.d. (65.0% with ≥ 1 log_{10} decrease in viral load; 47.5% with a viral load at Week 48 of < 50 copies/mL) demonstrated the durability of the activity of a DRV-containing regimen in ARV experienced pediatric subjects. The resistance profile of DRV in terms of predictors of response and development of resistance in this treatment-experienced pediatric population was similar to the treatment experienced adult population.

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