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APPLICATION NUMBER:

202895Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

ADDENDUM TO THE OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 202895	Submission Date: March 30, 2011
NDA: 21976 (SDN 201, S-20)	Submission Date: June 28, 2011
Brand Name	Prezista [®]
Generic Name	Darunavir
Reviewer	Stanley Au, Pharm.D., BCPS
Pharmacometrics Reviewer	Jiang Liu, Ph.D.
Pharmacometrics Team Leader	Pravin Jadhav, Ph.D.
Clinical Pharmacology Team Leader	Sarah Robertson, Pharm.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products
Applicant	Tibotec, Inc.
Formulation; strength(s) to-be-marketed	Darunavir oral suspension (100 mg/mL)
Currently marketed formulations	Darunavir tablets; 75 mg, 150 mg, 400 mg, 600 mg
Proposed darunavir suspension or tablet dosage regimens coadministered with ritonavir solution	Twice daily dosing with food: <u>10 kg to less than 15 kg</u> : Darunavir 20 mg/kg coadministered with ritonavir 3 mg/kg (revised dosage regimen) using darunavir suspension <u>15 kg to less than ^(b)₍₄₎ kg</u> : 375 mg (3.8 mL) of darunavir coadministered with 50 mg (0.6 mL) of ritonavir using darunavir tablets or suspension
Proposed Indication for the Application	Treatment of HIV-1 infection in pediatric patients 3 to less than 6 years old
Review Type(s)	New Drug Application for darunavir suspension formulation, priority review (NDA 202895) Labeling supplement (NDA 21976, SDN 201)

Subsequent to the finalization of the Clinical Pharmacology review for NDA 202895 (with the accompanying labeling supplement for NDA 21976), a number of additional review related issues occurred. The issues are discussed below.

1) Revised darunavir dosage regimen

The darunavir review team concluded that for HIV-1 infected pediatric patients weighing 10 kg to 15 kg, darunavir 20 mg/kg coadministered with ritonavir 3 mg/kg twice daily was the most appropriate dosage regimen. The Clinical Pharmacology secondary review (September 27, 2011) discusses the rationale for this decision.

2) Revised population PK analysis for the TMC114-C228 trial

The applicant provided additional information regarding the population pharmacokinetic (PK) analysis that was conducted for the TMC114-C228 trial in September 2011. For the visit two weeks after dosage adjustment (Visit 105), the body weight was not recorded unless this visit occurred at a scheduled visit. If a subject's weight was not recorded, the weight that was to be used was the weight recorded at the dosage adjustment visit (Visit 104). However, the applicant noted that due to a data analysis error, if a weight was not available for Visit 105, the subject's last available weight for the analysis dataset was used instead of the last available weight before Visit 105. Because the darunavir population PK model includes body weight as a covariate, corrected population PK parameters were derived. For the corrected darunavir population PK analysis for the TMC 114-C228 trial, the subject's weight for Visit 105 that was included in the dataset was either the actual weight for the visit (Visit 105) or the weight during the dosage adjustment visit (Visit 104). For each subject, the difference in the weight that was used in the original and corrected analysis for the visit two weeks after dosage adjustment (Visit 105) was 10% or less (see Table 1). In the revised population analysis, subjects 9 and 21 that were originally included in the 15 kg to < 20 kg weight group were included in the 10 kg to < 15 kg weight group.

Table 1-Comparison of the body weight values used for the visit two weeks after dosage adjustment (Visit 105) in the corrected and original darunavir population PK analyses

ID	Corrected Analysis		Original Analysis		% Difference
	Body Weight Group	Body Weight (kg)	Body Weight Group	Body Weight (kg)	
228-0001	15-20	15.8	15-20	16.4	-3.7
228-0003	15-20	16.78	15-20	18.5	-9.3
228-0006	10-15	13.6	10-15	14.45	-5.9
228-0007	15-20	19.7	15-20	21.5	-8.4
228-0009	10-15	14.35	15-20	15.95	-10.0
228-0012	10-15	12	10-15	12.5	-4.0
228-0015	15-20	17.1	15-20	17.6	-2.8
228-0017	10-15	13.3	10-15	15	-11.3
228-0019	15-20	15.2	15-20	15.9	-4.4
228-0020	15-20	17.25	15-20	18.05	-4.4
228-0021	10-15	15	15-20	15.2	-1.3
228-0022	15-20	18	15-20	19	-5.3
228-0025	15-20	16.3	15-20	16.8	-3.0
228-0027	15-20	17.3	15-20	17.7	-2.3
228-0029	10-15	14.1	10-15	14.3	-1.4
228-0034	15-20	15.9	15-20	16.3	-2.5
228-0040	10-15	13.7	10-15	14.3	-4.2
228-0041	15-20	15.5	15-20	16.45	-5.8

Reviewer note:

Subjects 9 and 21 that were originally included in the 15 kg to < 20 kg weight group were included in the 10 kg to < 15 kg weight group with the corrected analysis.

Table 2-Comparison of the AUC values derived from the original and corrected darunavir population PK analysis for the TMC114-C228 trial for the adjusted dosage regimen (darunavir 25 mg/kg combined with ritonavir 3 mg/kg twice daily [10 kg to <15 kg and 380 mg of darunavir combined with 50 mg of ritonavir twice daily [15 kg to < 20 kg])

CRF ID	Original AUC	Revised AUC	Revised AUC - Original AUC	% Difference
228-0001	60397	61028	631	1.0
228-0003	72756.5	73660	903.5	1.2
228-0005	69637	69637	0	0.0
228-0006	99639.5	100500	860.5	0.9
228-0007	114450	115960	1510	1.3
228-0009	83183.5	85521	2337.5	2.8
228-0010	71434	71434	0	0.0
228-0012	104493	105720	1227	1.2
228-0014	52745	52745	0	0.0
228-0015	53747.5	54103	355.5	0.7
228-0017	57108.5	58145	1036.5	1.8
228-0018	58278	58278	0	0.0
228-0019	59794.5	60084	289.5	0.5
228-0020	51976.5	52487	510.5	1.0
228-0021	158280	158710	430	0.3
228-0022	79244.5	80322	1077.5	1.4
228-0025	87626.5	88028	401.5	0.5
228-0027	64703.5	64918	214.5	0.3
228-0029	130025	130480	455	0.3
228-0034	85447	85967	520	0.6
228-0040	90660	91855	1195	1.3
228-0041	56650	57373	723	1.3
228-0042	68634	68634	0	0.0

Reviewer note:

Two subjects originally included in the 15 kg to < 20 kg weight group were included in the 10 kg to < 15 kg weight group with the corrected analysis.

After a review of the revised population PK analysis, the Clinical Pharmacology review team recommended the reinstatement of the population PK data for subject 21 in the 15 to < 20 kg weight group rather than in the 10 kg to < 15 kg group because the subject received 380 mg of darunavir in combination with 48 mg twice daily of ritonavir throughout the post dosage adjustment period. The applicant agreed with this recommendation. The subsequent updated population PK analysis that includes this change is displayed in section 4.

3) European Medicines Agency (EMA) clinical trial site inspection results

A major amendment was submitted to the U.S. Food and Drug Administration in September 2011 that contained the inspection results of three clinical trial sites that enrolled HIV-1 infected pediatric subjects in the TMC114-C228 trial. The inspections were conducted by the European Medicines Agency.

Based on the European Medicines Agency inspection results, the darunavir review team determined that the pharmacokinetic data for the TMC114-C228 trial should exclude all results obtained from the site where Robert Kimutai was the principal investigator.

The major Clinical Pharmacology issue that was identified from the inspection reports

was the storage of darunavir and ritonavir plasma samples at -70°C instead of -20°C at the clinical trial sites. The applicant had previously stated that all plasma samples were stored at -20°C. To date, the long term stability data for darunavir and ritonavir plasma samples has been generated at -20°C only. In response to comments from the Clinical Pharmacology reviewer, the following information in Table 3 was provided regarding the storage of plasma samples at -70°C instead of -20°C at the trial sites. In response to comments from the Division of Antiviral Products, the applicant stated that -70°C long term sample stability data would be generated for up to one year with submission of -70°C long term sample stability data for 37 days by December 15, 2011. The data was not available at the time the addendum was finalized. With the exclusion of plasma samples from the Kimuati clinical trial site (KE00004), the longest duration that plasma samples were stored at -70°C was 7 days. Overall, the storage of plasma samples at -70°C for up to 7 days is not anticipated to significantly impact the reported darunavir and ritonavir plasma concentrations for the TMC114-C228 trial.

Table 3-Information regarding storage of darunavir/ritonavir plasma samples at -70 °C at clinical trials sites

Site ID	Total number of subjects at site	Number of subjects with samples at -70 °C	Total number of samples stored at -70 °C	Maximum time at -70 °C of any sample (days)
AR00004	2	0	0	-
AR00038	1	0	0	-
AR00052	1	0	0	-
BR00008	2	2	26	4
BR00026	2	0	0	-
BR00051	2	2	26	6
IN00014	1	1	19	3
KE00004	6	6	75	106
ZA00017	4	4	64	7
ZA00042	1	1	17	4
ZA00164	5	0	0	-
	27	16	227	

Reviewer note:

There was one sample with a storage time that could not be determined. The clinical trial site that this sample was stored at was not specified by the applicant.

4) Revised population PK analysis data for the TMC114-C228 trial and revisions to the darunavir U.S. prescribing information

The applicant provided updated tables and figures below for the TMC114-C228 trial that include the changes discussed in sections 2 and 3 of this addendum.

A) Pre dose adjustment week 2 population PK analysis

The applicant did not provide updated week 2 population PK parameters for the pre dose adjustment week 2 population PK analysis (darunavir 20 mg/kg combined with ritonavir 3 mg/kg twice daily).

Reviewer note:

1) On page 39 of the original Clinical Pharmacology review for NDA 202895, subject 33, not subject 30, was excluded because the ritonavir plasma concentrations were all below the lower limit of quantification.

B) Post dose adjustment (2 weeks after dose adjustment) population PK analysis

Table 4-Corrected darunavir population PK analysis results from the Week 24 analysis for the adjusted dosage regimen 2 weeks after dose adjustment (darunavir 25 mg/kg combined with ritonavir 3 mg/kg twice daily [10 kg to <15 kg and 380 mg of darunavir combined with 50 mg of ritonavir twice daily [15 kg to < 20 kg])

Body Weight Group	N	Geometric Mean	Mean	SD	5 th Percentile	Median	95 th Percentile
<i>AUC_{12h} (ug.h/mL)</i>							
All subjects	18	84.2	89.5	33.3	54.8	84.3	145
10 to < 15 kg	6	102	105	28.7	68.1	107	137
15 to < 20 kg	12	76.6	81.6	33.7	53.6	70.3	136
<i>C_{0h} (ng/mL)</i>							
All subjects	18	5182	5762	2759	2829	5416	10218
10 to < 15 kg	6	6839	7234	2384	4026	7563	9707
15 to < 20 kg	12	4511	5027	2723	2828	4418	9433

Reviewer note:

1) For the post dose adjustment (2 weeks after dose adjustment) population PK analysis that was generated for the Data Safety Monitoring Board (DSMB) and the analysis presented in Table 4, the same subjects were excluded with one exception: instead of excluding subject 38 that did not have a AAG concentration measured by the central laboratory, subject 15 was excluded from the DSMB analysis due to a data management error.

Table 5-Original darunavir population PK analysis results derived from the Week 24 analysis for the adjusted dosage regimen 2 weeks after dose adjustment (darunavir 25 mg/kg combined with ritonavir 3 mg/kg twice daily [10 kg to <15 kg and 375 mg of darunavir combined with 50 mg of ritonavir twice daily [15 to < 20 kg])

Weight group	N	Geometric Mean	Mean	SD	5 th Percentile	Median	95 th Percentile
<i>AUC_{12h} (µg.h/mL)</i>							
All subjects	18	82.3	87.6	33.1	53.8	81.4	144
10 to <15 kg	4	117	118	19.1	97.2	119	137
15 to <20 kg	14	74.5	79.0	31.4	53.0	68.6	127
<i>C_{0h} (ng/mL)</i>							
All subjects	18	5061	5636	2737	2774	5168	10147
10 to <15 kg	4	8313	8394	1326	6924	8522	9686
15 to <20 kg	14	4392	4848	2526	2771	4365	8744

Reviewer note:

In the original Clinical Pharmacology review for NDA 202895, the corresponding table is Table 15, page 41.

C) Population PK analysis for the initial dosage regimens

Table 6-Corrected darunavir population PK analysis results for the initial dosage regimen (darunavir 20 mg/kg combined with ritonavir 3 mg/kg twice daily)

Parameter	Weight	N	Mean	Geo Mean	SE	SD	95% CI	Min	5 th Perc.	25 th Perc.	Median	75 th Perc.	95 th Perc.	Max
AUC _{tau} (µg.h/mL)	All subjects	19	66.9	62.7	5.9	25.7	55.3 - 78.4	31.1	35.8	49.9	61.4	79.9	113	131
	10 to <15 kg	10	68.7	65.3	8.1	25.5	52.9 - 84.5	46.0	46.6	52.8	61.6	71.2	113	131
	15 to <20 kg	9	64.8	59.8	9.1	27.2	47.1 - 82.6	31.1	33.2	48.8	53.4	85.8	103	111
C _{0h} (ng/mL)	All subjects	19	4218	3786	470	2047	3298 - 5139	1382	1811	2735	3769	5426	7574	9488
	10 to <15 kg	10	4429	4098	653	2064	3150 - 5709	2576	2642	3127	4010	4682	7937	9488
	15 to <20 kg	9	3984	3467	709	2126	2595 - 5373	1382	1572	2573	3296	6063	6905	7361
C _{ss,ave} (ng/mL)	All subjects	19	5573	5221	491	2139	4611 - 6534	2592	2980	4160	5120	6659	9447	10946
	10 to <15 kg	10	5725	5446	673	2128	4406 - 7044	3837	3885	4402	5135	5935	9379	10946
	15 to <20 kg	9	5403	4983	756	2267	3922 - 6884	2592	2764	4066	4449	7147	8616	9281
CL/F (L/h)	All subjects	19	5.08	4.74	0.47	2.06	4.16 - 6.01	2.13	3.03	3.79	4.24	6.08	9.01	10.7
	10 to <15 kg	10	4.25	4.10	0.35	1.11	3.56 - 4.94	2.13	2.58	3.89	4.24	4.78	5.77	6.17
	15 to <20 kg	9	6.01	5.58	0.84	2.51	4.37 - 7.65	3.65	3.65	3.73	6.00	7.04	9.93	10.7

Geo = Geometric; Perc. = Percentile

NB: Subjects 228-0005, 228-0010, 228-0014, 228-0018, 228-0033, 228-0038, 228-0042 and 228-0030 were the 8 subjects excluded from this table out of 27 subjects.

Reviewer note:

The population PK analysis includes the pharmacokinetic data from weeks 2 and 4.

Table 7-Original darunavir population PK analysis results for the initial dosage regimen (darunavir 20 mg/kg combined with ritonavir 3 mg/kg twice daily)

Parameter	Weight	N	Mean	Geometric Mean	SE	SD	95% CI	Minimum	5th Percentile	25th Percentile	Median	75th Percentile	95th Percentile	Maximum
AUC _{12h} (ng.h/mL)	All	19	66.9	62.4	6.0	26.1	55.1 - 78.7	27.1	35.4	50.0	61.8	80.5	114	132
	10 - < 15 kg	10	68.9	65.6	8.1	25.5	53.0 - 84.8	46.7	47.1	52.8	61.8	71.4	113	132
	15 - < 20 kg	9	64.7	59.1	9.4	28.1	46.3 - 83.1	27.1	30.8	49.0	53.5	86.9	104	112
C _{0h} (ng/mL)	All	19	4220	3749	477	2081	3285 - 5155	1057	1783	2761	3773	5432	7642	9498
	10 - < 15 kg	10	4445	4117	651	2059	3169 - 5721	2607	2682	3126	4025	4695	7943	9498
	15 - < 20 kg	9	3969	3379	733	2200	2532 - 5406	1057	1380	2588	3306	6124	6956	7435
C _{ss,ave} (ng/mL)	All	19	5575	5201	499	2175	4597 - 6553	2256	2951	4168	5151	6709	9514	10956
	10 - < 15 kg	10	5740	5463	671	2123	4425 - 7055	3889	3924	4402	5153	5951	9385	10956
	15 - < 20 kg	9	5391	4924	782	2345	3858 - 6924	2256	2565	4083	4460	7243	8667	9354
CL/F (L/h)	All	19	5.15	4.76	0.53	2.31	4.11 - 6.19	2.13	3.03	3.76	4.23	6.06	9.15	12.26
	10 - < 15 kg	10	4.23	4.09	0.35	1.10	3.54 - 4.92	2.13	2.58	3.89	4.22	4.78	5.72	6.13
	15 - < 20 kg	9	6.17	5.64	0.97	2.91	4.27 - 8.07	3.63	3.63	3.68	5.98	7.01	10.88	12.26

Reviewer notes:

- 1) The units in the table should be $\mu\text{g}/\text{mL} \cdot \text{hr}$ for $AUC_{(0-12h)}$
- 1) The population PK analysis includes the pharmacokinetic data from weeks 2 and 4.
- 2) In the original Clinical Pharmacology review for NDA 202895, the corresponding table is Table 17, page 42.

D) Population PK analysis for the adjusted dosage regimens

Table 8-Corrected darunavir population PK analysis results for the adjusted dosage regimen (darunavir 25 mg/kg combined with ritonavir 3 mg/kg twice daily [10 kg to <15 kg and 380 mg of darunavir combined with 50 mg of ritonavir twice daily [15 to < 20 kg])

Parameter	Weight	N	Mean	Geo Mean	SE	SD	95% CI	Min	5 th Perc.	25 th Perc.	Median	75 th Perc.	95 th Perc.	Max
AUC _{tau} ($\mu\text{g} \cdot \text{h}/\text{mL}$)	All subjects	18	84.7	80.5	6.87	29.1	71.3 - 98.2	52.5	53.9	60.3	82.9	98.3	135	159
	10 to <15 kg	6	95.4	92.7	9.77	23.9	76.2 - 115	58.1	65.0	87.1	96.2	104	124	130
	15 to <20 kg	12	79.4	75.1	8.94	31.0	61.9 - 96.9	52.5	53.4	59.4	69.3	86.5	135	159
C _{0h} (ng/mL)	All subjects	18	5383	4918	568	2412	4269 - 6497	2733	2753	3217	4926	7028	9351	11300
	10 to <15 kg	6	6433	6142	797	1953	4870 - 7996	3299	3791	5595	6879	7244	8572	9007
	15 to <20 kg	12	4858	4400	728	2521	3432 - 6284	2733	2746	3051	4469	5141	9341	11300
C _{ss,ave} (ng/mL)	All subjects	18	7059	6710	572	2428	5938 - 8181	4374	4488	5027	6910	8195	11226	13225
	10 to <15 kg	6	7947	7722	814	1993	6352 - 9542	4845	5416	7259	8015	8701	10357	10873
	15 to <20 kg	12	6615	6255	745	2580	5155 - 8076	4374	4448	4950	5774	7207	11266	13225
CL/F (L/h)	All subjects	18	4.87	4.63	0.363	1.54	4.16 - 5.59	2.40	2.72	3.60	4.79	6.19	7.06	7.24
	10 to <15 kg	6	3.92	3.78	0.494	1.21	2.95 - 4.89	2.78	2.80	3.01	3.80	4.23	5.58	6.03
	15 to <20 kg	12	5.35	5.12	0.434	1.50	4.50 - 6.20	2.40	2.89	4.46	5.51	6.43	7.13	7.24

Geo = Geometric; Perc. = Percentile

NB: Subjects 228-005, 228-0010, 228-0014, 228-0018, 228-0026, 228-0030, 228-0033, 228-0038 and 228-0042 were the 9 subjects excluded from this table out of the 27 subjects.

Reviewer note:

- 1) The population PK analysis includes the pharmacokinetic data from 2 weeks after dosage adjustment and week 24.
- 2) The following additional subjects were excluded: 5, 10, 14, 18 and 42.

Table 9-Original darunavir population PK analysis results for the adjusted dosage regimen (darunavir 25 mg/kg combined with ritonavir 3 mg/kg twice daily [10 kg to <15 kg and 380 mg of darunavir combined with 50 mg of ritonavir twice daily [15 to < 20 kg])

Parameter	Weight	N	Mean	Geometric Mean	SE	SD	95% CI	Minimum	5th Percentile	25th Percentile	Median	75th Percentile	95th Percentile	Maximum
AUC _{0-12h} (ng.h/mL)	All	23	79.6	75.9	5.7	27.1	68.4 - 90.8	52.0	52.8	59.0	71.4	89.1	128	158
	10 - < 15 kg	7	87.1	83.6	10.2	26.9	67.1 - 107	57.1	57.5	64.0	90.7	102	122	130
	15 - < 20 kg	16	76.3	72.8	6.8	27.4	63.0 - 89.6	52.0	52.6	59.0	70.0	83.7	125	158
C _{0h} (ng/mL)	All	23	4993	4600	463	2220	4086 - 5900	2708	2749	3221	4227	6121	8842	11270
	10 - < 15 kg	7	5833	5474	816	2158	4234 - 7432	3251	3358	3917	6488	7144	8442	8974
	15 - < 20 kg	16	4626	4263	553	2212	3542 - 5710	2708	2727	3050	4031	4955	8555	11270
C _{ss,ave} (ng/mL)	All	23	6634	6326	471	2258	5711 - 7557	4331	4404	4920	5953	7429	10706	13190
	10 - < 15 kg	7	7260	6963	848	2244	5598 - 8922	4759	4788	5330	7555	8506	10197	10835
	15 - < 20 kg	16	6360	6066	570	2281	5243 - 7477	4331	4379	4917	5836	6979	10451	13190
CL/F (L/h)	All	23	5.08	4.86	0.30	1.45	4.49 - 5.67	2.41	2.80	4.29	5.17	6.21	7.19	7.32
	10 - < 15 kg	7	4.26	4.09	0.48	1.28	3.32 - 5.20	2.79	2.82	3.17	4.24	5.16	5.84	6.13
	15 - < 20 kg	16	5.44	5.24	0.35	1.41	4.75 - 6.13	2.41	3.11	4.48	5.43	6.48	7.23	7.32

Reviewer notes:

1) The population PK analysis includes the pharmacokinetic data from 2 weeks after dosage adjustment and week 24.

2) In the original Clinical Pharmacology review for NDA 202895, the corresponding table is Table 19, page 43.

E) Exposure-response information

Figure 1-Corrected darunavir analysis for the comparison of AUC_(0-12h) and C_{0h} (for the adjusted darunavir dosage regimens) for subjects either achieving virologic response or not achieving virologic response (HIV-1 RNA less than 50 copies/mL)

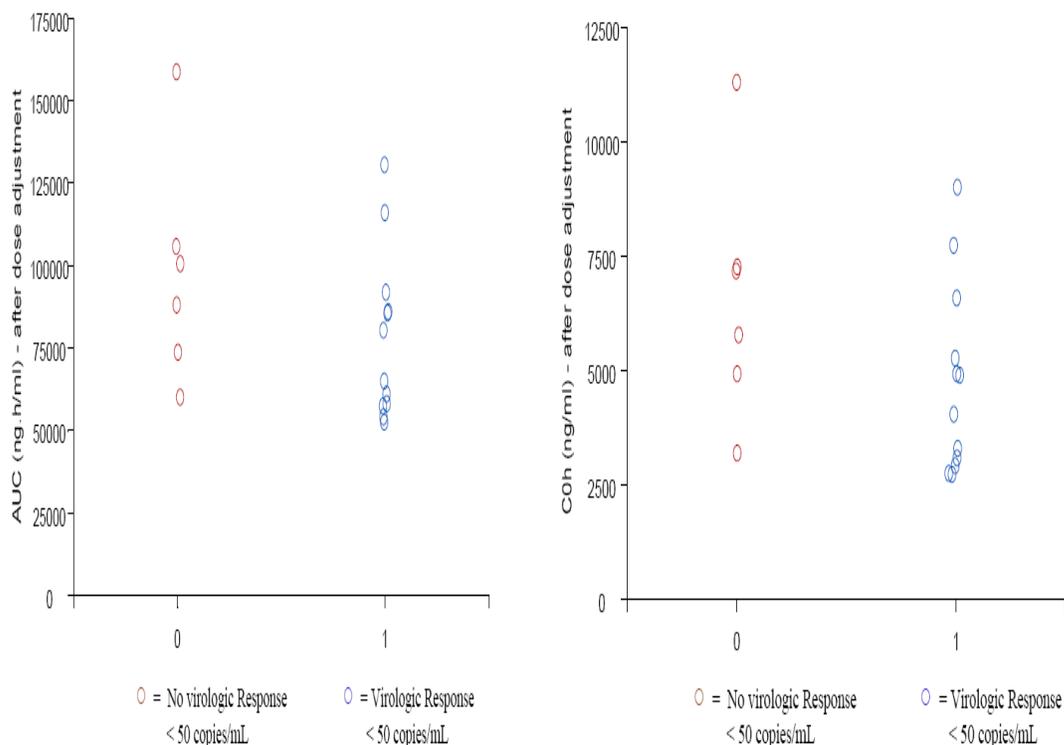
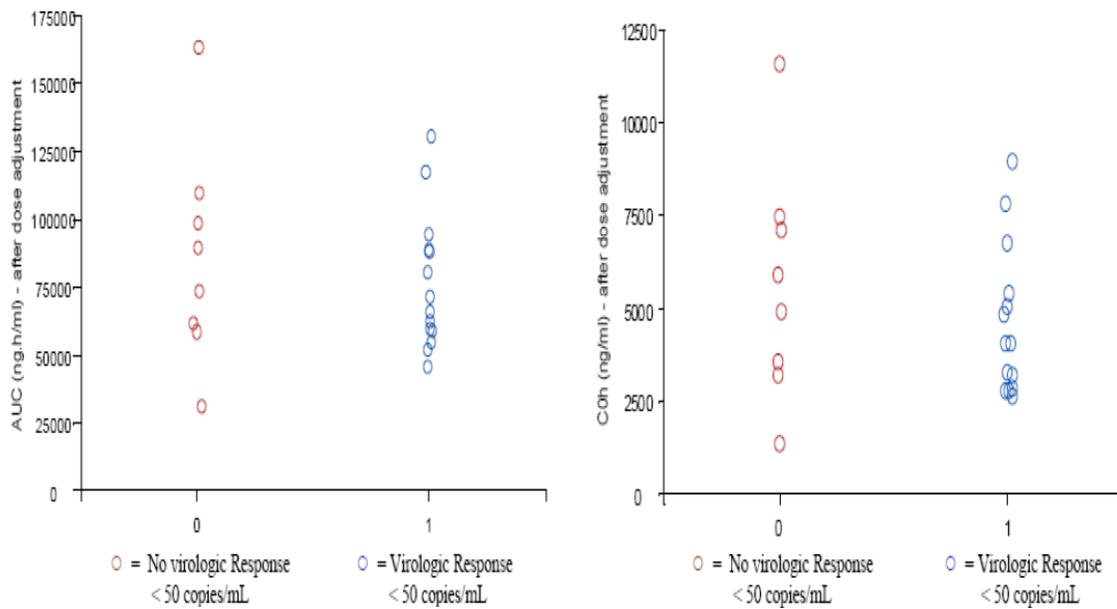


Figure 2-Original darunavir analysis for the comparison of $AUC_{(0-12h)}$ and C_{0h} (for the adjusted darunavir dosage regimens) for subjects either achieving virologic response or not achieving virologic response (HIV-1 RNA less than 50 copies/mL)



Reviewer note:

In the original Clinical Pharmacology review for NDA 202895, the corresponding figures are Figure 3 (page 9), and Figure 3 (page 47).

Table 10-Corrected comparison of the mean darunavir AUC_(0-12h) values prior to and subsequent to the adjustment of the darunavir dosage regimens to the mean target adult exposure (including the original and corrected analysis)

	Before Dose Adjustment			After Dose Adjustment		
	Overall	10 to <15 kg	15 to <20 kg	Overall	10 to <15 kg	15 to <20 kg
DSMB analysis ¹	105%	113%	95%	124%	142%	110%
Revised analysis ²	107%	110% ⁴	104%	136%	153%	127%
Original analysis ³	107%	111% ⁴	104%	128%	140%	122%

1: Subjects 228-0030, 228-0033 and 228-0042 where the 3 subjects excluded before dose adjustment. Subjects 228-0005, 228-0010, 228-0014, 228-0015, 228-0018, 228-0026, 228-0030, 228-0033 and 228-0042 where the 9 subjects excluded after dose adjustment (only DSMB analysis after dose adjustment contains Visit 105).

²: Subjects 228-0005, 228-0010, 228-0014, 228-0018, 228-0033, 228-0038, 228-0042 and 228-0030 were the 8 subjects excluded before dose adjustment; 228-0005, 228-0010, 228-0014, 228-0018, 228-0026, 228-0030, 228-0033, 228-0038 and 228-0042 were the 9 subjects excluded after dose adjustment.

³: Subjects 228-0005, 228-0010, 228-0014, 228-0018, 228-0033, 228-0038, 228-0042 and 228-0030 were the 8 subjects excluded before dose adjustment; Subjects 228-0026, 228-0033, 228-0038 and 228-0030 were the 4 subjects excluded after dose adjustment.

⁴: Difference in the percentages lies in the rounding of the values (the difference between the two values is 0.3%)

Reviewer notes:

- 1) The mean AUC_(0-12h) values in Tables 6 through 9 are compared to the mean adult target exposure of 62.3 µg/mL*hr
- 2) The mean of the median individual darunavir AUC_(0-12h) values are compared.
- 3) The higher percentage difference in AUC_(0-12h) for the 10 kg to < 15 group with the revised analysis is not attributed to a significant change in AUC values for individual subjects(see Table 2).

Table 11-Original comparison of the mean darunavir AUC_(0-12h) values prior to and subsequent to the adjustment of the darunavir dosage regimens to the mean target adult exposure

Before Dose Adjustment			After Dose Adjustment		
Overall	10 to < 15 kg	15 to < 20 kg	Overall	10 to < 15 kg	15 to < 20 kg
107%	111%	104%	128%	140%	122%

Reviewer notes:

- 1) The mean AUC_(0-12h) values in Tables 7 and 9 are compared to the mean adult target exposure of 62.3 µg/mL*hr.
- 2) The mean of the median individual darunavir AUC_(0-12h) values are compared.
- 3) In the original Clinical Pharmacology review for NDA 202895, the corresponding tables are Table 9 (page 8), and Table 20 (page 44).

F) Changes to the proposed revisions for the darunavir U.S. prescribing information (Table 11)

Table 12-Original proposed population PK parameters for the TMC114-C228 trial using the original population PK analysis

Table 11: Population Pharmacokinetic Estimates of Darunavir Exposure (Study TMC114-C212 and Study TMC114-C228) Following Administration of Doses in Tables 1 and 2

TMC114-C228	N=23
AUC _{24h} (ng·h/mL)*	142868 (103954-316560)
C _{0h} (ng/mL)	4227 (2708-11270)
N = number of subjects with data.	
*AUC _{24h} is calculated as AUC _{12h} *2	

Table 13-Final proposed population PK parameters that are included in Table 11 for the TMC114-C228 trial incorporating the changes discussed in the addendum

Table 11: Population Pharmacokinetic Estimates of Darunavir Exposure (Study TMC114-C212 and Study TMC114-C228) Following Administration of Doses in Tables 1 and 2

Parameter	Study TMC114-C212 PREZISTA/ ritonavir twice daily N = 74	Study TMC114-C228 PREZISTA/ ritonavir twice daily*	
		10 to less than 15 kg [†] N = 10	15 to less than 20 kg [§] N = 12
AUC _{24h} (ng·h/mL) [†]			
Mean ± Standard Deviation	126377 (34356)	137399 ± 51067	158773 ± 61932
Median (Range)	127340 (67054-230720)	123229 (92098-262720)	138578 (104974-317420)
C _{0h} (ng/mL)			
Mean ± Standard Deviation	3948 (1363)	4429 ± 2064	4858 ± 2521
Median (Range)	3888 (1836-7821)	4010 (2576-9488)	4469 (2733-11300)

N = number of subjects with data.

* Subjects may have contributed data to more than one weight category.

[†] AUC_{24h} is calculated as AUC_{12h}*2

[‡] Population pharmacokinetic parameter estimates based on the Week 2 and 4 analysis that evaluated a darunavir dose of 20 mg/kg twice daily with ritonavir 3 mg/kg twice daily.

[§] The 15 kg to less than 20 kg weight group received 380 mg (3.8 mL) PREZISTA oral suspension twice daily with 48 mg (0.6 mL) ritonavir oral solution twice daily in TMC114-C228. Population pharmacokinetic parameter estimates based on the Week 2 and Week 24 analysis that evaluated a darunavir dose of 380 mg twice daily.

The revised Table 11 in the darunavir U.S prescribing information is acceptable with the exception of the recommended change to one of the footnotes displayed below if the footnote is meant to convey that the same subjects may be included in both the 10 kg to <15 weight group and the 15 kg to < 20 kg weight group.

Original text	Revised Text
(b) (4)	Subjects may have contributed PK data to both the 10 kg to < 15 kg weight group and the 15 kg to < 20 kg weight group.

5) Conclusions

Overall, the changes that were made to the population pharmacokinetic analysis, the storage of darunavir and ritonavir plasma samples at (b) (4) C instead of -20°C at the clinical trial sites, and the exclusion of subjects from the Kimuati clinical trial site for the TMC114-C228 trial that are discussed in this addendum do not change the reviewer’s conclusions for the exposure-response or exposure-safety information from the TMC114-C228 trial.

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/s/

STANLEY AU
12/08/2011

SARAH M ROBERTSON
12/08/2011

CLINICAL PHARMACOLOGY - SECONDARY REVIEW

Date	September 21, 2011
From	Sarah Robertson, Pharm.D.
Subject	Secondary review
NDA #	202-895 21-976 (S-020)
Applicant	Tibotec, Inc
Date of Submission	March 29, 2011
PDUFA Goal Date	September 30, 2011
Proprietary Name / Established (USAN) names	PREZISTA (darunavir)
Dosage forms / Strength	Proposed: Oral suspension, 100 mg/mL Approved: 300 mg and 150 mg tablets
Proposed Indication(s)	Treatment of HIV-1 infection in pediatric patients 3 to 6 years

Introduction

I agree with the findings and conclusions of Dr. Stanley Au in his review of the NDA for Prezista Oral Suspension (review date 9-6-11). However, subsequent to finalizing Dr. Au's review, the interdisciplinary review team further discussed the dose proposed by the Sponsor and concluded that an alternative dose should be approved for children weighing 10 to <15 kg.

As summarized in Dr. Au's review, the applicant's proposed dose of Prezista Oral Suspension for pediatric patients weighing 10 to <15 kg is (b) (4) mg/kg with ritonavir 3 mg/kg twice daily. For pediatric patients weighing at least 15 kg, the proposed dose is 375 mg with 50 mg ritonavir twice daily. The applicant's proposed doses were based on PK and 24-week safety and efficacy findings in pediatric patients 3 to <6 years of age in Study C228. Upon further review of the PK data from C228, and when considering the scarcity of safety data for the higher dose of (b) (4) mg/kg, the review team has concluded the approved dose for children weighing 10 to <15 kg should be 20 mg/kg instead of (b) (4) mg/kg. The review team agrees with the applicant on the 375 mg dose for patients weighing at least 15 kg. This secondary review summarizes the clinical pharmacology data which support the final recommended darunavir dose of 20 mg/kg with ritonavir 3 mg/kg for pediatric patients weighing 10 to <15 kg.

Clinical Pharmacology Findings

The initial dose given to all weight groups enrolled in C228 was ~20 mg/kg of darunavir oral suspension with ~3 mg/kg ritonavir oral suspension twice daily. The Week 2 PK data derived from non-compartmental analysis of the 20 mg/kg dose showed that mean darunavir AUC_{12h} in both the 10 to <15 kg and 15 to <20 kg weight groups fell within the pre-defined exposure limits of 80-130% of the adult mean AUC_{12h} (62.3 µg.h/mL). However, at that time the applicant performed additional simulations using a previously developed population PK model which suggested low-weight children may have lower exposure. Based on their simulations, a decision was made to change the dose of darunavir to 25 mg/kg twice daily in patients weighing 10 to <15 kg and to a fixed 375 mg dose for patients weighing 15 to <20 kg. Subsequent to alteration in dose in C228, the applicant realized a relative bioavailability parameter was erroneously not accounted for in the model. The simulations were repeated with the bioavailability correction, and results of the repeated simulation indicated higher predicted exposure than the original simulation. Tibotec met with the DSMB to discuss the error, at which point safety data were available for Week 24. The DSMB found no safety concerns at Week 24 and agreed the study could continue at the higher dose of 25 mg/kg in children weighing 10 to <15 kg.

A summary of the PK parameter estimates for the 10 to < 15 kg cohort obtained before and after dose adjustment is as follows:

Table 1. Summary of darunavir PK estimates obtained before and after dose adjustment for the 10 to <15 kg weight cohort

Parameter	N	Mean (SD)	Geometric Mean	95% CI	Min	Max
20 mg/kg (before dose adjustment)						
AUC _{tau} (µg.h/mL)	10	68.7 (25.5)	65.3	52.9 – 84.5	46.0	131
C _{0h} (ng/mL)	10	4429 (2064)	4098	3150 – 5709	2576	9488
25 mg/kg (after dose adjustment)						
AUC _{tau} (µg.h/mL)	9	95.4 (33.4)	90.5	73.6 – 117	58.1	159
C _{0h} (ng/mL)	9	6414 (2637)	5943	4692 – 8137	3299	11300

Note: Data in table are based on the revised Week 24 analysis submitted as an addendum to the NDA on 9-9-11. See full review of the addendum by Dr. Stanley Au for further details.

Before dose adjustment, the mean AUC_{12h} for the 10 to <15 kg weight group was approximately 110% of the adult mean target. After dose adjustment, the mean AUC_{12h} increased to approximately 150% of the adult mean target. The following table displays the population PK model predicted estimates in adults receiving the commercial formulation of PREZISTA at the approved dose of 600/100 mg BID:

Table 2. Summary darunavir exposure estimates in adults for the commercial formation of PREZISTA at the approved dose of 600/100 mg BID

Study #	N	Mean (%CV)	Median	Min	Max
AUC_{tau} (µg.h/mL)					
202	135	67.1 (33%)	63.0	25.6	138
213	122	65.8 (36%)	61.6	38.0	233
215	292	65.1 (31%)	59.9	28.1	148
C_{0h} (ng/mL)					
202	135	3812 (44%)	3651	521	9958
213	122	3897 (39%)	3566	1611	9859
215	292	4119 (40%)	3806	1233	10761

Note: Data obtained from the pharmacometrics review of the original NDA for PREZISTA (6-23-06)

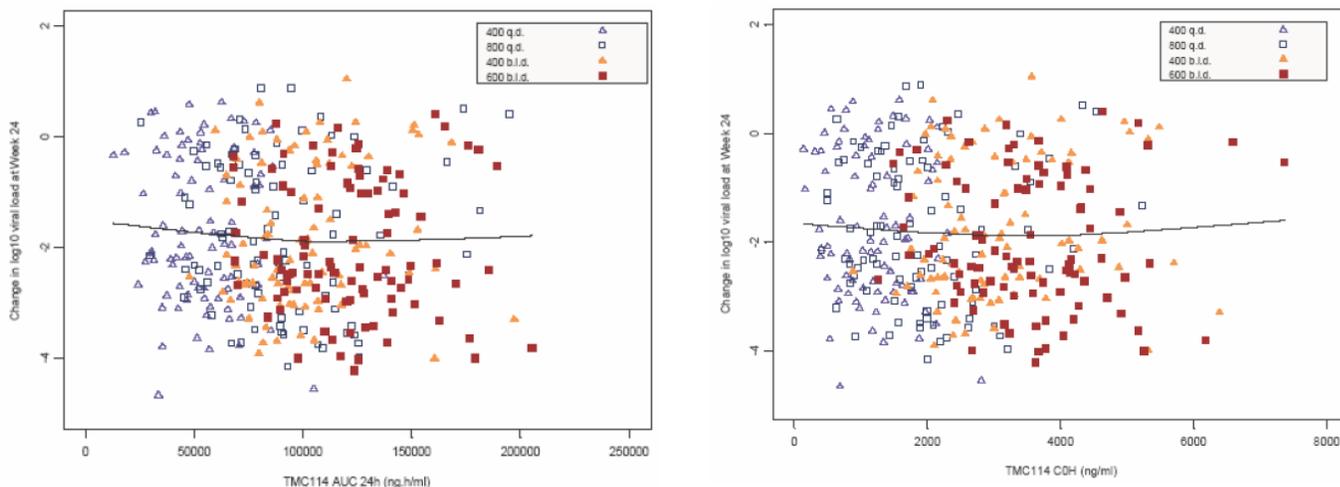
When comparing the variability observed in pediatric patients relative to that of adults, the %CV in children is similar to that observed in adults for both AUC and C_{0h}. In addition, the minimum and maximum value observed in children at the lower dose of 20 mg/kg is within the range of exposure observed in adults. In contrast, the higher dose of 25 mg/kg may result in higher exposure in some children relative to the upper margin of exposure observed in adults (95th percentile of AUC_{12h} = 137 µg.h/mL in children vs. maximum individual adult values of 138 – 233 µg.h/mL).

The exposure-response analysis for efficacy in the original Prezista NDA for treatment-experienced adults revealed a flat relationship for darunavir exposure down to a dose of 400/100 mg QD. Instead, virologic response was strongly correlated with the inhibitory quotient of darunavir, with the relationship primarily being driven by fold-change in susceptibility and less by exposure to darunavir. Figure 1 displays the individual change in viral load from baseline to Week 24 versus darunavir exposure. These data further support the appropriateness of the 20 mg/kg dose for pediatric subjects 10 to <15 kg, as the exposure

Team Leader Review

estimates at this dose are well within acceptable limits for efficacy as demonstrated in a treatment-experienced adult population, even for children with the lowest predicted exposure.

Figure 1. Individual change in \log_{10} viral load from baseline to Week 24 versus darunavir AUC_{24} and C_{0h} in treatment-experienced adults



Note: Figure from the pharmacometrics review of the original NDA for PREZISTA (6-23-06)

Recommendation

Based on my review of the comprehensive PK data submitted by the applicant, and taking into account previously reviewed exposure data and exposure-response data in adults, I concur with the review team and recommend the final approved dose of darunavir be 20 mg/kg for pediatric patients weighing 10 to <15 kg.

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/s/

SARAH M ROBERTSON
09/27/2011

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 202895	Submission Date: March 30, 2011
NDA: 21976 (SDN 201, S-20)	Submission Date: June 28, 2011
Brand Name	Prezista®
Generic Name	Darunavir
Reviewer	Stanley Au, Pharm.D., BCPS
Pharmacometrics Reviewer	Jiang Liu, Ph.D.
Pharmacometrics Team Leader	Pravin Jadhav, Ph.D.
Clinical Pharmacology Team Leader	Sarah Robertson, Pharm.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products
Applicant	Tibotec, Inc.
Formulation; strength(s) to-be-marketed	Darunavir oral suspension (100 mg/mL)
Currently marketed formulations	Darunavir tablets; 75 mg, 150 mg, 400 mg, 600 mg
Proposed darunavir suspension dosage regimens coadministered with ritonavir solution	Twice daily dosing with food:  (b) (4)
Proposed Indication for the Application	Treatment of HIV-1 infection in pediatric patients 3 to less than 6 years old
Review Type(s)	New Drug Application for darunavir suspension formulation, priority review (NDA 202895) Labeling supplement (NDA 21976, SDN 201)

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1 Executive Summary

This review summarizes the clinical pharmacology results for two trials evaluating darunavir oral suspension formulations. Darunavir, an inhibitor of the HIV-1 protease when coadministered with ritonavir, another HIV-1 protease inhibitor, is approved for the treatment of HIV-1 infection. In treatment naive patients and treatment experienced adult patients with no darunavir resistance associated substitutions, the recommended dosage regimen is 800 mg of darunavir coadministered with 100 mg of ritonavir once daily with food. In treatment experienced adult patients with one or more darunavir resistance associated substitutions, the recommended dosage regimen is 600 mg of darunavir coadministered with 100 mg of ritonavir twice daily with food. The recommended dosing for HIV-1 infected children 6 to less than 18 years old that weigh at least 20 kg using darunavir tablets is displayed in Table 1 below. For the current submission that extends dosing to pediatric patients weighing at least 10 kg using the darunavir oral suspension, the proposed dosage regimens are (b) (4)

Table 1-Current darunavir/ritonavir dosing recommendations for HIV-1 infected children 6 to less than 18 years old weighing at least 20 kg (administered with food)

Body Weight		Dose
(kg)	(lbs)	
≥ 20 kg – < 30 kg	≥ 44 lbs – < 66 lbs	375 mg PREZISTA/50 mg ritonavir twice daily
≥ 30 kg – < 40 kg	≥ 66 lbs – < 88 lbs	450 mg PREZISTA/60 mg ritonavir twice daily
≥ 40 kg	≥ 88 lbs	600 mg PREZISTA/100 mg ritonavir twice daily

Note: In Table 1, darunavir tablets are coadministered with ritonavir capsules, tablets, or oral solution

A New Drug Application for the darunavir oral suspension (NDA 202895) was submitted by the applicant to complete the fulfillment of postmarketing study commitments for deferred pediatric studies as required by the Pediatric Research Equity Act (PREA). In addition, a labeling supplement was submitted under the NDA for darunavir tablets (NDA 21976) that included the same proposed changes to the U.S. darunavir prescribing information that were submitted for NDA 202895.

Two trials were submitted as part of the New Drug Application for the darunavir oral suspension. The first trial (TMC114-C169) was a bioequivalence trial comparing a darunavir oral suspension formulation to darunavir tablets in healthy adult subjects. The trial evaluated an experimental darunavir oral suspension that was linked to the darunavir suspension formulation that is proposed for marketing in the United States through a biowaiver. Because the applicant proposed to permit darunavir tablet dosing in HIV-1

infected pediatric patients 15 kg to 20 kg and darunavir suspension dosing in HIV-1 infected adults and children who are not able to swallow darunavir tablets in the proposed revisions to the darunavir U.S. prescribing information, and no other clinical trial data is currently available to support these labeling changes, the TMC114-C169 trial was a pivotal bioequivalence trial. Based on the clinical trial site inspection, the Office of Scientific Investigations recommended that the results of the trial should not be accepted. While a 483 observation was not issued, the recommendation was made because the TMC114-C169 trial did not store reserve samples for the test and reference drug products. The applicant did not retain reserve samples because they did not view the TMC114-C169 trial as a pivotal bioequivalence trial. However, the Office of Clinical Pharmacology determined that it was acceptable to review the pharmacokinetic data from the multiple dosing portion of the TMC114-C169 trial. The inclusion of the additional adult and pediatric dosing recommendations in Tables 3, 4, and 5 as part of the U.S prescribing information for darunavir is supported by the following information:

1) In adults receiving 600 mg darunavir coadministered with ritonavir 100 mg twice daily with food, when the multiple dosing darunavir suspension $AUC_{(0-12h)}$ value of 58550 ng*hr/mL was compared to historical data for multiple dosing darunavir tablet $AUC_{(0-12h)}$ values of 46250 ng*hr/mL, 44750 ng*hr/mL, 52310 ng*hr/mL, and 46720 ng*hr/mL from the TMC125-C139 (darunavir-etravirine), TMC114-C123 (darunavir-didanosine), TMC114-C172 (darunavir-carbamazepine), and TMC114-C163 (darunavir-rifabutin) drug-drug interaction trials, the darunavir suspension $AUC_{(0-12h)}$ was higher by 27%, 31%, 12%, and 25%, respectively. The multiple dosing darunavir tablet values are derived from administration of darunavir/ritonavir by itself.

2) In adults receiving 600 mg darunavir coadministered with ritonavir 100 mg twice daily with food, when the multiple dosing darunavir suspension C_{max} value of 7390 ng/mL was compared to historical data for multiple dosing darunavir tablet C_{max} values of 5460 ng/mL, 5908 ng/mL, 6262 ng/mL, and 5874 ng/mL from the TMC125-C139 (darunavir-etravirine), TMC114-C123 (darunavir-didanosine), TMC114-C172 (darunavir-carbamazepine), and TMC114-C163 (darunavir-rifabutin) drug-drug interaction trials, the darunavir suspension C_{max} was higher by 35%, 25%, 18%, and 26%, respectively. The multiple dosing darunavir tablet values are derived from administration of darunavir/ritonavir by itself.

3) In HIV-1 infected adults, the higher multiple dosing darunavir suspension $AUC_{(0-12h)}$ and C_{max} values compared to historical data for multiple dosing darunavir tablet $AUC_{(0-12h)}$ and C_{max} values are not anticipated to result in clinically significant safety or efficacy issues based on the darunavir exposure-response and exposure-safety data.

4) In HIV-1 infected pediatric patients, there is no pharmacokinetic data available comparing the darunavir suspension to darunavir tablets in the same weight group. However, the Office of Clinical Pharmacology determined that it was acceptable to apply the results of the multiple dosing analysis in adults to include the pediatric dosing recommendations in Tables 3 and 4 as part of the U.S prescribing information for darunavir. These dosing recommendations are based on the approved dosing recommendation using darunavir tablets with the assumption that the bioavailability of the darunavir suspension is similar to the darunavir tablets within each weight range for which a dosing recommendation exists. Additionally, potential differences in the

ritonavir boosting effects of ritonavir capsules or tablets versus ritonavir solution and the lack of dose proportionality (less than dose proportional increases are observed for darunavir from 400 mg twice daily to 600 mg twice daily) are expected to have a minimal impact based on the darunavir exposure-response and exposure-safety data. The Pharmacometrics review (see section 4) provides additional discussion on this issue.

The second trial (TMC114-C228) evaluated the pharmacokinetics and antiviral activity of twice daily dosage regimens of darunavir administered in combination with ritonavir for the treatment of HIV-1 infection in pediatric subjects 3 to less than 6 years old weighing 10 to less than 20 kg using the darunavir suspension formulation (F052) that is proposed for marketing in the United States.

1.1 Recommendation

The clinical pharmacology information submitted in the NDA supports the approval of the application. Specifically, the application supports the use of darunavir oral suspension for the treatment of HIV-1 infection in pediatric patients weighing 10 kg to less than 20 kg with the dosage regimens displayed in Table 2 and the additional dosing recommendations for pediatric patients and adults in Tables 3, 4 and 5.

(b) (4)



1.2 Postmarketing Commitments or Requirements

There are no postmarketing commitments or requirements for this supplement.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The TMC114-C228 trial enrolled HIV-1 infected pediatric subjects 3 to less than 6 years old weighing 10 kg to less than 20 kg at screening. The pediatric subjects that were enrolled were receiving a stable but failing antiretroviral treatment regimen (HIV-1 viral load >1000 copies/mL) that required a modification and had less than three darunavir associated substitutions. For the background regimen, it was recommended that investigators select a minimum of two HIV-1 antiretroviral medications. The initial dosing using a darunavir oral suspension (F052) in combination with ritonavir oral solution is displayed in Table 6 below. The initial dosing regimen was approximately 20 mg/kg of darunavir combined with approximately 3 mg/kg of ritonavir administered twice daily.

Table 6-Initial dosing of darunavir oral suspension (F052) in combination with ritonavir oral solution in TMC114-C228

Body Weight (kg)	DRV		rtv	
	Dose of Oral Suspension in mL b.i.d. ^a	Actual Dose in mg b.i.d. ^a (Range in mg/kg ^b)	Dose of Oral Solution in mL b.i.d. ^a	Actual Dose in mg b.i.d. ^a (Range in mg/kg ^b)
10 - 10.9	2.0	200 (18.3 - 20.0)	0.4	32 (2.9 - 3.2)
11 - 11.9	2.2	220 (18.5 - 20.0)	0.4	32 (2.7 - 2.9)
12 - 12.9	2.4	240 (18.6 - 20.0)	0.5	40 (3.1 - 3.3)
13 - 13.9	2.6	260 (18.7 - 20.0)	0.5	48 (3.5 - 3.7)
14 - 14.9	2.8	280 (18.8 - 20.0)	0.6	48 (3.2 - 3.4)
15 - 15.9	3.0	300 (18.9 - 20.0)	0.6	48 (3.0 - 3.2)
16 - 16.9	3.2	320 (18.9 - 20.0)	0.6	48 (2.8 - 3.0)
17 - 17.9	3.4	340 (19.0 - 20.0)	0.6	48 (2.7 - 2.8)
18 - 18.9	3.6	360 (19.0 - 20.0)	0.6	48 (2.5 - 2.7)
19 - 19.9	3.8	380 (19.1 - 20.0)	0.6	48 (2.4 - 2.5)

^a The DRV oral suspension was administered with a pipette with a 0.2-mL accuracy gradation; the rtv oral solution was administered with a pipette with a 0.1-mL accuracy gradation. Due to the accuracy limitations of the pipettes, a rounding was performed when calculating the doses to be administered per weight band.

^b The actual dose in mg/kg varied given the dose was fixed for each weight band.

After the Week 2 pharmacokinetic data was analyzed using population pharmacokinetic analysis, the applicant determined that a dose adjustment for darunavir was required. The Week 2 population PK parameters are displayed in Table 7.

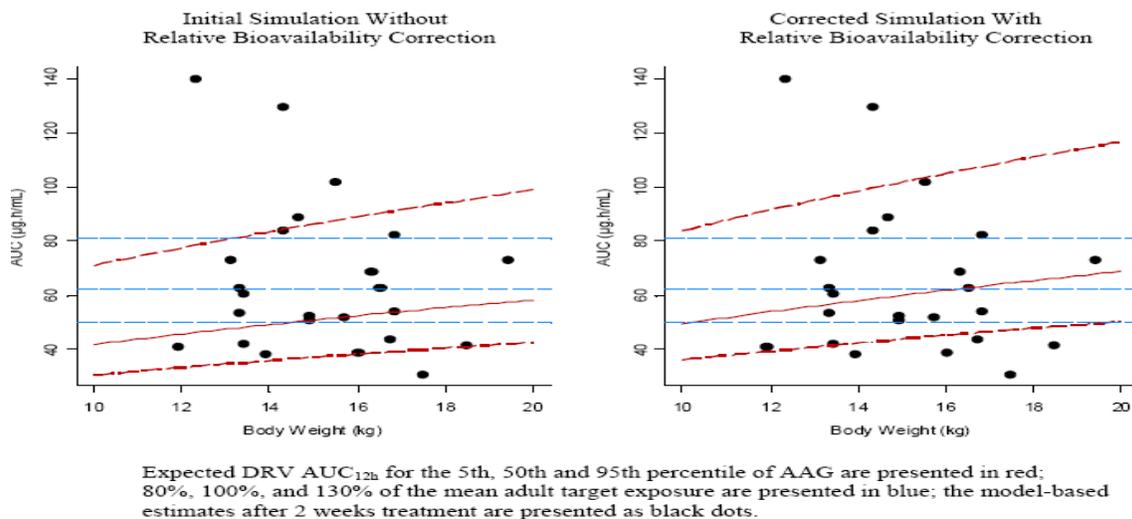
Table 7-Population pharmacokinetic parameters at Week 2 with darunavir 20 mg/kg combined with ritonavir 3 mg/kg twice daily

Weight group	N	Geometric Mean	Mean	SD	5th Percentile	Median	95th Percentile
<i>AUC_{12h} (µg.h/mL)</i>							
All subjects	24	60.7	65.4	27.8	38.8	57.6	125
10 - < 15 kg	13	65.0	70.7	32.3	40.2	61.0	133
15 - < 20 kg	11	56.0	59.3	21.0	35.3	54.2	91.9
<i>C_{0h} (ng/mL)</i>							
All subjects	24	3433	3927	2188	1662	3460	8779
10 - < 15 kg	13	3680	4289	2621	1950	3533	9411
15 - < 20 kg	11	3164	3500	1583	1607	3387	5897

While the AUC_(0-12h) data in Table 4 indicates that the darunavir exposure for both the 10 kg to less than 15 kg and the 15 kg to less than 20 kg groups were within 80% to 130% of the target AUC_(0-12h) of 62.3 µg*hr/mL, the applicant's rationale for increasing the darunavir dose was based on the simulations. The simulations are presented in Figure 1.

The simulations that were conducted did not include a relative bioavailability factor for the difference in darunavir bioavailability for the Phase 2 and the marketed tablet. The applicant repeated the simulations with the relative bioavailability factor included.

Figure 1-Predicted darunavir exposure for 3 to less than 6 year olds receiving darunavir 20 mg/kg combined with ritonavir 3 mg/kg twice daily



The simulations suggested the exposure with darunavir 20 mg/kg combined with ritonavir 3 mg/kg twice daily was low compared to the target exposure range and lower darunavir exposure with lower body weights was also observed in the simulations. When the applicant repeated the simulations with the relative bioavailability factor included, it was concluded that the rationale for adjusting the darunavir dose was still valid (see Figure 1).

The adjusted dosage regimens are displayed in Table 8. The adjusted dosage regimens were approximately 25 mg/kg of darunavir combined with approximately 3 mg/kg of ritonavir administered twice daily for pediatric subjects weighing between 10 kg to less than 15 kg and 375 mg of darunavir combined with approximately 50 mg of ritonavir administered twice daily for pediatric subjects weighing between 15 kg to less than 20 kg.

Table 8-Adjusted dosing of darunavir oral suspension in combination with ritonavir oral solution in TMC114-C228

Body Weight (kg)	DRV		rtv	
	Dose of Oral Suspension in mL b.i.d. ^a	Actual Dose in mg b.i.d. ^a (Range in mg/kg ^b)	Dose of Oral Solution in mL b.i.d. ^b	Actual Dose in mg b.i.d. ^a (Range in mg/kg ^b)
10 - 10.9	2.6	260 (23.8 - 26.0)	0.4	32 (2.9 - 3.2)
11 - 11.9	2.8	280 (23.5 - 25.5)	0.4	32 (2.7 - 2.9)
12 - 12.9	3.0	300 (23.3 - 25.0)	0.5	40 (3.1 - 3.3)
13 - 13.9	3.4	340 (24.5 - 26.1)	0.5	40 (2.9 - 3.1)
14 - 14.9	3.6	360 (24.2 - 25.7)	0.6	48 (3.2 - 3.4)
15 - 19.9	3.8	380	0.6	48

^a The DRV oral suspension was administered with a pipette with a 0.2-mL accuracy gradation; the rtv oral solution was administered with a pipette with a 0.1-mL accuracy gradation. Due to the accuracy limitations of the pipettes, a rounding was performed when calculating the doses to be administered per weight band.

^b The actual dose in mg/kg varied given the dose was fixed for each weight band.

Subsequent to the dosage adjustment, the population PK analysis was repeated two weeks after dosage adjustment. It was concluded that the trial could proceed using the adjusted darunavir dosage regimens. The data is presented in the individual trial review for TMC114-C228 (see section 3). Comparative results of the mean darunavir AUC_(0-12h) values with the initial and adjusted darunavir dosage regimens to the mean target adult exposure of 62.3 µg/mL*hr in adults are presented in Table 9 below.

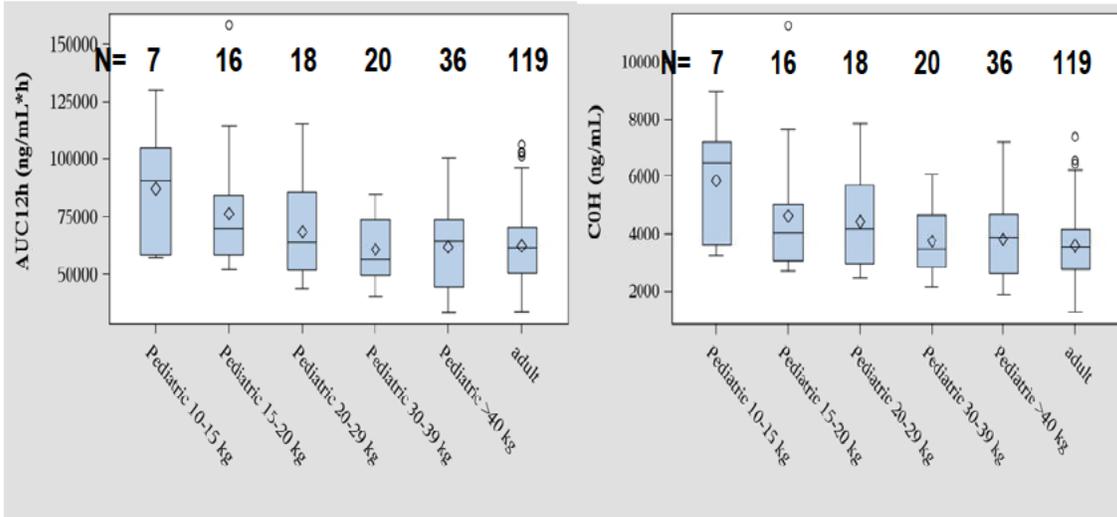
Table 9-Comparison of the mean darunavir AUC_(0-12h) values prior to and subsequent to the adjustment of the darunavir dosage regimens to the mean target adult exposure

Before Dose Adjustment			After Dose Adjustment		
Overall	10 to < 15 kg	15 to < 20 kg	Overall	10 to < 15 kg	15 to < 20 kg
107%	111%	104%	128%	140%	122%

For the initial darunavir dosage regimens (before dosage adjustment), the darunavir mean AUC_(0-12h) value was within 80% to 130% of the target mean adult AUC_(0-12h) for pediatric subjects weighing 10 kg to < 15 kg or 15 kg to < 20 kg. After the darunavir dosage regimens were adjusted, the darunavir mean AUC_(0-12h) value was within 80% to 130% of the target mean adult AUC_(0-12h) for pediatric subjects weighing 15 kg to < 20 kg but was greater than 130% for pediatric subjects weighing 10 kg to < 15 kg. The 40% higher AUC_(0-12h) for pediatric subjects weighing 10 kg to < 15 kg compared to the target adult exposure is not expected to result in any safety issues based on the exposure-safety information for darunavir.

A comparison of the darunavir exposure after dosage adjustment for pediatric subjects 3 to < 6 years old (10 kg to < 20 kg) compared to 6 to <18 year olds (20 kg to > 40 kg) and adults is displayed in Figure 2.

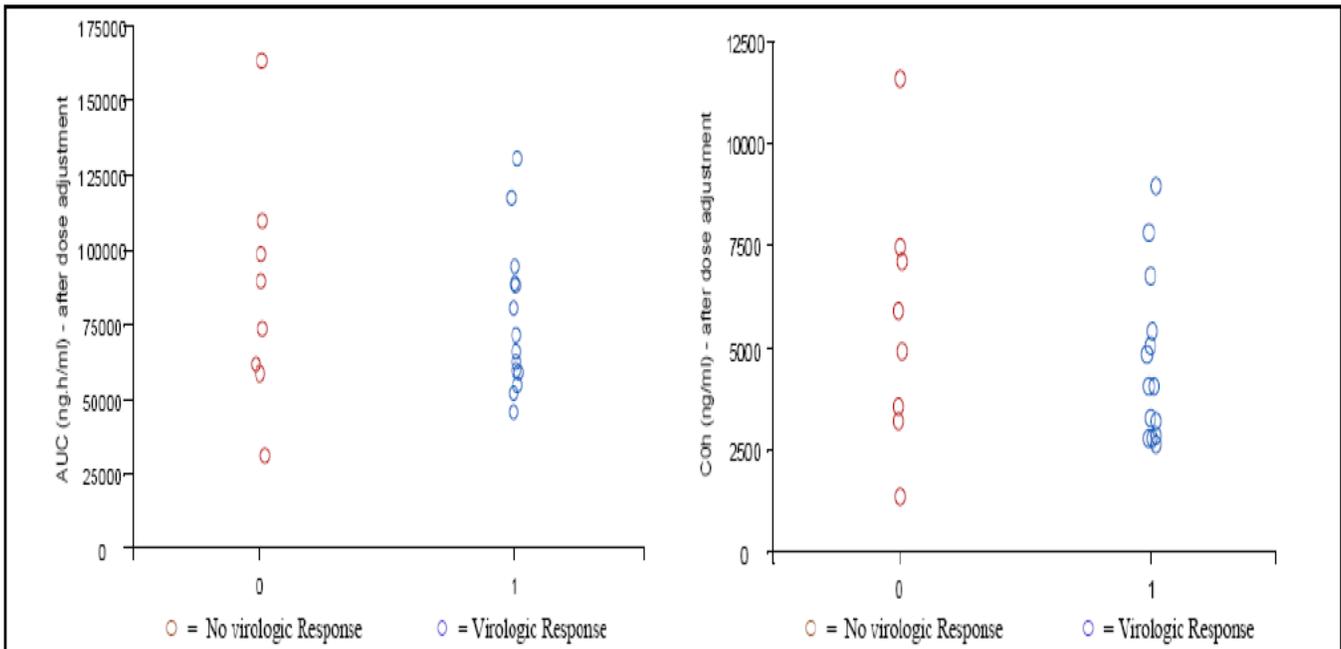
Figure 2-Darunavir AUC_(0-12h) and C_{0h} after dosage adjustment in 3 to < 6 year olds (10 kg to < 20 kg) compared to 6 to <18 year olds (20 kg to > 40 kg) and adults



The comparison of the darunavir exposure after dosage adjustment for pediatric subjects 3 to < 6 years old (10 kg to < 20 kg) compared to 6 to <18 year olds (20 kg to > 40 kg) and adults indicates that the range of AUC_(0-24h) and C_{0h} values were generally similar with the exception of the 10 kg to <15 kg group.

The exposure response analysis conducted by the applicant compared the range of darunavir AUC_(0-12h) and C_{0h} values (for the adjusted darunavir dosage regimens) for subjects achieving virologic response to subjects that did not achieve virologic response (HIV-1 RNA less than 50 copies/mL (see Figure 3).

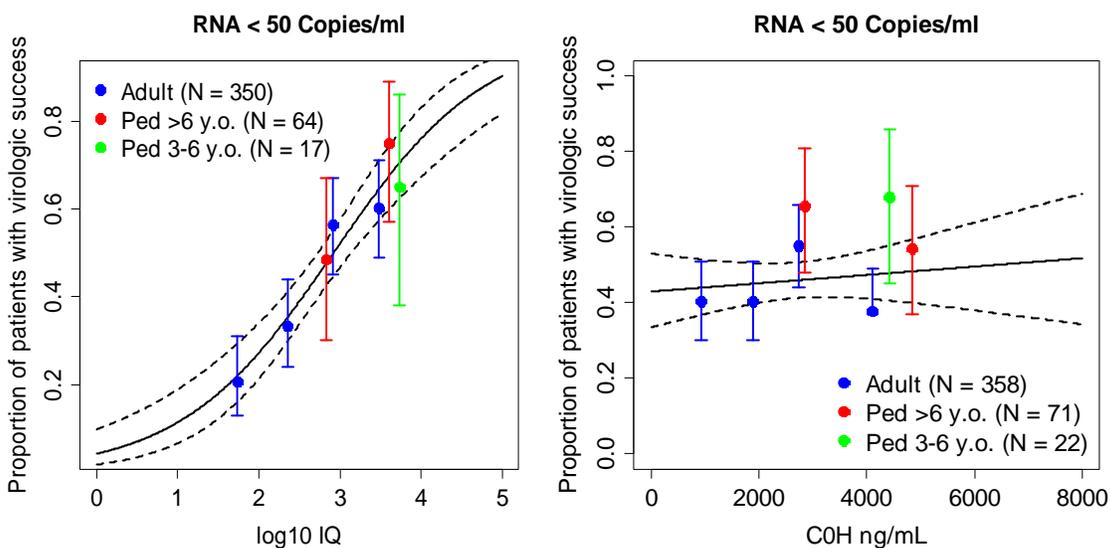
Figure 3-Comparison of AUC_(0-12h) and C_{0h} (for the adjusted darunavir dosage regimens) for subjects either achieving virologic response or not achieving virologic response (HIV-1 RNA less than 50 copies/mL)



Based on the results displayed in Figure 3, the range of darunavir $AUC_{(0-12h)}$ and C_{0h} values were similar for the two groups.

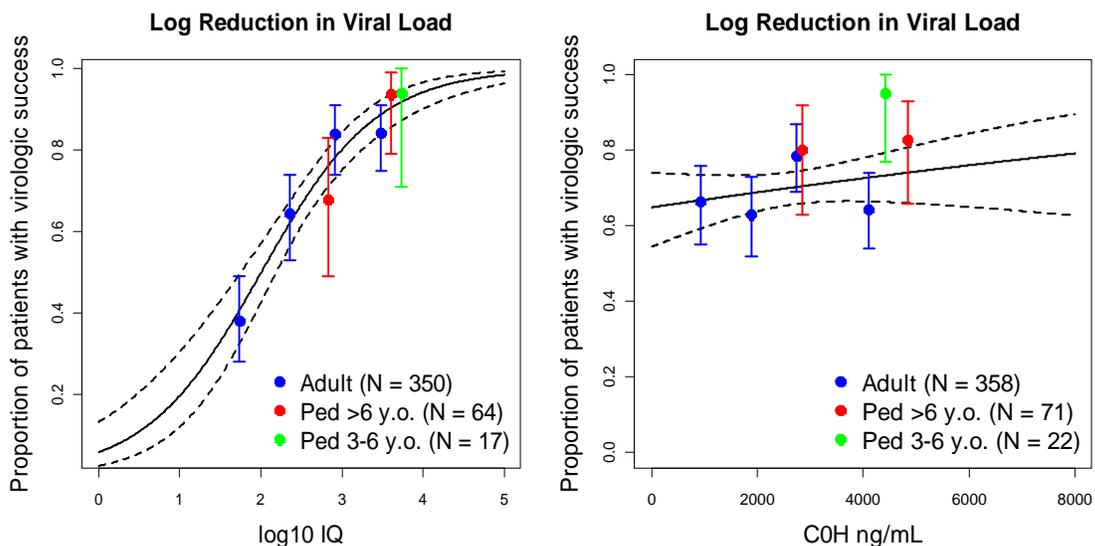
The Pharmacometrics reviewer conducted additional darunavir exposure-response analyses. The additional analyses evaluated the inhibitory quotient (IQ) and the proportion of subjects achieving HIV-1 RNA less than 50 copies/mL and IQ and the proportion of subjects achieving a one log reduction in viral load. For the analyses that was conducted for the review, the IQ was defined as the ratio of the darunavir C_{0h} (exposure) values after dosage adjustment at steady state and IC_{50} (a measurement of the ability of darunavir to inhibit HIV-1 virus). In addition, the analysis was compared to the results that were previously obtained in older pediatric subjects (6 to less than 18 years old) and adults. The results are displayed in Figures 4 and 5.

Figure 4-Evaluation of IQ and darunavir C_{0h} (for the adjusted darunavir dosage regimens) and the proportion of subjects achieving virologic response (HIV-1 RNA less than 50 copies/mL)



Note: Each vertical bar represents the proportion of subjects with virologic success (and the 95% confidence interval) at the median value ($\log_{10} IQ$ ratio or darunavir C_{0h}) for a given dataset.

Figure 5-Evaluation of IQ and darunavir C_{0h} (for the adjusted darunavir dosage regimens) and the proportion of subjects achieving virologic response (one log reduction in viral load)



Note: Each vertical bar represents the proportion of subjects with virologic success (and the 95% confidence interval) at the median value ($\log_{10}IQ$ ratio or darunavir C_{0h}) for a given dataset.

The data for pediatric subjects 3 to less than 6 years old were not broken down into multiple groups and therefore the relationship between the inhibitory quotient (IQ) and the proportion of subjects achieving HIV-1 RNA less than 50 copies/mL or IQ and a one log reduction in viral load could not be evaluated. In Figures 4 and 5, each vertical bar in the plots represents the proportion of subjects with virologic success (and the 95% confidence interval) at the median value ($\log_{10}IQ$ ratio or darunavir C_{0h}) for a given dataset. For pediatric subjects 3 to less than 6 years old, the vertical bar was generally consistent with the vertical bars from older pediatric subjects (6 to less than 18 years old) and adults.

Based on the conclusion that the reported adverse events for the trial did not warrant further exposure response analysis, there were no additional exposure-safety analyses that were conducted by the FDA for pediatric subjects 3 to less than 6 years old. No relevant trends were identified for the exposure safety analyses that were conducted by the applicant.

The Office of Scientific Investigations was requested to conduct an inspection of (b) (4) the bioanalytical laboratory that analyzed the darunavir and ritonavir plasma samples for the TMC114-C228 trial. The results are discussed in the individual trial review (see section 3).

The following conclusions from the TMC114-C228 trial support the proposed darunavir/ritonavir doses in Table 2:

- The darunavir mean AUC_(0-12h) value was within 80% to 130% of the target mean

- adult $AUC_{(0-12h)}$ of $62.3 \mu\text{g}\cdot\text{hr}/\text{mL}$ for pediatric subjects weighing 15 kg to < 20 kg (22% higher) but was greater than 130% for pediatric subjects weighing 10 kg to < 15 kg (the 40% higher exposure is not expected to result in any safety issues).
- When compared to 6 to <18 years olds (20 kg to > 40 kg) and adults, the darunavir $AUC_{(0-24h)}$ and C_{0h} values for pediatric subjects 3 to < 6 years old (10 kg to < 20 kg), were generally similar with the exception of the 10 kg to <15 kg group.
 - When pediatric subjects achieving HIV-1 RNA less than 50 copies/mL were compared to pediatric subjects that did not achieve HIV-1 RNA less than 50 copies/mL, the range of darunavir $AUC_{(0-12h)}$ and C_{0h} values were similar.
 - When the proportion of subjects with virologic success (<50 copies/mL or one log reduction in viral load) at the median value (\log_{10} IQ ratio or darunavir C_{0h}) were evaluated, the results for pediatric subjects 3 to < 6 years old were generally consistent with the previous results from older pediatric subjects (6 to less than 18 years old) and adults.

2 Labeling Recommendations

The labeling changes below as of September 2011 include the proposed revisions for relevant clinical pharmacology sections of the darunavir/ritonavir U.S. prescribing information.

Section 2-Dosage and Administration



(b) (4)

2 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS)
immediately following this page

3 Appendices

3.1 Individual Trial Reviews

3.1.1 TMC114-C169 trial

Reviewer note: the Office of Clinical Pharmacology did not accept the results from the TMC114-C169 trial pertaining to the bioequivalence analysis comparing darunavir suspension to darunavir tablets based on the recommendation from the Office of Scientific Investigations that the results of the TMC114-C169 trial should not be accepted-see section 9 (Bioanalysis) for further details.

1. Title

A Phase I, open-label, randomized, crossover trial in healthy subjects to compare the oral bioavailability of a suspension formulation of darunavir (DRV) to that of the commercial 300 mg tablet formulation in the presence of low-dose ritonavir, under fasted and fed conditions, and to assess multiple dose pharmacokinetics of the suspension formulation of DRV in the presence of low dose ritonavir

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at Kendle International B.V., Clinical Pharmacology unit, Bolognalaan 40, 3584 CJ Utrecht, the Netherlands from April 15, 2008 to August 18, 2008.

3. Objectives

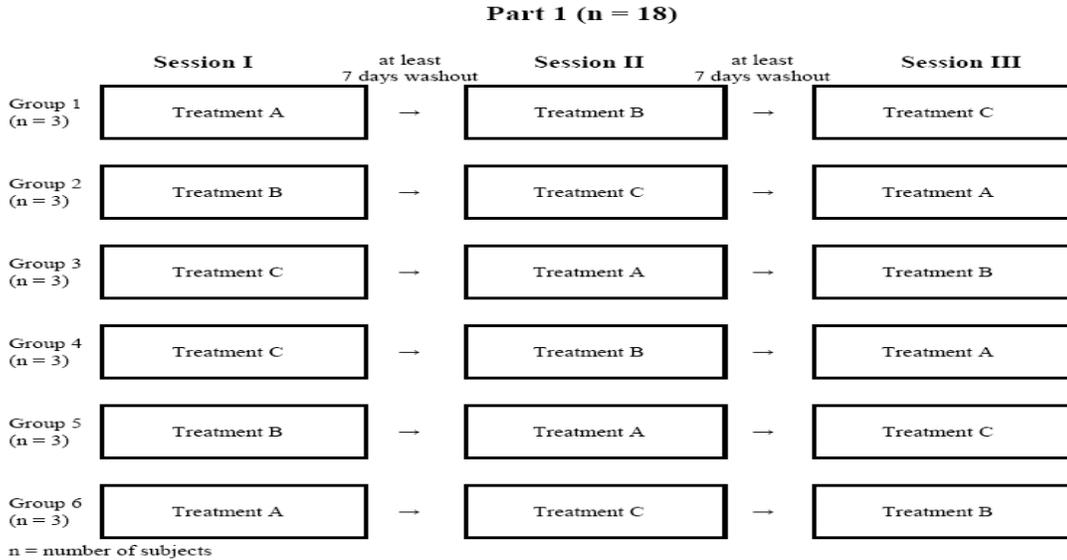
The primary objectives of the trial were to evaluate the single dose bioavailability under fed or fasted conditions of a darunavir suspension formulation (F051) coadministered with ritonavir capsules compared to a darunavir tablet formulation under fed conditions and to evaluate the single dose bioavailability of a darunavir suspension formulation (F051) under fed and fasted conditions. In addition, the multiple dosing pharmacokinetics of the darunavir suspension formulation was to be evaluated either under fasted or fed conditions.

4. Trial Design

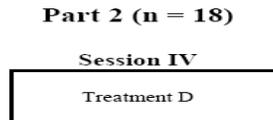
TMC114-C169 was a Phase I open label, randomized, crossover clinical trial that enrolled healthy male and female subjects between 18 and 55 years old. The washout period was a minimum of 7 days after each dose of darunavir/ritonavir was administered. The trial design is displayed in Figure 1. The trial was divided into two parts. In Part 1, the pharmacokinetics of single doses of the darunavir oral suspension or darunavir tablets combined with ritonavir capsules under fed conditions was evaluated. In Part 2, the pharmacokinetics of multiple doses of the darunavir oral suspension coadministered with ritonavir capsules under fasted or fed conditions was evaluated. The treatments that were

administered are listed in Table 1 and the treatment sequences are displayed in Table 2.

Figure 1-TMC114-C169 trial design



Results from Part 1 were evaluated before the start of Part 2 of the trial.



Preferably, the subjects participating in Part 1 of the trial were the same as those in Part 2, but additional subjects could be entered in case of dropout.

Table 1-Treatments administered for the TMC114-C169 trial

Part	Number of subjects	Treatment	Volume
1	18	Treatment A: DRV: single dose of 600 mg on Day 3 (fed) Ritonavir: 100 mg b.i.d. on Days 1-5	2 tablets of F016 (DRV eq. 300 mg/tablet) 1 capsule of ritonavir (Norvir®) per intake (ritonavir eq. 100 mg/capsule)
1	18	Treatment B: DRV: single dose of 600 mg on Day 3 (fasted) Ritonavir: 100 mg b.i.d. on Days 1-5	6 mL of suspension F051 (DRV eq. 100 mg/mL) 1 capsule of ritonavir (Norvir®) per intake (ritonavir eq. 100 mg/capsule)
1	18	Treatment C: DRV: single dose of 600 mg on Day 3 (fed) Ritonavir: 100 mg b.i.d. on Days 1-5	6 mL of suspension F051 (DRV eq. 100 mg/mL) 1 capsule of ritonavir (Norvir®) per intake (ritonavir eq. 100 mg/capsule)
2	18	Treatment D: DRV: 600 mg b.i.d. on Days 1-6 and a 600 mg morning dose on Day 7 (fed) ^a Ritonavir: 100 mg b.i.d. on Days 1-9	6 mL of suspension F051 per intake (DRV eq. 100 mg/mL) ^a 1 capsule of ritonavir (Norvir®) per intake (ritonavir eq. 100 mg/capsule)

^a DRV dose, volume of suspension per intake and food recommendations for DRV/rtv intake for Part 2 (Treatment D) were determined based on the results of Part 1 (Treatments A, B and C) of the trial.

Table 2-Treatment sequences for the TMC114-C169 trial

Number of subjects	Treatment sequence
3	ABC
3	BCA
3	CAB
3	CBA
3	BAC
3	ACB

5. Exclusion and Inclusion Criteria/Other Restrictions and Exceptions

Use of acetaminophen, hormone replacement therapy, and hormonal contraceptives was permitted during the trial. All other medications, including nonprescription and natural medicines, were to be discontinued a minimum of 14 days before the first dose of trial medication.

Other restrictions during the trial included prohibiting the use of beverages containing alcohol or quinine from 24 hours before the first dose of trial medication until the collection of the last pharmacokinetic (PK) blood sample in each session. In both Parts 1 and 2, grapefruit and grapefruit juice was prohibited from 7 days before the first dose of trial medication until the collection of the last pharmacokinetic (PK) blood sample in either Part 1 or 2.

In the event of an adverse event, the following medications were permitted:

- A) Rash or an allergic reaction: cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents (specific medications were not included in the trial report)
- B) Nausea: antiemetics (specific medications were not included in the trial report)
- C) Diarrhea: loperamide

6. Dosage and Administration

When darunavir was administered as a suspension, the dose was administered in a bottle that was shaken extensively and then rinsed with water that the subject had to drink.

In Part 1, for treatments A and C, ritonavir was administered within ten minutes after completing a meal, and on Day 3, darunavir was administered within 5 minutes after ritonavir. For treatment B, ritonavir was administered within ten minutes after completing a meal, except on Day 3 when both darunavir and ritonavir were administered under fasted conditions and darunavir was administered within 5 minutes after ritonavir. For treatments A, B, and C, subjects fasted overnight for a minimum of ten hours for Day 3 dosing. Additionally, with the exception of water (e.g. 200 mL) that was administered with a dose, water was not permitted from 2 hours before to 2 hours after darunavir/ritonavir administration.

In Part 2, ritonavir was administered within ten minutes after completing a meal. When darunavir was combined with ritonavir, darunavir was administered within 5 minutes

after ritonavir. Subjects fasted overnight for a minimum of ten hours for Day 7 dosing. Additionally, with the exception of water (e.g. 200 mL) that was administered with a dose, water was not permitted from 2 hours before to 2 hours after darunavir/ritonavir administration.

When darunavir/ritonavir was administered with food in both Parts 1 and 2, in response to an information request, the applicant clarified that the meal provided approximately 21 grams of fat (189 kcal), 67 grams of carbohydrates (268 kcal), and 19 grams of protein (76 kcal), and in total, the meal provided approximately 533 kcal.

7. Rationale for Doses Used in the Trial

Currently, twice daily dosing with food of darunavir 600 mg coadministered with ritonavir 100 mg, is the currently approved treatment regimen for treatment experienced adult patients with at least one darunavir resistance associated substitution.

8. Drugs Used in the Trial

The darunavir suspension that was administered in the trial (F051) is an experimental darunavir suspension formulation. A different darunavir suspension formulation (F052) is proposed for marketing in the United States. However, the Office of New Drug Quality Assessment (ONDQA) determined that based on the results of the TMC114-C169 trial, the use of the F052 formulation in the pediatric 3 to < 6 years old clinical trial (TMC114-C228), and the in vitro dissolution results comparing the F051 and F052 darunavir suspension formulations, a comparison of the bioavailability of the two formulations in a clinical trial was not necessary and therefore, a biowaiver could be granted (please refer to the biopharmaceutics review for IND 62477, supporting document number 1247).

The darunavir 300 mg tablets (F016) that were administered in the trial are no longer commercially marketed in the United States. However, based on the results from a clinical trial (TMC114-C162), the 300 mg tablets (F016) administered as two 300 mg tablets are bioequivalent under fasted conditions to the currently U.S. marketed 600 mg tablets (F032) [please refer to the Clinical Pharmacology review for NDA 21-976, supporting document number 40]. In addition, ONDQA has approved biowaivers for the other U.S. marketed darunavir tablet strengths: 75 mg (F029), 150 mg (F050), and 400 mg (F030).

Ritonavir capsules were administered in the trial. The trial does not reflect the clinical use of ritonavir oral solution with darunavir oral suspension. In addition, the ritonavir capsules that were administered are the European marketed ritonavir capsules. The applicant states that based on information provided by Abbott Laboratories (the manufacturer of ritonavir capsules, tablets, and oral solution) there are no differences in either the composition or bioavailability of the U.S. and European marketed ritonavir capsules, tablets, and oral solution. The inhibitory effects of ritonavir on darunavir exposure have not been directly compared for ritonavir capsules (or ritonavir tablets)

versus ritonavir oral solution. However, the differences in ritonavir bioavailability between the different ritonavir formulations are not expected to result in any clinically significant differences in darunavir exposure when coadministered with ritonavir capsules, tablets or oral solution.

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

In Part 1, ritonavir blood samples were obtained on Day 1 (within 2 hours of administration of trial medication) and darunavir and ritonavir blood samples were obtained on Day 3 at predose and up to 12 hours postdose, and at 24, 48, and 72 hours postdose on Days 4, 5, and 6, respectively. In Part 2, darunavir and ritonavir blood samples were obtained on Day 1, 5, 6, and 7 immediately prior to administration of trial medication, on Day 7 at predose and up to 12 hours postdose, and at 24, 48, and 72 hours postdose on Days 8, 9, and 10, respectively.

Bioanalysis

The method and bioanalysis of darunavir and ritonavir are acceptable. Darunavir and ritonavir plasma samples were analyzed using a validated LC/MS/MS method in lithium heparin anticoagulated plasma by [REDACTED] (b) (4). The blood samples for analysis of darunavir and ritonavir were collected in tubes containing lithium heparin as an anticoagulant. For darunavir, the lower limit of quantification was 5 ng/mL and the upper limit of quantification was 10000 ng/mL. There were no precision or accuracy issues identified for darunavir based on the bioanalytical report. For the TMC114-C169 trial, precision and accuracy were evaluated using plasma darunavir QC samples at three concentration levels: 13.6 ng/mL, 240 ng/mL, and 7680 ng/mL. The corresponding darunavir inter-run accuracy values were 0% for 13.6 ng/mL, -4.6% for 240 ng/mL, and -7.7% for 7680 ng/mL. The darunavir inter-run precision values were 6.5% for 13.6 ng/mL, 6.4% for 240 ng/mL, and 5.7% for 7680 ng/mL. For ritonavir, the lower limit of quantification was 5 ng/mL and the upper limit of quantification was 10000 ng/mL. There were no precision or accuracy issues identified for ritonavir based on the bioanalytical report. For the TMC114-C169 trial, precision and accuracy were evaluated using plasma ritonavir QC samples at three concentration levels: 13.6 ng/mL, 240 ng/mL, and 7680 ng/mL. The corresponding ritonavir inter-run accuracy values were 1.5% for 13.6 ng/mL, -2.9% for 240 ng/mL, and -3.4% for 7680 ng/mL. The ritonavir inter-run precision values were 7% for 13.6 ng/mL, 4.6% for 240 ng/mL, and 5.1% for 7680 ng/mL.

For the TMC114-C169 trial, the darunavir and ritonavir plasma samples were stored at -20°C at both at the clinical trial site and at the bioanalytical laboratory. The long term stability darunavir and ritonavir data of 1597 days covers the duration of long term stability data necessary for the TMC114-C169 trial.

The FDA Office of Scientific Investigations (OSI) was requested to conduct an inspection of the bioanalytical laboratory that analyzed darunavir and ritonavir plasma samples and the clinical trial site for the TMC114-C169 trial. The clinical trial site is currently not operated by Kendle. There was one 483 observation issued to the bioanalytical laboratory [REDACTED] ^{(b) (4)}. The 483 observation was issued because of the failure to use fresh calibration standards during the 5 day reinjection stability experiment during method validation. The experiment was repeated and the submitted data was acceptable. For the clinical trial site inspection, the Office of Scientific Investigations recommended that the results of the trial should not be accepted. While a 483 observation was not issued, the recommendation was made because reserve samples were not stored for the test and reference drug products. The applicant did not retain reserve sample because they did not view the TMC114-C169 trial as a pivotal bioequivalence trial. However, because the applicant proposed to permit darunavir tablet dosing in HIV-1 infected pediatric patients 15 kg to 20 kg and darunavir suspension dosing in HIV-1 infected adults and children who are not able to swallow darunavir tablets in the proposed revisions to the darunavir U.S. prescribing information, and no other clinical trial data is currently available to support these labeling changes, the TMC114-C169 trial is a pivotal bioequivalence trial. The Office of Clinical Pharmacology subsequently determined that it was acceptable to review the pharmacokinetic data from the multiple dosing portion of the TMC114-C169 trial and include the pediatric and adult dosing recommendations that are displayed in section 1, Tables 3, 4, and 5.

Pharmacokinetic Assessments

Noncompartmental analysis was performed to calculate darunavir and ritonavir plasma pharmacokinetic parameters. In Part 1, on Day 3, the pharmacokinetic parameters that were derived included C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-inf)}$ for darunavir, and C_{max} , C_{0h} , C_{min} , and $AUC_{(0-12h)}$ for ritonavir. In Part 2, on Day 7, the pharmacokinetic parameters that were derived included C_{max} , C_{0h} , C_{min} , and $AUC_{(0-12h)}$ for both darunavir and ritonavir. If a major difference (> 10.00% deviation from the scheduled time) was observed for a subject during a specific treatment arm, the actual sampling time was used instead of the scheduled sampling time.

Statistical Analysis

Descriptive statistics were calculated for darunavir and ritonavir plasma concentrations and pharmacokinetic parameters, including the number of subjects (n), mean, standard deviation, the coefficient of variation (CV%), median, and the minimum and maximum values in both Parts 1 and 2.

In Part 1, the statistical analysis for darunavir involved the following comparisons for the log transformed C_{max} , $AUC_{(0-inf)}$, and $AUC_{(0-inf)}$ parameters: a) treatment B (test arm) to treatment A (reference arm), b) treatment C (test arm) to treatment A (reference arm), and c) treatment C (test arm) to treatment B (reference arm). Using a linear mixed effects model, least squares means were calculated and 90% confidence intervals were derived.

For the 90% confidence interval, the applicant did not provide a predefined range (lower and upper limit) for achieving bioequivalence in exposure for C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-inf)}$. For the purposes of this review, 90% confidence interval limits of 80%-125% will be used as the criteria for achieving bioequivalence in exposure.

In Part 1, for ritonavir, the predose concentrations on Days 3, 4, 5, and 6 were graphically evaluated to determine if steady state for ritonavir was achieved by Day 3.

In Part 2, for a darunavir/ritonavir 600 mg/100 mg twice daily dosage regimen, the darunavir and ritonavir multiple dose pharmacokinetic parameters for the suspension were compared to historical data for darunavir and ritonavir multiple dose pharmacokinetic parameters for the 300 mg tablet formulation (F016). The historical data was from the following clinical trials: TMC114-C123, TMC114-C163, and TMC114-C171. For ritonavir, the predose concentrations on Days 5, 6, 7, 8, 9, and 10 were graphically evaluated to determine if steady state for ritonavir was achieved by Day 7. For darunavir, the predose concentrations on Days 5, 6, and 7, were graphically evaluated to determine if steady state for ritonavir was achieved by Day 7.

10. Results

Reviewer note: The results section will not discuss the ritonavir single or multiple dose pharmacokinetic data or the comparison of the darunavir exposure under fasted conditions with the darunavir suspension (test arm) to the darunavir exposure under fed conditions with darunavir tablets (reference arm).

10.1 Subject Demographics and Disposition

Table 3-TMC114-C169 subject demographics

Parameter	All Subjects N = 23
Age, years Median (range)	30.0 (20-53)
Height, cm Median (range)	178.0 (159-198)
Weight, kg Median (range)	80.0 (53-95)
BMI, kg/m ² Median (range)	23.90 (19.5-28.7)
Gender, n (%)	
Male	18 (78.3)
Female	5 (21.7)
Ethnic Origin, n (%)	
Caucasian/White	20 (87.0)
Black	1 (4.3)
Other	2 (8.7) ^a

N = number of subjects, n = number of subjects with that observation

^a One subject was Asian Pacific and one subject was of mixed Asian/Caucasian origin.

10.3.1 Pharmacokinetic and Statistical Analysis

Part 1-darunavir (DRV)

Table 4-Pharmacokinetic parameters for a single 600 mg dose of darunavir (combined with 100 mg twice daily of ritonavir) administered as 300 mg tablets under fed conditions (treatment A) or as an oral suspension under fasted conditions (treatment B) or fed conditions (treatment C)

Pharmacokinetics of DRV (mean ± SD, t _{max} : median [range])	600 mg DRV tablet + 100 mg rtv b.i.d. (fed) (Trt A, reference)	600 mg DRV suspension + 100 mg rtv b.i.d. (fasted) (Trt B, test 1)	600 mg DRV suspension + 100 mg rtv b.i.d. (fed) (Trt C, test 2)
n	17 ^a	17	17
C _{max} , ng/mL	5654 ± 1478	5176 ± 1411	5885 ± 1724
t _{max} , h	3.0 (2.5-5.0)	2.0 (1.0-3.0)	4.0 (1.5-4.0)
AUC _{last} , ng.h/mL	85240 ± 38020	83510 ± 33540	88410 ± 32590
AUC _∞ , ng.h/mL	87330 ± 40890	88520 ± 35570	92270 ± 33540
t _{1/2term} , h	15.04 ± 7.884	16.08 ± 7.236	15.36 ± 6.438

^a n=16 for AUC_∞ and t_{1/2 term}. Trt = treatment

Table 5-Statistical analysis for a single 600 mg dose of darunavir (combined with 100 mg twice daily of ritonavir) administered as an oral suspension under fed conditions (treatment C-test arm) or as 300 mg tablets under fed conditions (treatment A-reference arm)

Parameter	LSmeans ^a		LSmeans ratio, %	90% CI,% ^c	p-value	
	600 mg DRV tablet + 100 mg rtv b.i.d. (fed) (Trt A, reference)	600 mg DRV suspension + 100 mg rtv b.i.d. (fed) (Trt C, test 2)			Period	Sequence
C _{max} , ng/mL	5434	5676	104.4	99.38 - 109.8	0.0036*	0.4093
AUC _{last} , ng.h/mL	77480	83320	107.5	101.1 - 114.4	0.0011*	0.5269
AUC _∞ , ng.h/mL ^b	81270	86940	107.0	100.3 - 114.1	0.0036*	0.5592
Parameter	Median ^a		Treatment difference median	90% CI,% ^c	p-value	
	600 mg DRV tablet + 100 mg rtv b.i.d. (fed) (Trt A, reference)	600 mg DRV suspension + 100 mg rtv b.i.d. (fed) (Trt C, test 2)			Period	Sequence
t _{max} , h	3.0	4.0	0.00	(-0.75) - (0.50)	0.7326	0.3023

Trt = treatment

^a n= 17 for reference and test

^b n = 16 for reference

^c 90% confidence intervals.

* Statistically significant difference

Statistical analyses were conducted for 600 mg single doses of darunavir comparing a darunavir oral suspension administered under fed conditions (test arm) to darunavir 300 mg tablets administered under fed conditions (reference arm). The 90% confidence interval for darunavir C_{max}, AUC_(0-last), and AUC_(0-inf) were within 80%-125%.

For the darunavir oral suspension, the trial did not evaluate the effect of food with high fat meals compared to fasted conditions. The trial did compare the effect of the meal that was administered to subjects in the trial (which included 21 grams of fat [189 kcal] and in

total, approximately 533 kcal) compared to fasted conditions for the darunavir oral suspension. The results are displayed in Table 6.

Table 6-Statistical analysis for a single 600 mg dose of darunavir (combined with 100 mg twice daily of ritonavir) administered as an oral suspension under fed conditions (treatment C-test arm) or fasted conditions (treatment B-reference arm)

Parameter	LSmeans ^a		LSmeans ratio, %	90% CI,% ^b	p-value	
	600 mg DRV suspension + 100 mg rtv b.i.d. (fasted) (Trt B, test 1)	600 mg DRV suspension + 100 mg rtv b.i.d. (fed) (Trt C, test 2)			Period	Sequence
C _{max} , ng/mL	4954	5662	114.3	105.9 - 123.3	0.0931	0.2335
AUC _{last} , ng.h/mL	77590	82920	106.9	100.1 - 114.1	0.0057*	0.1612
AUC _∞ , ng.h/mL	81900	86590	105.7	98.66 - 113.3	0.0153*	0.2190
Parameter	Median ^a		Treatment difference median	90% CI,% ^b	p-value	
	600 mg DRV suspension + 100 mg rtv b.i.d. (fasted) (Trt B, test 1)	600 mg DRV suspension 1 + 100 mg rtv b.i.d. (fed) (Trt C, test 2)			Period	Sequence
t _{max} , h	2.0	4.0	1.13	(0.76) - (1.50)	0.4007	0.5916

Trt = treatment

^a n= 17 for reference and test

^b 90% confidence intervals.

* Statistically significant difference

When the darunavir exposure under fed conditions with the darunavir suspension (test arm) was compared to the darunavir exposure under fasted conditions with the darunavir suspension (reference arm), the 90% confidence interval for darunavir C_{max}, AUC_(0-last), and AUC_(0-inf) were within 80%-125%.

Part 2- darunavir (DRV)

The applicant evaluated the multiple dose pharmacokinetics of the darunavir oral suspension under fed conditions. The applicant did not conduct any statistical analyses using the multiple dosing darunavir pharmacokinetic data. Based on a review of the individual profiles of the darunavir C_{0h} values on Days 5 and 6, and 7, darunavir steady state appeared to have been achieved by Day 7 in most subjects.

Table 7-Pharmacokinetic parameters for 600 mg twice daily of darunavir oral suspension (combined with ritonavir 100 mg twice daily) and historical data for darunavir tablets from the TMC114-C171, TMC114-C123, and TMC114-C163 trials

Pharmacokinetics of DRV (mean ± SD, t _{max} ; median [range])	600 mg DRV suspension b.i.d. + 100 mg rtv b.i.d. (fed) (Treatment D)		
n	17		
C _{0h} , ng/mL	4029 ± 1677		
C _{min} , ng/mL	3345 ± 1172		
C _{max} , ng/mL	7390 ± 1540		
t _{max} , h	3.0 (2.0-4.0)		
AUC _(0-12h) , ng.h/mL	58550 ± 17570		
Pharmacokinetics of DRV (mean ± SD, t _{max} ; median [range])	600/100 mg DRV/rtv b.i.d. (Historical data: TMC114-C171)	600/100 mg DRV/rtv b.i.d. (Historical data: TMC114-C123)	600/100 mg DRV/rtv b.i.d. (Historical data: TMC114-C163)
n	17	17	16 ^a
C _{0h} , ng/mL	3450 ± 944.1	2742 ± 625.0	2768 ± 1077
C _{min} , ng/mL	3132 ± 1006	2353 ± 744.2	2349 ± 1006
C _{max} , ng/mL	6894 ± 1654	5908 ± 916.8	5874 ± 1637
t _{max} , h	3.0 (1.0 - 5.0)	3.0 (2.0 - 5.0)	4.0 (1.0 - 9.0)
AUC _(0-12h) , ng.h/mL	58550 ± 17200	44750 ± 7773	46720 ± 15430

^a n = 15 for C_{0h}

There are no clinically significant differences observed based on evaluating the multiple dose data for darunavir or ritonavir C_{max} and AUC_(0-12h) for the oral suspension and the data for darunavir tablets using historical data that was selected by the applicant from the TMC114-C171, TMC114-C123, and TMC114-C163 trials.

Reviewer note: The results of the TMC114-C171 trial were not included in the multiple dosing analysis that is discussed in section 1 because the results were obtained with administration of buprenorphine/naloxone in combination with darunavir/ritonavir.

11. Discussion and Conclusions

Based on the results from the TMC114-C169 trial, the following conclusions for darunavir can be made based on the applicant's analysis:

- Under fed conditions, when 600 mg single doses of darunavir were administered as oral suspension compared to 300 mg tablets, the darunavir C_{max}, AUC_(0-last), and AUC_(0-inf) ratios were increased by 4%, 8%, and 7%, respectively. The 90% confidence interval for darunavir C_{max}, AUC_(0-last), and AUC_(0-inf) were within 80%-125%.
- When 600 mg single doses of darunavir were administered as an oral suspension under fed conditions compared to fasted conditions, the darunavir C_{max}, AUC_(0-last), and AUC_(0-inf) ratios were increased by 4%, 7% and 6%, respectively. The 90% confidence interval for darunavir C_{max}, AUC_(0-last), and AUC_(0-inf) were within 80%-125%.
- With multiple dosing, clinically significant differences were not observed based on evaluating the multiple dose data for darunavir C_{max} and AUC_(0-12h) for the oral suspension and the data for darunavir tablets using historical data from the TMC114-C171, TMC114-C123, and TMC114-C163 trials.

The applicant did not evaluate 600 mg single doses of darunavir for the darunavir suspension compared to darunavir tablets under fasted conditions. This is the standard bioequivalence trial design for immediate release products evaluating formulation differences. However, based on the current or proposed darunavir US prescribing information, both darunavir tablets and darunavir suspension are recommended to be administered with food, and the evaluation of 600 mg single doses of darunavir for the darunavir suspension compared to darunavir tablets under fed conditions is a reasonable alternative.

There were multiple issues that were reviewed in evaluating whether the results of the TMC114-C169 trial are applicable to the darunavir suspension formulation (F052) that is proposed for marketing in the United States. The following issues are not anticipated to affect the applicability of the TMC114-C169 trial results to the proposed US marketed darunavir suspension: a) the darunavir suspension that was administered in the trial (F051) is an experimental darunavir suspension formulation, b) the ritonavir capsules that were administered are the European marketed ritonavir capsules, and c) ritonavir capsules instead of ritonavir oral solution were used in combination with darunavir oral suspension. The results of the trial are also expected to be applicable to the current US marketed darunavir tablet strengths (75 mg, 150 mg, 400 mg, and 600 mg) based either on the results of a bioequivalence trial (for the 600 mg tablet strength) or through the approval of biowaivers.

3.1.2 TMC114-C228 trial

1. Title

A Phase II, open-label trial to evaluate pharmacokinetics, safety, tolerability and antiviral activity of DRV in combination with low-dose ritonavir (DRV/rtv) in treatment-experienced HIV-1 infected children from 3 to < 6 years of age. Week-24 Primary analysis. (Additional applicant information: This trial is referred to as ARIEL.)

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at multiple clinical trial sites in Argentina, Brazil, India, Kenya, and South Africa from September 29, 2009 to August 3, 2010.

3. Objectives

The primary objective of the trial was to evaluate the pharmacokinetics and antiviral activity of darunavir when combined with ritonavir in HIV-1 infected pediatric subjects 3 to less than 6 years old and to develop darunavir/ritonavir dosing recommendations for the 3 to less than 6 years old age group.

4. Trial Design

TMC114-C228 was an open label, clinical trial that enrolled HIV-1 infected pediatric subjects 3 to less than 6 years old weighing 10 kg to less than 20 kg at screening. The trial design included enrolling approximately 24 male and female HIV-1 infected pediatric subjects that were currently receiving a stable but failing antiretroviral treatment regimen (HIV-1 viral load >1000 copies/mL) that required a modification and had less than three darunavir associated substitutions. The subjects were to be categorized into two weight bands: 10 kg to < 15 kg and 15 kg to <20 kg. The initial dosing using a darunavir oral suspension (F052) in combination with ritonavir oral solution is displayed in Table 1 below. The initial dosing regimen was approximately 20 mg/kg of darunavir combined with approximately 3 mg/kg of ritonavir administered twice daily. The options available for trial investigators in choosing a background regimen are displayed in Table 2 (it was recommended that investigators select a minimum of two HIV-1 antiretroviral medications).

Table 1-Initial dosing of darunavir oral suspension (F052) in combination with ritonavir oral solution in TMC114-C228

Body Weight (kg)	DRV		rtv	
	Dose of Oral Suspension in mL b.i.d. ^a	Actual Dose in mg b.i.d. ^a (Range in mg/kg ^b)	Dose of Oral Solution in mL b.i.d. ^a	Actual Dose in mg b.i.d. ^a (Range in mg/kg ^b)
10 - 10.9	2.0	200 (18.3 - 20.0)	0.4	32 (2.9 - 3.2)
11 - 11.9	2.2	220 (18.5 - 20.0)	0.4	32 (2.7 - 2.9)
12 - 12.9	2.4	240 (18.6 - 20.0)	0.5	40 (3.1 - 3.3)
13 - 13.9	2.6	260 (18.7 - 20.0)	0.5	48 (3.5 - 3.7)
14 - 14.9	2.8	280 (18.8 - 20.0)	0.6	48 (3.2 - 3.4)
15 - 15.9	3.0	300 (18.9 - 20.0)	0.6	48 (3.0 - 3.2)
16 - 16.9	3.2	320 (18.9 - 20.0)	0.6	48 (2.8 - 3.0)
17 - 17.9	3.4	340 (19.0 - 20.0)	0.6	48 (2.7 - 2.8)
18 - 18.9	3.6	360 (19.0 - 20.0)	0.6	48 (2.5 - 2.7)
19 - 19.9	3.8	380 (19.1 - 20.0)	0.6	48 (2.4 - 2.5)

^a The DRV oral suspension was administered with a pipette with a 0.2-mL accuracy gradation; the rtv oral solution was administered with a pipette with a 0.1-mL accuracy gradation. Due to the accuracy limitations of the pipettes, a rounding was performed when calculating the doses to be administered per weight band.

^b The actual dose in mg/kg varied given the dose was fixed for each weight band.

Table 2-List of permitted and prohibited HIV-1 antiretroviral medications for the TMC114-C228 trial

ARV Class	Allowed	Disallowed
PIs	DRV/rtv	All other PIs
NRTIs	All NRTIs with available pediatric dose recommendations	-
NNRTIs	nevirapine efavirenz	Investigational NNRTI etravirine ^a delavirdine
Entry inhibitors (including fusion inhibitor)	-	maraviroc ^a , enfuvirtide ^a
Integrase inhibitors	-	raltegravir ^a

^a Once there were sufficient safety data on this ARV and there were dose recommendations for children between 3 and < 6 years, the ARV was allowed as part of the OBR.

5. Exclusion and Inclusion Criteria/Other Restrictions and Exceptions

Other than the prohibited HIV-1 antiretroviral medications listed in Table 2, use of CYP 3A inducers was not permitted from 14 days before the first administration of trial medication until the end of the treatment period and CYP 3A substrates with a narrow therapeutic index was not permitted from the first administration of trial medication until the end of the treatment period.

Other restrictions during the trial included prohibiting the use of liquids containing quinine or intake of grapefruit and grapefruit juice from 24 hours before the first administration of trial medication until Day 15.

6. Dosage and Administration

Darunavir oral suspension and ritonavir oral suspension were administered within 30

minutes after the end of a meal on a twice daily (every 12 hours) schedule. There were no restrictions on the type of meal that could be administered. The darunavir suspension was shaken prior to dose administration. Both the darunavir oral suspension and ritonavir oral suspension were administered using a syringe. The syringe for the darunavir oral suspension displayed measurements of 0.2 mL and the syringe for the ritonavir oral solution displayed measurements of 0.1 mL.

7. Rationale for Doses Used in the Trial

The initial darunavir doses (approximately 20 mg/kg) administered twice directly were based on the highest darunavir mg/kg dose (18.75 mg/kg) that was administered in the pediatric TMC114-C212 trial that evaluated the pharmacokinetics of darunavir/ritonavir in older pediatric subjects 6 to less than 18 years old. The highest darunavir dose of 18.75 mg/kg was selected in anticipation of preventing underdosing because of potential increased clearance in younger pediatric patients. The ritonavir doses (approximately 3 mg/kg) administered twice daily were designed to minimize the differences in the darunavir to ritonavir ratios between the different weight bands. For the ritonavir doses that were administered in the trial, the initial darunavir to ritonavir ratios ranged from 6:1 to 7.6:1.

After the Week 2 pharmacokinetic data was analyzed using population pharmacokinetic analysis, the applicant determined that a dose adjustment for darunavir was required. The adjusted dosage regimens are displayed in Table 3. The rationale for the dosage adjustment and the results of the population pharmacokinetic analysis are discussed in section 10. The adjusted dosage regimens were approximately 25 mg/kg of darunavir combined with approximately 3 mg/kg of ritonavir administered twice daily for pediatric subjects weighing between 10 kg to less than 15 kg and 375 mg of darunavir combined with approximately 50 mg of ritonavir administered twice daily for pediatric subjects weighing between 15 kg to less than 20 kg. The reasons for selecting these adjusted dosage regimens included limiting the need for weight based dosing to pediatric patients weighing less than 15 kg, and allowing interchangeability between darunavir tablets and darunavir oral suspension for pediatric patients weighing between 15 kg to less than 20 kg.

Table 3-Adjusted dosing of darunavir oral suspension (F052) in combination with ritonavir oral solution in TMC114-C228

Body Weight (kg)	DRV		rtv	
	Dose of Oral Suspension in mL b.i.d. ^a	Actual Dose in mg b.i.d. ^a (Range in mg/kg ^b)	Dose of Oral Solution in mL b.i.d. ^b	Actual Dose in mg b.i.d. ^a (Range in mg/kg ^b)
10 - 10.9	2.6	260 (23.8 - 26.0)	0.4	32 (2.9 - 3.2)
11 - 11.9	2.8	280 (23.5 - 25.5)	0.4	32 (2.7 - 2.9)
12 - 12.9	3.0	300 (23.3 - 25.0)	0.5	40 (3.1 - 3.3)
13 - 13.9	3.4	340 (24.5 - 26.1)	0.5	40 (2.9 - 3.1)
14 - 14.9	3.6	360 (24.2 - 25.7)	0.6	48 (3.2 - 3.4)
15 - 19.9	3.8	380	0.6	48

^a The DRV oral suspension was administered with a pipette with a 0.2-mL accuracy gradation; the rtv oral solution was administered with a pipette with a 0.1-mL accuracy gradation. Due to the accuracy limitations of the pipettes, a rounding was performed when calculating the doses to be administered per weight band.

^b The actual dose in mg/kg varied given the dose was fixed for each weight band.

8. Drugs Used in the Trial

Information regarding the darunavir and ritonavir formulations that were administered in the trial is displayed in Table 4. The darunavir oral suspension that was administered in the trial (F052) is the formulation that is proposed for marketing in the United States.

Table 4-Information on the darunavir and ritonavir formulations administered in the TMC114-C228 trial

Treatment	DRV suspension	Rtv solution	DRV tablet ^a
Concentration	100 mg/mL	80 mg/mL	75-mg tablet
Formulation Number	F052	-	F029
Usage	Oral	Oral	Oral
Batch Numbers	361887: (b) (4) 362473: (b) (4) 363405: (b) (4)	-	362432: (b) (4)

^a After the Week-24 analysis, upon guidance of the DSMB, children weighing ≥ 20 kg, and able and willing to swallow tablets, could switch to the DRV tablet formulation.

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Darunavir and ritonavir blood samples were obtained at week 2 at predose and up to 12 hours postdose. At weeks 4, 24, and 48 and for the visit two weeks after dose adjustment, two darunavir and ritonavir blood samples were obtained with the first sample collected prior to dose administration and the second sample collected a minimum of one hour or later after the first blood sample.

Reviewer note: the blood sampling for weeks 2 and 4 occurred with the initial darunavir dosage regimens and the blood sampling 2 weeks after dosage adjustment and at week 24 occurred with the adjusted darunavir dosage regimens.

Bioanalysis

The method and bioanalysis of darunavir and ritonavir are acceptable. Darunavir and ritonavir plasma samples were analyzed using a validated LC/MS/MS method in lithium heparin anticoagulated plasma by (b) (4) (a partial validation was later conducted and the calibration curve range for both darunavir and ritonavir was modified to include a lower limit of quantification of 5 ng/mL and the upper limit of quantification of 10000 ng/mL). The blood samples for analysis of darunavir and ritonavir were collected in tubes containing sodium heparin as an anticoagulant. An experiment to determine whether there are any accuracy or precision issues with using different anticoagulants was conducted and no issues were identified. For the TMC 114-C228 plasma samples that were analyzed for this submission that included data for the Week 24 analysis, for darunavir, the lower limit of quantification for darunavir was 5 ng/mL and the upper limit of quantification was 5000 ng/mL. There were no precision or accuracy

issues identified for darunavir based on the bioanalytical report, except for the low QC. For the TMC114-C228 trial, precision and accuracy were evaluated using plasma darunavir QC samples at four concentration levels: 15 ng/mL, 250 ng/mL, 1500 ng/mL (for runs 6 to 12 only), and 4000 ng/mL (in response to an information request, it was clarified that the 1500 ng/mL darunavir and ritonavir QC samples was added because the reported concentrations were at the upper end of the calibration curve range). The corresponding darunavir inter-run accuracy values were 12% for 15 ng/mL, -1.2% for 250 ng/mL, -4% for 1500 ng/mL and -4% for 4000 ng/mL. The darunavir inter-run precision values were 55.5% for 15 ng/mL, 5.8% for 250 ng/mL, 4% for 1500 ng/mL, and 3% for 4000 ng/mL. For the low darunavir QC, in each analytical run that was accepted, at least one of the two analyzed low QC samples met acceptance criteria. The lower limit of quantification for ritonavir was 5 ng/mL and the upper limit of quantification was 5000 ng/mL. There were no precision or accuracy issues identified for ritonavir based on the bioanalytical report. For the TMC114-C228 trial, precision and accuracy were evaluated using plasma ritonavir QC samples at 15 ng/mL, 250 ng/mL, 1500 ng/mL (for runs 6 to 12 only), and 4000 ng/mL. The corresponding ritonavir inter-run accuracy values were -2.7% for 15 ng/mL, -3.2% for 250 ng/mL, -9.3% for 1500 ng/mL and -0.3% for 4000 ng/mL. The ritonavir inter-run precision values were 4.8% for 15 ng/mL, 2.5% for 250 ng/mL, 3.5% for 1500 ng/mL, and 1.8% for 4000 ng/mL.

For the TMC114-C228 trial, the darunavir and ritonavir plasma samples were stored at -20°C at both at the clinical trial site and at the bioanalytical laboratory. The long term stability darunavir and ritonavir data of 1597 days covers the duration of long term stability data necessary for the TMC114-C228 trial.

The FDA Office of Scientific Investigations (OSI) was requested to conduct an inspection of the bioanalytical laboratory that analyzed darunavir and ritonavir plasma samples for the TMC114-C228 trial. Three 483 observations were issued, however the Office of Scientific Investigations does not believe that the 483 observations impact the trial results:

- 1) Failure to use fresh calibration standards in evaluating autosampler stability during method validation.
- 2) Lack of maintaining relevant documentation:
 - Failure to investigate the cause of a failed 21 hour autosampler stability experiment
 - Not tracking whether the multiple use calibration standard and quality control samples used for the bioanalysis of the TMC114-C228 samples were used within the established number of freeze thaw stability cycles.
- 3) Failure to maintain the audit trail for the initial data processing results for the darunavir and ritonavir samples analyzed for the TMC114-C228 trial.

To address the first 483 observation, (b) (4) will conduct an additional autosampler stability method validation experiment using freshly prepared calibration standards. The results of the second autosampler stability method validation experiment were acceptable. To address the second 483 observation related to the failure to

investigate the cause of a failed 21 hour autosampler stability experiment, a procedure was implemented mandating an investigation for failed validation experiment and a retroactive investigation concluded that contamination was the most likely reason for the failed experiment. To address the second 483 observation related to not tracking whether the multiple use calibration standard and quality control samples used for the bioanalysis of the TMC114-C228 samples were used within the established number of freeze thaw stability cycles, in the future, (b) (4) will label the calibration standard and quality control samples with identifiers that will be documented in the laboratory notebook. To address the third 483 observation related to the failure to maintain the audit trail for the initial data processing results for the darunavir and ritonavir samples analyzed for the TMC114-C228 trial, a new procedure was implemented and the data was reprocessed for the TMC114-C228 trial. The plasma concentration results were similar for both procedures.

Pharmacokinetic Assessments

Prior to dosage adjustment, at week 2, both population pharmacokinetic (PK) and noncompartmental analysis was performed. For the population PK analysis, darunavir $AUC_{(0-12h)}$ and C_{0h} were derived. For the noncompartmental analysis, darunavir and ritonavir plasma pharmacokinetic parameters were calculated, including t_{max} , C_{max} , C_{0h} , C_{min} , and $AUC_{(0-12h)}$.

After dosage adjustment, based on the pharmacokinetic data obtained two weeks after dosage adjustment, darunavir $AUC_{(0-12h)}$ and C_{0h} were derived using population PK analysis.

A population PK analysis was also performed to derive $AUC_{(0-12h)}$ and C_{0h} values for the initial and adjusted darunavir dosage regimens.

Statistical Analysis

For the noncompartmental analysis, descriptive statistics were calculated for darunavir and ritonavir plasma concentrations and pharmacokinetic parameters, including the number of subjects (n), mean, standard deviation, the coefficient of variation (CV%), median, and the minimum and maximum values.

The criterion to determine whether the darunavir dosage regimens provided sufficient darunavir exposure compared to adults receiving darunavir/ritonavir 600 mg/100 mg twice daily was based on evaluating the $AUC_{(0-12h)}$ that was derived using population PK analysis. If the $AUC_{(0-12h)}$ was less than 80% or greater than 130% of the target $AUC_{(0-12h)}$ of 62.3 $\mu\text{g}\cdot\text{hr}/\text{mL}$, a dosage adjustment could be implemented.

10. Results

10.1 Subject Demographics and Disposition

Table 5-TMC114-C228 subject demographics

Demographic Parameter	DRV/rtv
Sex, n (%), N	27
Female	12 (44.4)
Male	15 (55.6)
Age (years), N	27
Mean (SE)	4.6 (0.17)
Median (range)	4.5 (3.1; 5.8)
Race, n (%), N	27
Asian	1 (3.7)
Black or African American	18 (66.7)
Black or African American/White	2 (7.4)
White	6 (22.2)
Ethnicity, n (%), N	27
Hispanic or Latino	10 (37.0)
Not Hispanic or Latino	17 (63.0)
Height (cm), N	27
Mean (SE)	101.2 (1.43)
Median (range)	102.0 (90.0; 117.0)
Weight (kg), N	27
Overall Mean (SE)	15.3 (0.40)
Overall Median (range)	14.9 (11.9; 19.8)
BMI (kg/m²), N	27
Mean (SE)	14.9 (0.29)
Median (range)	14.7 (10.9; 18.3)
Z-Score for height, N	27
Mean (SE)	-1.4 (0.20)
Median (range)	-1.4 (-3.9; 0.6)
Z-Score for weight, N	27
Mean (SE)	-1.1 (0.18)
Median (range)	-1.1 (-3.6; 1.7)
Z-Score for BMI, N	27
Mean (SE)	-0.4 (0.24)
Median (range)	-0.4 (-4.4; 1.9)

N = number of subjects; n = number of observations

Table 6-Baseline HIV-1 infection information

Baseline Characteristic	DRV/rtv
Log₁₀ viral load (copies/mL), N	27
Mean (SE)	4.43 (0.150)
Median (Range)	4.51 (2.85; 5.74)
Viral load (copies/mL), n (%), N	27
< 20,000	11 (40.7)
20,000 - < 50,000	5 (18.5)
50,000 - < 100,000	4 (14.8)
≥ 100,000	7 (25.9)
CD4+ Percentage, N	21
Mean (SE)	30.1 (2.19)
Median (Range)	27.7 (15.6; 51.1)
CD4+ Percentage, N	21
≥ 25%	14 (66.7)
< 25%	7 (33.3)
CD4+ cell count (x 10⁶/L), N	21
Mean (SE)	1091 (131.6)
Median (Range)	927 (209 - 2429)
CD4+ cell count (x 10⁶/L), n (%), N	27
Missing	6 (22.2)
≥ 200	21 (77.8)
Known duration of HIV infection (years)	27
Mean (SE)	3.5 (0.25)
Median (range)	3.8 (0.1; 5.4)
DRV FC, n (%), N	22
Mean	0.55
Median (range)	0.5 (0.2; 2.3)
WHO Clinical Stage of HIV infection¹⁹, n (%), N	27
Clinical Stage 1 (asymptomatic)	6 (22.2)
Clinical Stage 2 (mild symptoms)	5 (18.5)
Clinical Stage 3 (advanced symptoms)	12 (44.4)
Clinical Stage 4 (severe symptoms)	4 (14.8)
Mode of HIV infection, n (%), N	27
Mother-to-child transmission	27 (100)
Clade, n (%), N	27
A1	5 (18.5)
B	5 (18.5)
C	11 (40.7)
CRF12_BF	4 (14.8)
D	1 (3.7)
F1	1 (3.7)
Hepatitis B or C coinfection status, n (%), N	27
Negative	12 (44.4)
Missing	15 (55.6)

N = number of subjects; n = number of observations

Table 7-TMC114-C228 subject disposition

n (%)	DRV/rtv
ITT Population	
N screened	42
N treated	27
N not treated	15
Discontinuations - Reason, n (%)	
AE	1 (3.7)
Ongoing	26 (96.3)

N = number of subjects; n = number of observations

10.2 Prior and Concomitant Medications

Information regarding the antiretroviral medications that HIV-1 infected pediatric subjects were receiving at screening and the initial antiretroviral medications that HIV-1 infected pediatric subjects were receiving on Day 7 or, for subjects that discontinued, the last treatment day during the first seven days is displayed in Tables 8 and 9. Information regarding the non antiretroviral medications that subjects received during the trial is displayed in Table 10. The concomitant medications that were administered in the trial are not anticipated to alter the trial's conclusions.

Table 8-Antiretroviral medications at screening

ARV, n (%)	DRV/rtv
Number of ARVs Used at Screening	
PIs, N	27
0	14 (51.9)
1	13 (48.1)
NRTIs, N	27
1	2 (7.4)
2	22 (81.5)
3	3 (11.1)
NNRTIs, N	27
0	19 (70.4)
1	8 (29.6)
ARVs Used at Screening	
PIs	13
Lopinavir	12 (44.4)
Nelfinavir	1 (3.7)
NRTIs	27
Abacavir	6 (22.2)
Didanosine	2 (7.4)
Lamivudine	23 (85.2)
Stavudine	11 (40.7)
Zidovudine	13 (48.1)
NNRTIs	8
Efavirenz	3 (11.1)
Nevirapine	5 (18.5)

N = number of subjects; n = number of observations

Table 9-Initial antiretroviral background medications

ARVs, n (%)	DRV/rtv
Number of ARVs in the Initial OBR	
NRTIs, N	27
2	25 (92.6)
3	2 (7.4)
ARVs Used in the Initial OBR	
NRTIs, N	27
Abacavir	14 (51.9)
Didanosine	5 (18.5)
Lamivudine	14 (51.9)
Stavudine	8 (29.6)
Tenofovir disoproxil fumarate	1 (3.7)
Zidovudine	14 (51.9)
NRTI Combinations in the Initial OBR, N	
	27
Abacavir + didanosine	4 (14.8)
Abacavir + lamivudine	1 (3.7)
Abacavir + lamivudine + zidovudine	1 (3.7)
Abacavir + stavudine	4 (14.8)
Abacavir + zidovudine	4 (14.8)
Didanosine + zidovudine	1 (3.7)
Lamivudine + stavudine	4 (14.8)
Lamivudine + tenofovir disoproxil fumarate + zidovudine	1 (3.7)
Lamivudine + zidovudine	7 (25.9)

N = number of subjects; n = number of observations

Table 10-Non antiretroviral medications administered during the trial in > 10% of subjects

Class, n (%)	DRV/rtv N = 27
Analgesics	11 (40.7)
Antianemic preparations	3 (11.1)
Antibacterials for systemic use	20 (74.1)
Antibiotics and chemotherapy for dermatological use	5 (18.5)
Antidiarr., intest. antiinfl./antiinfect. agents	6 (22.2)
Antifungals for dermatological use	5 (18.5)
Antihistamines for systemic use	4 (14.8)
Nasal preparations	3 (11.1)
Stomatological preparations	10 (37.0)
Vaccines	3 (11.1)
Vitamins	5 (18.5)

N = number of subjects; n = number of observations

10.3 Pharmacokinetic and Statistical Analysis

Table 11-Subjects with protocol deviations related to incorrect darunavir or ritonavir dose administration

CRF ID	Details on Dosing Error ^a	Dosing Error in mg ^b	Duration	Time Point(s)
Incorrect dose of DRV				
228-0005 ^c	93% of DRV dose ^d : 2.6 ISO 2.8 mL b.i.d.	260 ISO 280 mg b.i.d.	6 weeks	Week 8 to dose switch
	95% of DRV dose: 3.6 ISO 3.8 mL b.i.d.	360 ISO 380 mg b.i.d.	5 weeks	Dose switch to cut-off
228-0010	94% of DRV dose: 3.2 ISO 3.4 mL b.i.d.	320 ISO 340 mg b.i.d.	5.5 weeks	Week 8 to dose switch
228-0014 ^c	94% of DRV dose: 3.0 ISO 3.2 mL b.i.d.	300 ISO 320 mg b.i.d.	6 weeks	Week 8 to dose switch
	79% of DRV dose: 3.0 ISO 3.8 mL b.i.d.	300 ISO 380 mg b.i.d.	2 weeks	Dose switch to dose-switch follow-up
228-0018 ^c	175% of DRV dose: 4.2 ISO 2.4 mL b.i.d.	420 ISO 240 mg b.i.d.	2 weeks	Baseline to Week 2
228-0025	103% of DRV dose: 3.3 ISO 3.2 mL b.i.d.	330 ISO 320 mg b.i.d.	11 weeks	Baseline to dose switch
228-0033	88% of DRV dose: 3.0 ISO 3.4 mL b.i.d.	300 ISO 340 mg b.i.d.	16 weeks	Weeks 16 to 32
228-0038	94% of DRV dose: 3.4 ISO 3.6 mL b.i.d.	340 ISO 360 mg b.i.d.	8 weeks	Weeks 16 to 24
Incorrect dose of rtv				
228-0005 ^c	83% of rtv dose ^e : 0.5 ISO 0.6 mL b.i.d.	40 ISO 48 mg b.i.d.	4 weeks	Weeks 8 to 12
228-0038	83% of rtv dose: 0.5 ISO 0.6 mL b.i.d.	40 ISO 48 mg b.i.d.	8 weeks	Weeks 16 to 24
228-0042	83% of rtv dose: 0.5 ISO 0.6 mL b.i.d.	40 ISO 48 mg b.i.d.	4 weeks	Baseline to Week 4

ISO = instead of, '-' = missing data

^a Verbatim as on the CRF.

^b Equivalent of dosing in mg.

^c For this subject, see also Section 4.2.1.2.

^d DRV dose according to body weight following Table 1 or Table 20

^e Rtv dose according to body weight following Table 1 or Table 20

The applicant states in the TMC114-C228 trial report that the protocol deviations in Table 11 did not affect the trial's efficacy or safety results. The subjects listed in Table 11 that were excluded from one or more of the pharmacokinetic analyses displayed in 10.3A to 10.3E were as follows: 5, 10, 14, 18, 33, 38, and 42. The reasons for excluding specific subjects are discussed below.

A) Pre dose adjustment week 2 population PK analysis

Three subjects were excluded from the pre dose adjustment week 2 population PK analysis:

- 1) Subject 30 was excluded because the ritonavir plasma concentrations were all below the lower limit of quantification.
- 2) Subject 42 did not have blood samples drawn for pharmacokinetic analysis at week 2.
- 3) Subject 30 discontinued from the trial and did not have blood samples drawn for pharmacokinetic analysis at week 2.

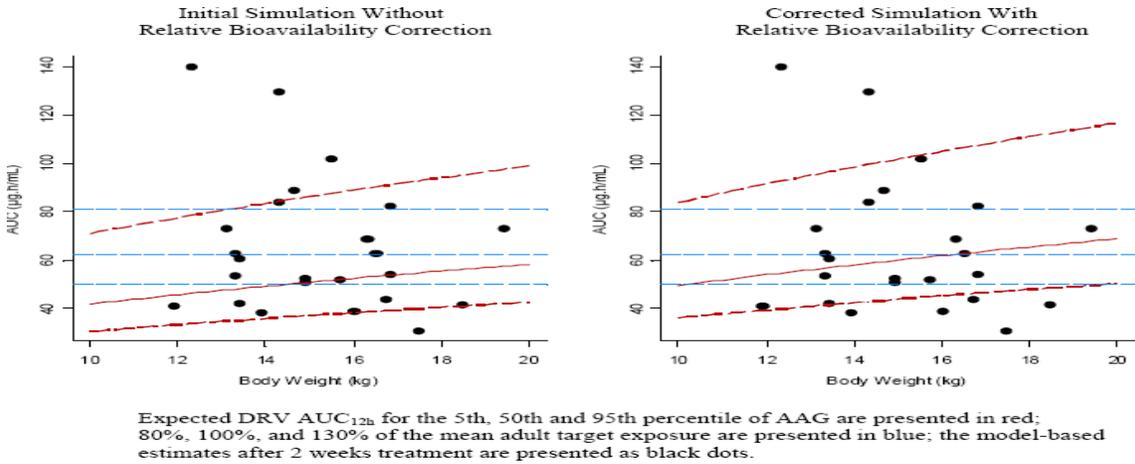
Table 12-Population pharmacokinetic parameters at Week 2 with darunavir 20 mg/kg combined with ritonavir 3 mg/kg twice daily

Weight group	N	Geometric Mean	Mean	SD	5th Percentile	Median	95th Percentile
<i>AUC_{12h} (µg.h/mL)</i>							
All subjects	24	60.7	65.4	27.8	38.8	57.6	125
10 - < 15 kg	13	65.0	70.7	32.3	40.2	61.0	133
15 - < 20 kg	11	56.0	59.3	21.0	35.3	54.2	91.9
<i>C_{0h} (ng/mL)</i>							
All subjects	24	3433	3927	2188	1662	3460	8779
10 - < 15 kg	13	3680	4289	2621	1950	3533	9411
15 - < 20 kg	11	3164	3500	1583	1607	3387	5897

The AUC_(0-12h) data in Table 12 indicates that the darunavir exposure for both the 10 kg to < 15 kg and the 15 kg to < 20 kg groups were within 80% to 130% of the target AUC_(0-12h) of 62.3 µg*hr/mL. The applicant's rationale for increasing the darunavir dose was based on the simulations that suggested the exposure with darunavir 20 mg/kg combined with ritonavir 3 mg/kg twice daily was low compared to the target exposure range. Lower darunavir exposure with lower body weights was also predicted based on the simulations.

However, the simulations that were conducted did not include a relative bioavailability factor for the difference in darunavir bioavailability for the Phase 2 and the marketed tablet. The applicant subsequently conducted an analysis with the relative bioavailability factor included and concluded that the rationale for adjusting the darunavir dose was still valid (see Figure 1).

Figure 1-Predicted darunavir exposure for 3 to less than 6 year olds receiving darunavir 20 mg/kg combined with ritonavir 3 mg/kg twice daily



B) Pre dose adjustment week 2 noncompartmental PK analysis

Table 13-Noncompartmental pharmacokinetic parameters at Week 2 with darunavir 20 mg/kg combined with ritonavir 3 mg/kg twice daily

<i>Pharmacokinetics of DRV at Week 2 (mean [SD], t_{max}: median [range])</i>	DRV/rtv 20/3 mg/kg b.i.d.
n	22 ^a
C _{0h} (ng/mL)	4321 (2955)
C _{min} (ng/mL)	2568 (1706)
C _{max} (ng/mL)	8196 (3284)
t _{max} (h)	3.00 (0.87 - 6.00)
AUC _{12h} (ng.h/mL)	60100 (25520)
FI (%)	112 (44.2)

^a n = 23 for C_{0h}, C_{max} and t_{max}

<i>Pharmacokinetics of rtv at Week 2 (mean [SD], t_{max}: median [range])</i>	DRV/rtv 20/3 mg/kg b.i.d.
n	22 ^a
C _{0h} (ng/mL)	646 (805)
C _{min} (ng/mL)	213 (140)
C _{max} (ng/mL)	1178 (842)
t _{max} (h)	3.08 (0.87-6.05)
AUC _{12h} (ng.h/mL)	8085 (4741)
FI (%)	149 (50.7)

^a n = 23 for C_{0h}, C_{max} and t_{max}

The subjects that were excluded from the noncompartmental analysis were as follows: 30 (discontinued prior to week 2), 42 (outlier for patient randomization date [no further explanation was provided]), 18 (received 175% of the darunavir dose), and 33 (suspected nonadherence). One subject (10) did not have darunavir and ritonavir C_{min}, AUC_(0-12h), and fluctuation index values calculated because the 12 hour sample at week 2 was taken postdose.

The applicant did not provide a comparison of the data in Table 12 to the adult

pharmacokinetic data in subjects receiving 600 mg of darunavir combined with 100 mg of ritonavir twice daily. However, based on evaluating the $AUC_{(0-12h)}$ data in Table 13, the darunavir exposure was within 80% to 130% of the target $AUC_{(0-12h)}$ of 62.3 $\mu\text{g}\cdot\text{hr}/\text{mL}$. The same conclusion was reached using the population PK analysis in Table 12.

C) Post dose adjustment (2 weeks after dose adjustment) population PK analysis

Nine subjects were excluded from the post dose adjustment (2 weeks after dose adjustment) population PK analysis. Subject 30 discontinued from the trial and did not have blood samples drawn for pharmacokinetic analysis and the following additional eight subjects were excluded:

Table 14-Subjects excluded from the post dose adjustment (2 weeks after dose adjustment) population PK analysis

Subject Number	Reason for exclusion
05	AAG measured in local lab, not central lab
10	AAG measured in local lab, not central lab
14	AAG measured in local lab, not central lab
18	AAG measured in local lab, not central lab
26	No ritonavir exposure in sample
33	No ritonavir exposure in sample
38	AAG measured in local lab, not central lab
42	AAG measured in local lab, not central lab, no PK sample available at Week 2

Reviewer's note: The information provided by the applicant in Table 15 differs from the information presented as part of the Data Safety Monitoring Board meeting minutes for June 30, 2010. The $AUC_{(0-12h)}$ pharmacokinetic data that were included in the meeting minutes was as follows: a) Overall mean: 77.3 $\mu\text{g}\cdot\text{hr}/\text{mL}$ (n=18), b) Mean (< 15 kg): 88.4 $\mu\text{g}\cdot\text{hr}/\text{mL}$ [n=8], and c) Mean: ≥ 15 kg: 68.3 $\mu\text{g}\cdot\text{hr}/\text{mL}$ [n=10].

Table 15-Darunavir population PK analysis results derived from the Week 24 analysis for the adjusted dosage regimen 2 weeks after dose adjustment (darunavir 25 mg/kg combined with ritonavir 3 mg/kg twice daily [10 kg to <15 kg and 375 mg of darunavir combined with 50 mg of ritonavir twice daily [15 to < 20 kg])

Weight group	N	Geometric Mean	Mean	SD	5 th Percentile	Median	95 th Percentile
<i>AUC_{12h} ($\mu\text{g}\cdot\text{h}/\text{mL}$)</i>							
All subjects	18	82.3	87.6	33.1	53.8	81.4	144
10 to <15 kg	4	117	118	19.1	97.2	119	137
15 to <20 kg	14	74.5	79.0	31.4	53.0	68.6	127
<i>C_{0h} (ng/mL)</i>							
All subjects	18	5061	5636	2737	2774	5168	10147
10 to <15 kg	4	8313	8394	1326	6924	8522	9686
15 to <20 kg	14	4392	4848	2526	2771	4365	8744

Based on the pharmacokinetic data that was presented to the Data Safety Monitoring

Board, it was concluded that the trial could proceed using the adjusted darunavir dosage regimens.

Reviewer note: For the analysis in “D”, the data includes the population PK parameters for weeks 2 and 4 with the initial darunavir dosage regimens and for the analysis in “E”, the data includes the population PK parameters for 2 weeks after dosage adjustment and at week 24 with the adjusted darunavir dosage regimens.

D) Population PK analysis for the initial dosage regimens

Eight subjects were excluded from the population PK analysis for the initial dosage regimens. Subject 30 discontinued from the trial and did not have blood samples drawn for pharmacokinetic analysis and the following additional seven subjects were excluded:

Table 16-Subjects excluded from the population PK analysis for the initial dosage regimens

Subject Number	Visit number	Time post dose (h)	Reason for exclusion
05	3, 4	All	AAG measured in local lab, not central lab
10	3, 4	All	AAG measured in local lab, not central lab
14	3, 4	All	AAG measured in local lab, not central lab
18	3, 4	All	AAG measured in local lab, not central lab
33	3, 4	All	No ritonavir exposure in sample
38	3, 4	All	AAG measured in local lab, not central lab
42	4	All	AAG measured in local lab, not central lab, no PK sample available at Visit 3

Visit 3 corresponds to Week 2, Visit 4 corresponds to Week 4.

Note: Subject 42 also did not have blood samples drawn for pharmacokinetic analysis at week 2

Table 17-Darunavir population PK analysis results for the initial dosage regimen (darunavir 20 mg/kg combined with ritonavir 3 mg/kg twice daily)

Parameter	Weight	N	Mean	Geometric Mean	SE	SD	95% CI	Minimum	5th Percentile	25th Percentile	Median	75th Percentile	95th Percentile	Maximum
AUC _{12h} (ng·h/mL)	All	19	66.9	62.4	6.0	26.1	55.1 - 78.7	27.1	35.4	50.0	61.8	80.5	114	132
	10 - < 15 kg	10	68.9	65.6	8.1	25.5	53.0 - 84.8	46.7	47.1	52.8	61.8	71.4	113	132
	15 - < 20 kg	9	64.7	59.1	9.4	28.1	46.3 - 83.1	27.1	30.8	49.0	53.5	86.9	104	112
C _{0h} (ng/mL)	All	19	4220	3749	477	2081	3285 - 5155	1057	1783	2761	3773	5432	7642	9498
	10 - < 15 kg	10	4445	4117	651	2059	3169 - 5721	2607	2682	3126	4025	4695	7943	9498
	15 - < 20 kg	9	3969	3379	733	2200	2532 - 5406	1057	1380	2588	3306	6124	6956	7435
C _{ss,ave} (ng/mL)	All	19	5575	5201	499	2175	4597 - 6553	2256	2951	4168	5151	6709	9514	10956
	10 - < 15 kg	10	5740	5463	671	2123	4425 - 7055	3889	3924	4402	5153	5951	9385	10956
	15 - < 20 kg	9	5391	4924	782	2345	3858 - 6924	2256	2565	4083	4460	7243	8667	9354
CLF (L/h)	All	19	5.15	4.76	0.53	2.31	4.11 - 6.19	2.13	3.03	3.76	4.23	6.06	9.15	12.26
	10 - < 15 kg	10	4.23	4.09	0.35	1.10	3.54 - 4.92	2.13	2.58	3.89	4.22	4.78	5.72	6.13
	15 - < 20 kg	9	6.17	5.64	0.97	2.91	4.27 - 8.07	3.63	3.63	3.68	5.98	7.01	10.88	12.26

Notes:

1) The units in the table should be µg/mL*hr for AUC_(0-12h).

2) The population PK analysis includes the pharmacokinetic data from weeks 2 and 4.

E) Population PK analysis for the adjusted dosage regimens

Four subjects were excluded from the population PK analysis for the initial dosage regimens. Subject 30 discontinued from the trial and did not have blood samples drawn for pharmacokinetic analysis and three additional subjects were excluded (26, 33, and 38) that are included in Table 18 below:

Table 18-Subjects excluded from the population PK analysis for the adjusted dosage regimens

Subject Number	Visit number	Time post dose (h)	Reason for exclusion
05	105	All	AAG measured in local lab, not central lab
10	105	All	AAG measured in local lab, not central lab
14	105	All	AAG measured in local lab, not central lab, Protocol deviation : >20% difference in DRV dose
18	105	All	AAG measured in local lab, not central lab
26	105, 8	All	No ritonavir exposure in sample
33	105, 8	All	No ritonavir exposure in sample
38	105, 8	All	AAG measured in local lab, not central lab
42	105	All	AAG measured in local lab, not central lab

Visit 105 corresponds to post-dose adjustment visit, Visit 8 corresponds to Week 24.

Table 19-Darunavir population PK analysis results for the adjusted dosage regimen (darunavir 25 mg/kg combined with ritonavir 3 mg/kg twice daily [10 kg to <15 kg and 375 mg of darunavir combined with 50 mg of ritonavir twice daily [15 to < 20 kg])

Parameter	Weight	N	Mean	Geometric Mean	SE	SD	95% CI	Minimum	5th Percentile	25th Percentile	Median	75th Percentile	95th Percentile	Maximum
AUC _{0-12h} (ng.h/mL)	All	23	79.6	75.9	5.7	27.1	68.4 - 90.8	52.0	52.8	59.0	71.4	89.1	128	158
	10 - < 15 kg	7	87.1	83.6	10.2	26.9	67.1 - 107	57.1	57.5	64.0	90.7	102	122	130
	15 - < 20 kg	16	76.3	72.8	6.8	27.4	63.0 - 89.6	52.0	52.6	59.0	70.0	83.7	125	158
C _{0h} (ng/mL)	All	23	4993	4600	463	2220	4086 - 5900	2708	2749	3221	4227	6121	8842	11270
	10 - < 15 kg	7	5833	5474	816	2158	4234 - 7432	3251	3358	3917	6488	7144	8442	8974
	15 - < 20 kg	16	4626	4263	553	2212	3542 - 5710	2708	2727	3050	4031	4955	8555	11270
C _{ss,ave} (ng/mL)	All	23	6634	6326	471	2258	5711 - 7557	4331	4404	4920	5953	7429	10706	13190
	10 - < 15 kg	7	7260	6963	848	2244	5598 - 8922	4759	4788	5330	7555	8506	10197	10835
	15 - < 20 kg	16	6360	6066	570	2281	5243 - 7477	4331	4379	4917	5836	6979	10451	13190
CL/F (L/h)	All	23	5.08	4.86	0.30	1.45	4.49 - 5.67	2.41	2.80	4.29	5.17	6.21	7.19	7.32
	10 - < 15 kg	7	4.26	4.09	0.48	1.28	3.32 - 5.20	2.79	2.82	3.17	4.24	5.16	5.84	6.13
	15 - < 20 kg	16	5.44	5.24	0.35	1.41	4.75 - 6.13	2.41	3.11	4.48	5.43	6.48	7.23	7.32

Notes:

- 1) The units in the table should be µg/mL*hr for AUC_(0-12h).
- 2) The population PK analysis includes the pharmacokinetic data from 2 weeks after dosage adjustment and week 24.

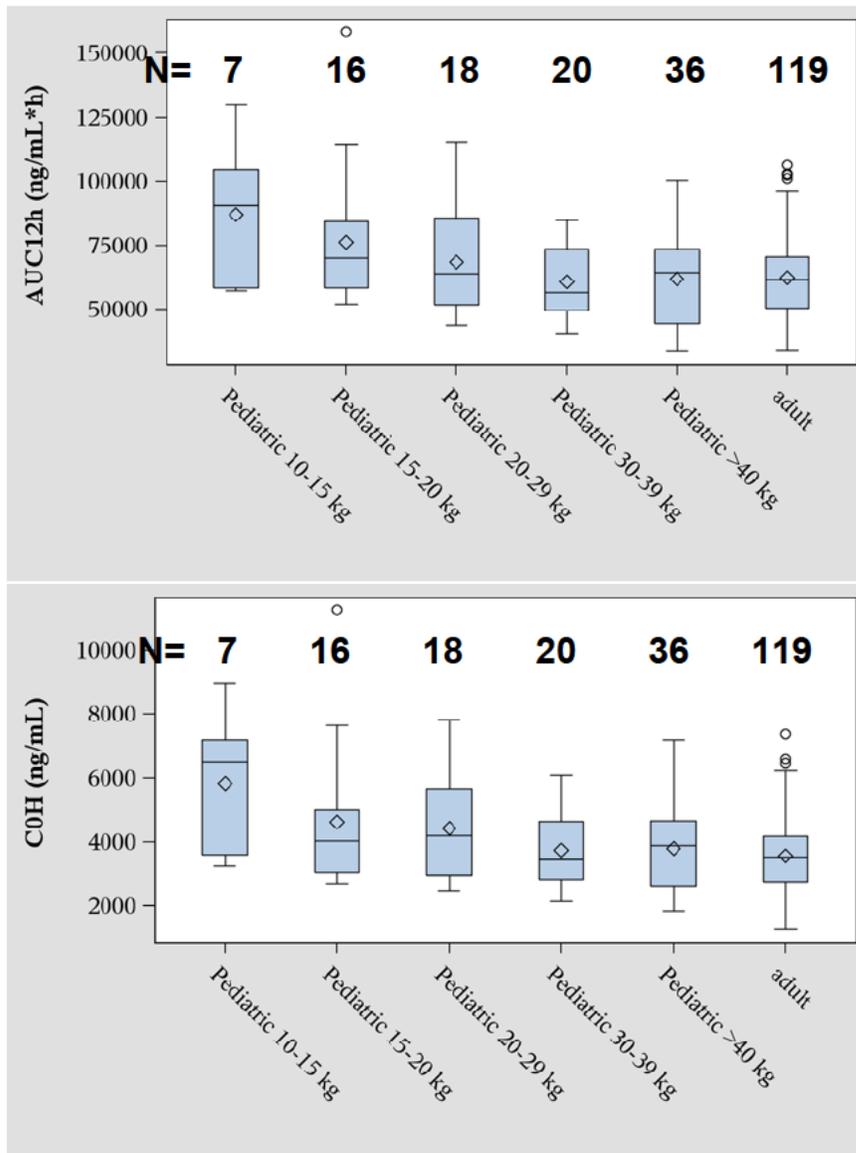
Table 20-Comparison of the mean darunavir AUC_(0-12h) values prior to and subsequent to the adjustment of the darunavir dosage regimens to the mean target adult exposure

Before Dose Adjustment			After Dose Adjustment		
Overall	10 to < 15 kg	15 to < 20 kg	Overall	10 to < 15 kg	15 to < 20 kg
107%	111%	104%	128%	140%	122%

Note:

1) The mean AUC_(0-12h) values in Tables 14 and 15 are compared to the mean adult target exposure of 62.3 µg/mL*hr.

Figure 2-Darunavir AUC_(0-12h) and C_{0h} after dosage adjustment in 3 to < 6 year olds (10 kg to < 20 kg) compared to 6 to < 18 year olds (20 kg to > 40 kg) and adults



For the initial darunavir dosage regimens, the darunavir mean $AUC_{(0-12h)}$ value was within 80% to 130% of the target mean adult $AUC_{(0-12h)}$ of 62.3 $\mu\text{g}\cdot\text{hr}/\text{mL}$ for pediatric subjects weighing 10 kg to less than 15 kg or 15 kg to less than 20 kg. For the adjusted darunavir dosage regimens, the darunavir mean $AUC_{(0-12h)}$ value was within 80% to 130% of the target mean adult $AUC_{(0-12h)}$ of 62.3 $\mu\text{g}\cdot\text{hr}/\text{mL}$ for pediatric subjects weighing 15 kg to less than 20 kg but was greater than 130% for pediatric subjects weighing 10 kg to less than 15 kg. The 40% higher $AUC_{(0-12h)}$ for pediatric subjects weighing 10 kg to less than 15 kg compared to the target adult exposure is not expected to result in any safety issues based on the exposure-safety information for darunavir (see section 10.6). When the darunavir exposure after dosage adjustment for pediatric subjects 3 to less than 6 years old (10 kg to < 20 kg) was compared to 6 to less than 18 year olds (20 kg to greater than 40 kg) and adults, the range of $AUC_{(0-24h)}$ and C_{0h} values were generally similar with the exception of the 10 kg to less than 15 kg group.

In prior darunavir Clinical Pharmacology reviews, based on the population PK modeling, lower darunavir exposure were observed in subjects with lower baseline AAG concentration. Consistent with these results, in the current trial, lower $AUC_{(0-12h)}$ values were observed in subjects with lower AAG concentrations. In the Clinical Pharmacology review evaluating the pharmacokinetics of darunavir in older HIV-1 infected subjects 6 to less than 18 years old (NDA 21976-supplement 9), a slight trend was observed of greater changes in viral load from baseline for subjects with higher baseline AAG concentrations. An analysis was not conducted by the applicant to determine if a similar trend is observed in HIV-1 infected pediatric subjects 3 to less than 6 years old. However, in older HIV-1 infected subjects, it was concluded an increase in the darunavir dose was not warranted in pediatric subjects with lower baseline AAG concentrations.

10.4 Efficacy Analysis

The result of the Week 24 efficacy analysis evaluating the percentage of HIV-1 infected subjects with HIV-1 RNA viral load less than 50 copies/mL was analyzed by the applicant using two methods: TLOVR and the FDA snapshot. An efficacy analysis was also conducted evaluating the percentage of HIV-1 infected subjects with HIV-1 RNA viral load less than 400 copies/mL using TLOVR. The results are displayed in Tables 21, 22, and 23.

Table 21-Efficacy analysis evaluating the percentage of HIV-1 infected subjects with HIV-1 RNA viral load less than 50 copies/mL using TLOVR at Week 24

Analysis	DRV/rtv	
	N	n (%)
TLOVR	27	15 (55.6)
Observed Case	25	16 (64.0)
NC = F	27	16 (59.3)
TLOVR non-VF censored	26	15 (57.7)

N = number of subjects; n = number of responders

Table 22-Efficacy analysis evaluating the percentage of HIV-1 infected subjects with HIV-1 RNA viral load less than 50 copies/mL using FDA snapshot at week 24^a

n (%)	DRV/rtv N = 27
Virologic success (< 50 copies/mL) at Week 24	16 (59.3)
Virologic failure ^b	9 (33.3)
No virologic data at Week 24 - Discontinued due to AE/death ^c	1 (3.7)
Missing data at Week 24	1 (3.7)

N = number of subjects; n = number of responders

^a Visit window; Week 20 to 28.

^b Includes a) subjects who had ≥ 50 copies/mL in the Week-24 window, b) subjects who discontinued prior to Week 24 for lack or loss of efficacy, c) subjects who had a switch in their OBR that was not permitted by the protocol (provided the switch occurred before the earliest onset of an AE leading to permanent stop of trial medication), and d) subjects who discontinued for reasons other than AEs/death, and lack or loss of efficacy (provided their last available viral load was detectable).

^c Includes subjects who discontinued due to AE or death at any time point from Day 1 through the Week-24 time window if this resulted in no virologic data on treatment during the specified window (provided the earliest AE leading to permanent stop was not preceded by a switch in the OBR that was not permitted by the protocol).

Table 23-Efficacy analysis evaluating the percentage of HIV-1 infected subjects with HIV-1 RNA viral load less than 400 copies/mL using TLOVR

Time Point	DRV/rtv	
	N	n (%)
Viral Load < 400 Copies/mL		
Week 2	27	9 (33.3)
Week 4	27	12 (44.4)
Week 8	27	19 (70.4)
Week 16	27	24 (88.9)
Week 24	27	24 (88.9)

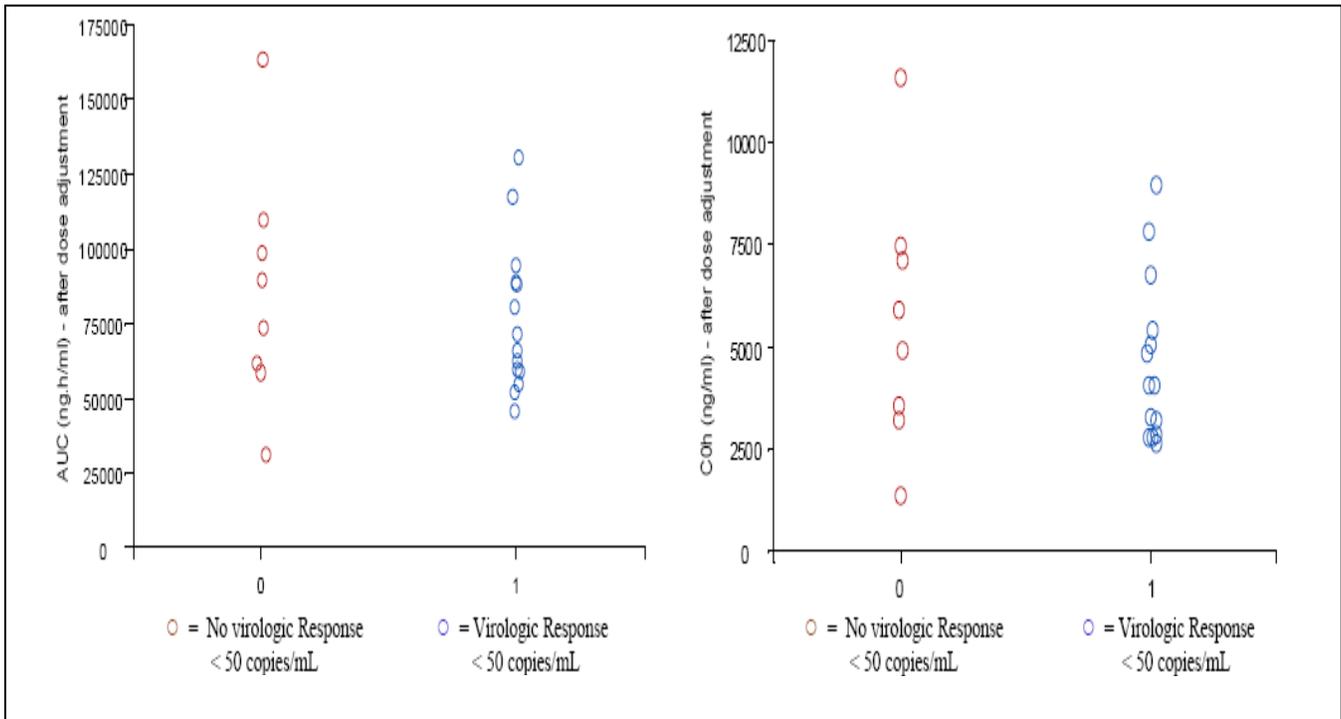
N = number of subjects; n = number of responders

10.5 Exposure-Response Analysis

10.5.1 Applicant Exposure-Response Analysis

In Figure 3, the applicant compared the range of darunavir $AUC_{(0-12h)}$ and C_{0h} (for the adjusted darunavir dosage regimens) for subjects achieving virologic response to subjects that did not achieve virologic response (HIV-1 RNA less than 50 copies/mL).

Figure 3-Comparison of AUC_(0-12h) and C_{0h} (for the adjusted darunavir dosage regimens) for subjects either achieving virologic response or not achieving virologic response (HIV-1 RNA less than 50 copies/mL)

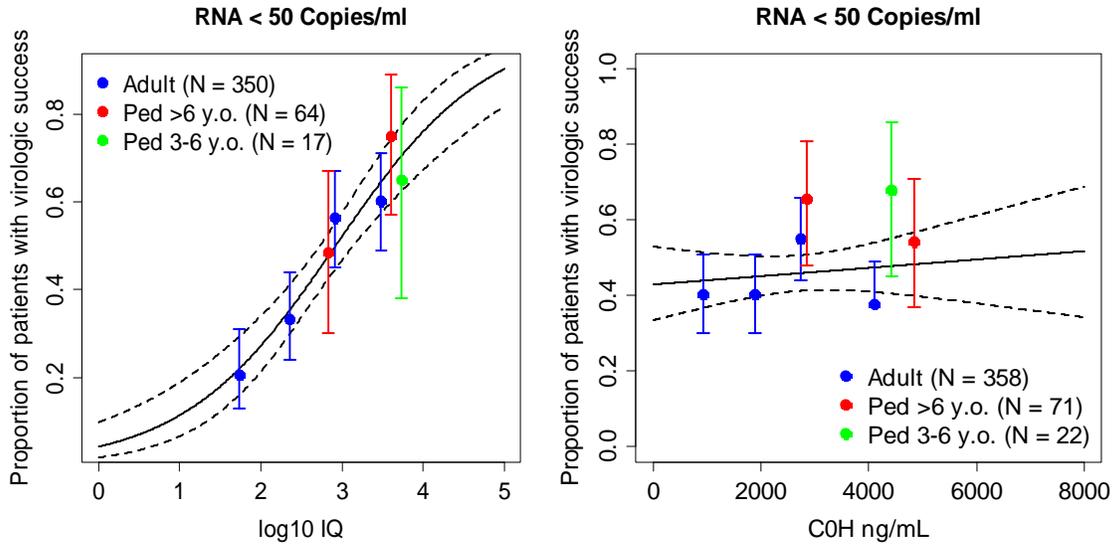


When pediatric subjects achieving HIV-1 RNA less than 50 copies/mL were compared to pediatric subjects that did not achieve HIV-1 RNA less than 50 copies/mL, the range of darunavir AUC_(0-12h) and C_{0h} values were similar.

10.5.2 FDA Exposure-Response Analysis

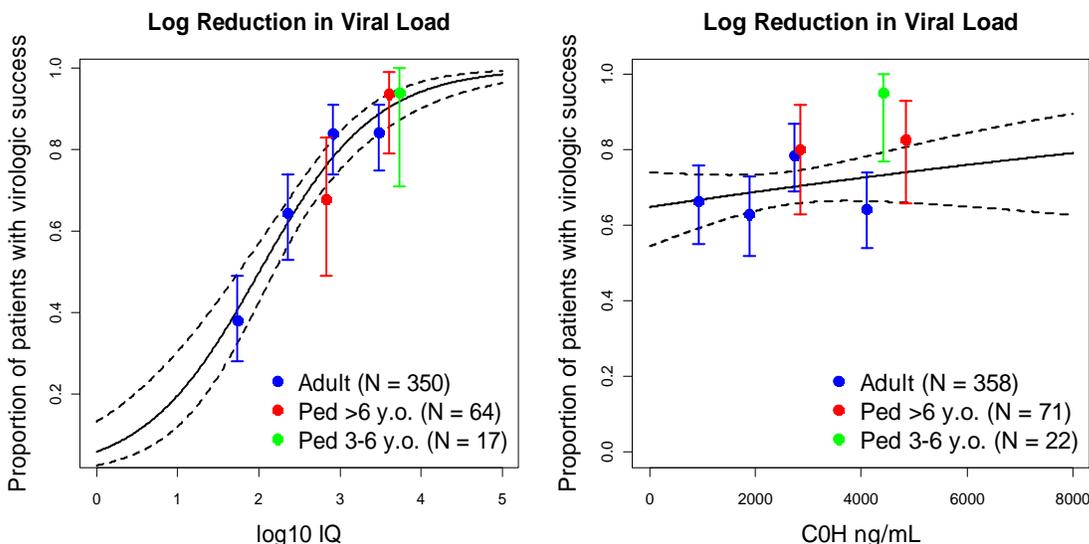
The Pharmacometrics reviewer conducted additional darunavir exposure-response analyses that included an evaluation of the inhibitory quotient (IQ) and the proportion of subjects achieving HIV-1 RNA less than 50 copies/mL and IQ and the proportion of subjects achieving a one log reduction in viral load. For the analysis that was conducted for the review, the IQ was defined as the ratio of darunavir C_{0h} (exposure) at steady state and IC₅₀ (a measurement of the ability of darunavir to inhibit HIV-1 virus). The C_{0h} concentrations reflect the values obtained after adjustment of the darunavir dosage regimens. In addition, the analysis was compared to the results that were previously obtained in older pediatric subjects (6 to less than 18 years old) and adults. The analyses are displayed in Figures 4 and 5.

Figure 4-Evaluation of IQ and darunavir C_{0h} (for the adjusted darunavir dosage regimens) and the proportion of subjects achieving virologic response (HIV-1 RNA less than 50 copies/mL)



Note: Each vertical bar represents the proportion of subjects with virologic success (and the 95% confidence interval) at the median value (log₁₀ IQ ratio or darunavir C_{0h}) for a given dataset.

Figure 5-Evaluation of IQ and darunavir C_{0h} (for the adjusted darunavir dosage regimens) and the proportion of subjects achieving virologic response (one log reduction in viral load)



Note: Each vertical bar represents the proportion of subjects with virologic success (and the 95% confidence interval) at the median value (\log_{10} IQ ratio or darunavir C_{0h}) for a given dataset.

The data for pediatric subjects 3 to less than 6 years old were not broken down into multiple groups (the data for older pediatric subjects 6 to less than 18 years old was divided into two quantiles and the adult data was divided into quartiles). Therefore, for pediatric subjects 3 to less than 6 years old, the relationship between the inhibitory quotient (IQ) and the proportion of subjects achieving HIV-1 RNA less than 50 copies/mL or IQ or a one log reduction in viral load could not be evaluated. In Figures 4 and 5, each vertical bar in the plots represents the proportion of subjects with virologic success (and the 95% confidence interval) at the median value (\log_{10} IQ ratio or darunavir C_{0h}) for a given dataset. For pediatric subjects 3 to less than 6 years old, the vertical bar was generally consistent with the vertical bars from older pediatric subjects (6 to less than 18 years old) and adults.

10.6 Safety Analysis

Adverse event information for the TMC114-C228 trial is displayed in Tables 24 and 25.

Table 24-TMC114-C228 adverse event summary information

n (%)	DRV/rtv		
	Overall N = 27	Before Dose Adjustment N = 27	After Dose Adjustment N = 26
<i>Mean Exposure (Weeks)</i>	<i>30.5</i>	<i>12.8</i>	<i>18.4</i>
≥ 1 AE	23 (85.2)	19 (70.4)	17 (65.4)
≥ 1 grade 3 or 4 AE	5 (18.5)	4 (14.8)	1 (3.8)
≥ 1 AE at least possibly related to DRV	5 (18.5)	3 (11.1)	2 (7.7)
≥ 1 AE ≥ grade 2 and at least possibly related to DRV	2 (7.4)	1 (3.7)	1 (3.8)
≥ 1 SAE	3 (11.1)	2 (7.4)	1 (3.8)
≥ 1 AE leading to permanent discontinuation	1 (3.7)	1 (3.7)	0

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

Note: Because subjects can have different AEs before compared to after dose adjustment, the sum of the incidences before and after dose adjustment can be greater than the incidence for the overall treatment period.

Table 25-TMC114-C228 adverse events reported in greater than one subject (regardless of severity or causality)

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv		
	Overall N = 27	Before Dose Adjustment N = 27	After Dose Adjustment N = 26
<i>Mean Exposure (Weeks)</i>	<i>30.5</i>	<i>12.8</i>	<i>18.4</i>
<i>Any AE</i>	<i>23 (85.2)</i>	<i>19 (70.4)</i>	<i>17 (65.4)</i>
Blood and Lymphatic System Disorders	3 (11.1)	3 (11.1)	0
Neutropenia	2 (7.4)	2 (7.4)	0
Cardiac Disorders	2 (7.4)	2 (7.4)	0
Tachycardia	2 (7.4)	2 (7.4)	0
Eye Disorders	2 (7.4)		
Gastrointestinal Disorders	12 (44.4)	11 (40.7)	1 (3.8)
Diarrhea	8 (29.6)	8 (29.6)	0
Vomiting	3 (11.1)	3 (11.1)	0
General Disorders and Administration Site Conditions	3 (11.1)	2 (7.4)	1 (3.8)
Pyrexia	3 (11.1)	2 (7.4)	1 (3.8)
Infections and Infestations	20 (74.1)	12 (44.4)	12 (46.2)
Impetigo	2 (7.4)	2 (7.4)	0
Nasopharyngitis	4 (14.8)	0	4 (15.4)
Otitis media acute	2 (7.4)	1 (3.7)	1 (3.8)
Otitis media chronic	2 (7.4)	1 (3.7)	1 (3.8)
Pharyngitis	2 (7.4)	1 (3.7)	1 (3.8)
Pneumonia	2 (7.4)	1 (3.7)	1 (3.8)
Rhinitis	3 (11.1)	3 (11.1)	0
Tinea capitis	2 (7.4)	1 (3.7)	1 (3.8)
Upper respiratory tract infection	9 (33.3)	7 (25.9)	2 (7.7)
Injury, Poisoning and Procedural Complications	3 (11.1)	1 (3.7)	2 (7.7)
Investigations	6 (22.2)	3 (11.1)	4 (15.4)
Metabolism and Nutrition Disorders	6 (22.2)	6 (22.2)	0
Acidosis	3 (11.1)	3 (11.1)	0
Alkalosis	4 (14.8)	4 (14.8)	0
Hypokalemia	5 (18.5)	5 (18.5)	0
Hyponatremia	2 (7.4)	2 (7.4)	0
Respiratory, Thoracic and Mediastinal Disorders	5 (18.5)	5 (18.5)	2 (7.7)
Cough	4 (14.8)	4 (14.8)	-
Nasal congestion	2 (7.4)	1 (3.7)	1 (3.8)
Rhinorrhea	2 (7.4)	1 (3.7)	1 (3.8)
Skin and Subcutaneous Tissue Disorders	5 (18.5)	3 (11.1)	3 (11.5)

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

10.7 Exposure-Safety Analysis

There were no additional exposure-safety analyses that were conducted by the FDA for pediatric subjects 3 to less than 6 years old. The adverse events that were reported for the trial did not warrant further exposure response analysis (see Tables 20 and 21). No

relevant trends were identified for the exposure-safety analyses that were conducted by the applicant.

11. Discussion and Conclusions

Based on the results from the TMC114-C228 trial, the following conclusions can be made regarding the proposed darunavir/ritonavir pediatric dosage regimens in pediatric patients (b) (4)

- The darunavir mean $AUC_{(0-12h)}$ value was within 80% to 130% of the target mean adult $AUC_{(0-12h)}$ of 62.3 $\mu\text{g}\cdot\text{hr}/\text{mL}$ for pediatric subjects weighing 15 kg to < 20 kg (22% higher) but was greater than 130% for pediatric subjects weighing 10 kg to < 15 kg (40% higher).
- The 40% higher $AUC_{(0-12h)}$ value for pediatric subjects weighing 10 kg to < 15 kg compared to the target adult exposure is not expected to result in any safety issues.
- When compared to 6 to <18 years olds (20 kg to > 40 kg) and adults, the darunavir $AUC_{(0-24h)}$ and C_{0h} values for pediatric subjects 3 to < 6 years old (10 kg to < 20 kg), were generally similar with the exception of the 10 kg to <15 kg group.
- When pediatric subjects achieving HIV-1 RNA less than 50 copies/mL were compared to pediatric subjects that did not achieve HIV-1 RNA less than 50 copies/mL, the range of darunavir $AUC_{(0-12h)}$ and C_{0h} values were similar.
- When the proportion of subjects with virologic success (<50 copies/mL or one log reduction in viral load) at the median value (\log_{10} IQ ratio or darunavir C_{0h}) were evaluated, the results for pediatric subjects 3 to < 6 years old were generally consistent with the previous results from older pediatric subjects (6 to less than 18 years old) and adults.
- No relevant exposure-safety trends were identified for the trial.

**OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW**

Application Number	NDA 202895
Submission Number (Date)	23 Nov 2010
Drug Name	Darunavir
Proposed Indication	Treatment of HIV-1 infection in pediatric subjects 3 to 6 years old
Clinical Division	DAVP
Primary CP Reviewer	Stanley Au, Pharm.D., BCPS
Primary PM Reviewer	Jiang Liu, Ph.D.
Secondary CP Reviewer	Sarah Robertson, Pharm.D.
Secondary PM Reviewer	Pravin Jadhav, Ph.D.
Applicant	Tibotec, Inc.

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The main purpose of this review is to determine whether the proposed dosing regimen for darunavir(DRV)/ritonavir(RTV) in pediatric subjects 3 to < 6 years of age (Table 1) is acceptable.

Table 1. Proposed Dosing Regimen for DRV Oral Suspension in Combination with RTV for Pediatric Subjects 3 to < 6 Years of Age

Body Weight		Dose (twice daily)
(kg)	(lbs)	

(b) (4)

The review will focus on the following sub-questions.

1.1.1 Does the proposed DRV/RTV dosing regimen in pediatric subjects 3 to < 6 years of age (10^{(b) (4)} kg) achieve similar exposures to that of other pediatric subjects (>20 kg) and adults receiving the approved dosing regimens?

The proposed DRV/RTV dosing regimen (Table 1) in pediatric subjects 3 to < 6 years of age achieve higher exposures compared to exposures in other pediatric subjects (>20 kg) and adults receiving the approved dosing regimen. The pharmacokinetic data were

derived from subjects weighing 10-<15 kg (N=7) and 15-<20 kg (N=16) after DRV oral suspension doses were adjusted in the TMC114-C228 trial. The results showed that the mean DRV exposure (AUC_{12} and C_{0h}) was about 40% and 20% higher in the 10-<15 kg and 15-<20 kg weight groups after receiving DRV oral suspension compared to exposures in adults at the approved 600 mg DRV/100 mg RTV b.i.d. tablets (TMC114-C202 and TMC114-C213 trials) (Figure 1 and Figure 2). The AUC_{12} and C_{0h} in other pediatric subjects (≥ 20 kg from TMC114-C212) at the approved twice daily regimen were within the exposures observed in adults and pediatric subjects weighing 10- <20 kg.

Figure 1. DRV AUC_{12} (ng*h/mL) in adult and pediatric subjects at the proposed dosing regimen

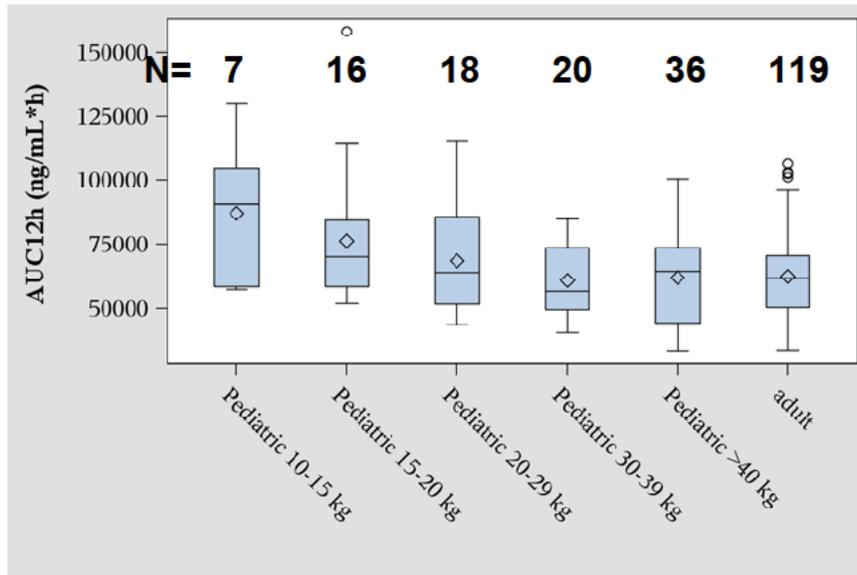
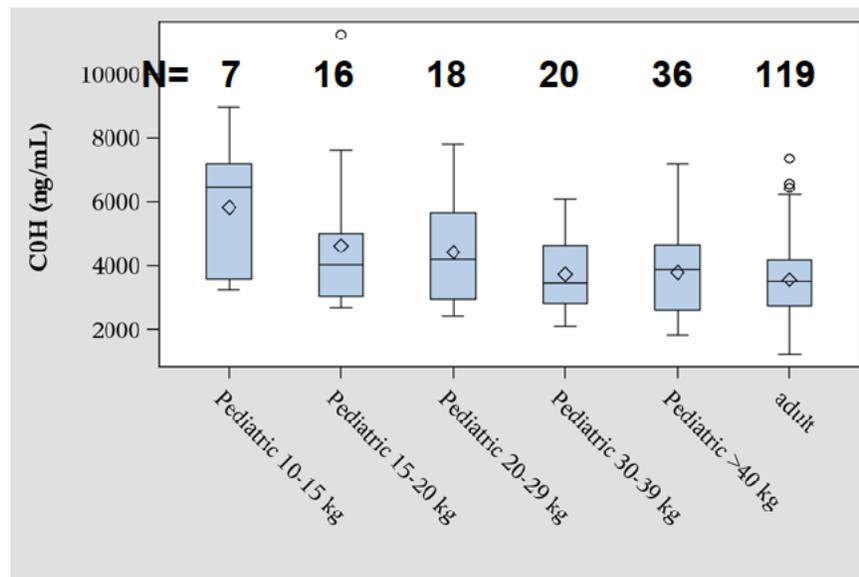


Figure 2. DRV C_{0h} (ng/mL) in adult and pediatric subjects at the proposed dose



1.1.2 Is the inhibitory quotient (IQ)-response relationship for efficacy in pediatric subjects 3 to < 6 years of age consistent with that of other pediatric subjects (6 to <18 years) and adults?

The IQ-response relationship in pediatric subjects 3 to <6 years of age was consistent with the relationship observed in other pediatric subjects (6 to < 18 years old) and adults. The inhibitory quotient (IQ) is the ratio of steady-state trough concentration (C_{0h}) and the baseline IC₅₀ value. The IQ combines the drug concentration and the susceptibility of the virus to DRV. As observed in other pediatric subjects and adults, the fold-change (FC) resistance is the primary driver of the virologic success in pediatric subjects 3 to <6 years of age. The pharmacometric review of DRV for the treatment-experienced adults from the TMC114-C202 and TMC114-C213 trials and for pediatric subjects 6 to < 18 years of age from the TMC114-C212 trial demonstrated that the probability of virologic response or success (measured as HIV-1 RNA <50 copies/mL or 1 log reduction in viral load by week 24) was strongly related to increasing IQ values. On the other hand, the relationship between C_{0h} and the probability of virologic response or success was shallow. The data in pediatric subjects 3 to <6 years of age from the study TMC114-C228 was consistent with the previously observed relationships between IQ and C_{0h} (Figure 3 and Figure 4). For those subjects 3 to <6 years of age with complete IQ and viral load data at week 24, 68% of subjects had a viral load < 50 copies/ml and 95% of subjects experienced at least a one log drop decrease in plasma viral load.

Figure 3. Relationship between IQ (left) or C_{0h} (right) and the Probability of Virologic Success (HIV-1 RNA < 50 copies/mL at Week 24) in Adults and Pediatric Subjects. The solid line represents the logistic regression model fit for the data in adults. The dotted lines represent the 95% confidence interval.

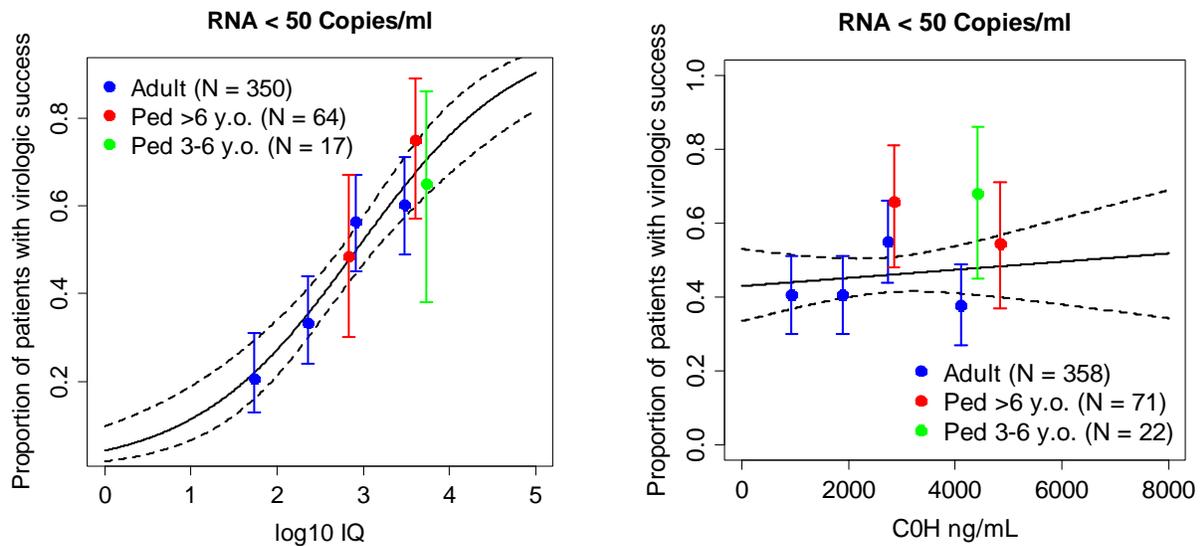
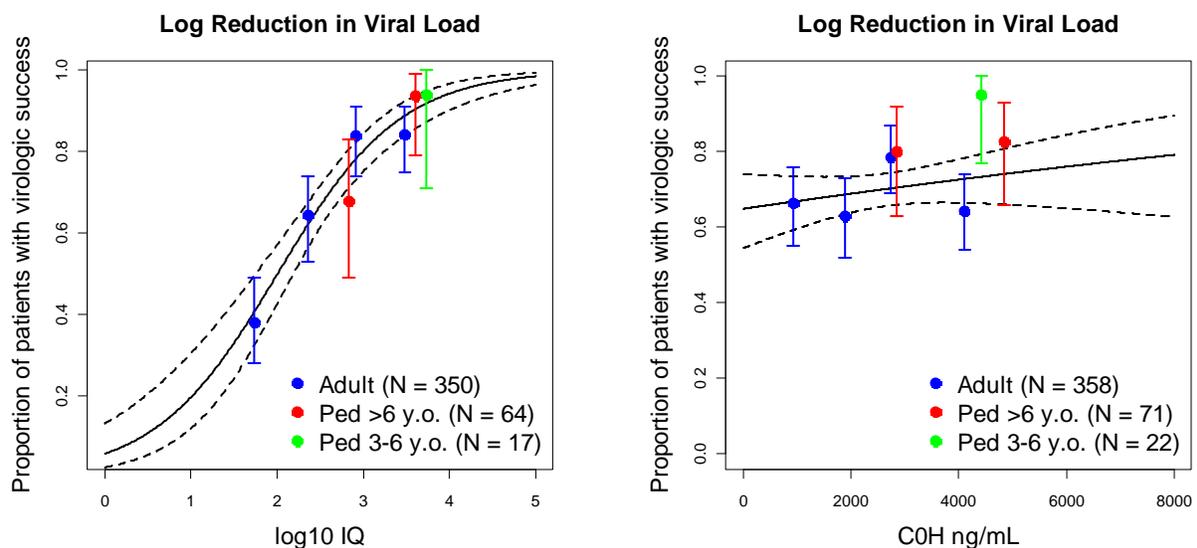


Figure 4. Relationship between IQ (left) or C_{0h} (right) and the Probability of 1 Log Reduction in Viral Load at Week 24 in Adults and Pediatric Subjects. The solid line represents the logistic regression model fit for the data adult. The dotted lines represent the 95% confidence interval.



1.1.3 What are the characteristics of the exposure-safety relationship in pediatric subjects 3 to < 6 years of age?

Twenty-seven subjects (15 males and 12 females) were enrolled in the trial and only one subject prematurely discontinued (due to vomiting, grade 2 that was considered to be not related to DRV). The initial dose of DRV was 20 mg/kg in combination with RTV (3 mg/kg) to target DRV exposure between 80% to 130% of the mean adult exposure of 62.3 µg.h/mL that was achieved with DRV/RTV 600/100 mg twice daily. The initial dose was adjusted to DRV/RTV 25/3 mg/kg twice daily for children weighing between 10 and < 15 kg, and to a fixed dose of DRV/r 375/50 mg twice daily for children between 15 and < 20 kg based on the applicant's interim simulation.

Most of the adverse events were not considered related to DRV. According to the medical reviewer, “the Applicant demonstrated an acceptable safety profile for darunavir co-administered with ritonavir in combination with other antiretroviral drugs.” Adverse events considered at least possibly related to DRV were in Table 2. Three events occurred before the dose adjustment and two events occurred after the dose adjustment. Therefore, it appears there is no clear exposure-safety relationship which is also consistent with the observations in the adults and pediatric subjects 6 to < 18 years of age.

Table 2. Adverse Events Considered at Least Possibly Related to DRV During the Treatment Period – TMC114-C228

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv		
	Overall N = 27	Before Dose Adjustment N = 27	After Dose Adjustment N = 26
<i>Mean Exposure (Weeks)</i>	<i>30.5</i>	<i>12.8</i>	<i>18.4</i>
<i>Any AE at Least Possibly Related to DRV</i>	<i>5 (18.5)</i>	<i>3 (11.1)</i>	<i>2 (7.7)</i>
Gastrointestinal Disorders	2 (7.4)	2 (7.4)	0
Diarrhea	2 (7.4)	2 (7.4)	0
Infections and Infestations	1 (3.7)	1 (3.7)	0
Rash pustular	1 (3.7)	1 (3.7)	0
Investigations	3 (11.1)	1 (3.7)	2 (7.7)
AST increased	1 (3.7)	1 (3.7)	0
Blood cholesterol increased	1 (3.7)	0	1 (3.8)
ECG QT prolonged	1 (3.7)	0	1 (3.8)
Skin and Subcutaneous Tissue Disorders	1 (3.7)	0	1 (3.8)
Rash papular	1 (3.7)	0	1 (3.8)

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

Source: Sponsor's Summary of Clinical Safety report, Table 8, page 25

Due to the lack of any major safety signal, the higher exposures in pediatric subjects 3 to <6 years of age are acceptable. These higher exposures also ensure that the coverage for efficacy is sufficient.

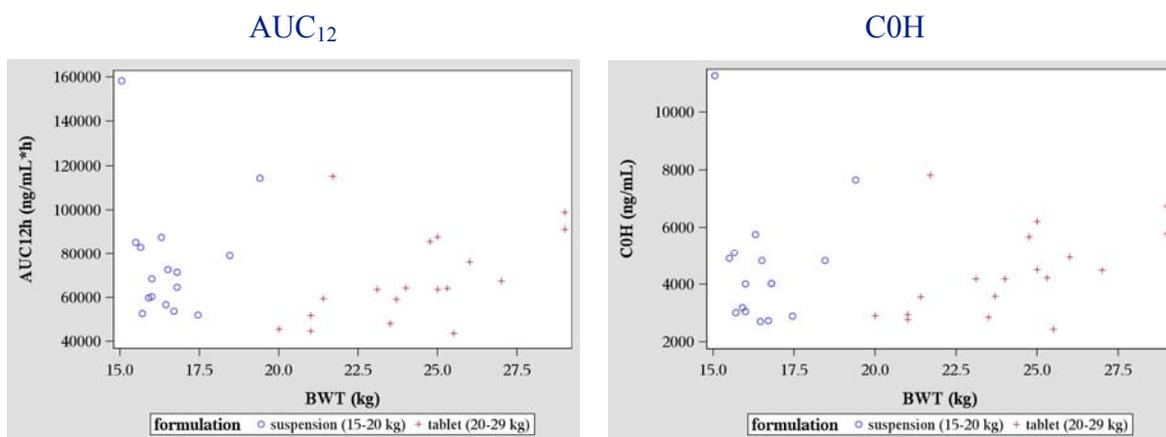
1.1.4 Does the clinical evidence support using DRV suspension in pediatrics weighing > 20 kg and adults and DRV tablet in pediatrics weighing 15 to 20 kg who can swallow?

Yes. The use of DRV suspension in pediatrics weighing > 20 kg and adults and using DRV tablet in pediatrics weighing 15 to 20 kg are acceptable.

The sponsor conducted a relative BA/BE study (TMC114-C169) in healthy subjects to compare the suspension formulation to that of the commercial 300 mg tablet formulation in the presence of low-dose RTV. Coadministration of a single 600 mg dose of DRV with low-dose ritonavir resulted in comparable C_{max}, AUC_{last}, and AUC_∞ values of DRV following administration of an oral suspension and commercial tablet with 90% confidence intervals within the limits of bioequivalence. However, OSI recommended that the C169 data should not be accepted based on the regulatory compliance issue (Tibotec did not maintain reserve samples of either reference or test drug for the C169 trial).

The DRV exposures (AUC₁₂ and C_{0H}) for pediatric subjects who received 380 mg of DRV suspension (rounding due to the dosing pipette) in Study TMC114-C228 and 375 mg tablets in Study TMC114-C21 were compared. As shown in Figure 5, the DRV exposure values were comparable between these groups. To derive the ratio between the exposures after two formulations, AUC₁₂ was normalized for 20 kg of body weight and was adjusted for the AAG level by using SAS “proc glm lsmeans” method for log transformed AUC_{12_WT20} (both body weight and AAG were significant covariates for CL in population PK analysis). The ratio of DRV AUC₁₂ geometric means (normalized at 20 kg and adjusted for AAG) between the suspension and tablet was found to be 97% (with 90% CI: 80% - 118%). Based on these data, the suspension and tablet formulations yield comparable exposures at 375 mg DRV dose in combination with RTV.

Figure 5. DRV exposure in pediatric subjects with 380 mg DRV suspension or 375 mg DRV tablet (by body weight)



There are no data on interchangeability of these formulations at doses higher than 375 mg. DRV exposures for tablet formulation increase in less than dose-proportional manner

(increasing the dose from 400 to 600 (1.5 fold) results in 1.18 to 1.29 fold increase in DRV exposures). Therefore, dose proportionality of the suspension formulation cannot be derived from the lower dose strength. However, the exposures at the 450 mg (pediatric subjects weighing 30 to 39 kg) or 600 mg (pediatric subjects weighing >40 kg and adults) doses are comparable to the exposure of that of 375 mg dose in the subjects weighing 15 to 29 kg. Therefore, the concerns about the potential nonlinearity PK are less important. On the other hand, the exposure-response for both efficacy and safety is shallow. The viral response and safety profiles in the first quartile of exposure (median AUC=25071 ng*h/mL or C_{trough}=934 ng/mL) in adults were comparable to those in the last quartile (median AUC=68813 ng*h/mL or C_{trough}=4113 ng/mL). Therefore, if the change in exposures after suspension formulation is slightly different from those observed with the tablet formulation, the shallow exposure-response relationship supports *the use of either the oral suspension or the commercial tablets*.

1.2 Recommendations

The proposed dosing recommendation of DRV/RTV in pediatric subjects 3 to < 6 years of age (Table 1) is acceptable.

2 PERTINENT REGULATORY BACKGROUND

Darunavir (DRV), a HIV protease inhibitor (PI), in combination with the low-dose ritonavir (RTV) is currently approved by the FDA for the use in treatment-experienced pediatric subjects aged 6 years to < 18 years old. The current approved dose is shown in Table 3.

Table 3. Currently Approved Dose of DRV/RTV for Subjects 6 Years to < 18 Years Old

Body Weight		Dose
(kg)	(lbs)	(twice daily)
> 20 kg - < 30 kg	> 44 lbs - < 66 lbs	375 mg DRV/50 mg RTV
≥ 30 kg - < 40 kg	≥ 66 lbs - < 88 lbs	450 mg DRV/60 mg RTV
≥ 40 kg	≥ 88 lbs	600 mg DRV/100 mg RTV

The currently NDA 202-895 is submitted to fulfill the remaining requirements for the Pediatric Written Request for PREZISTA® (DRV). The new open-label Phase 2 trial, TMC114-C228, provides pharmacokinetic, safety, tolerability and virologic success data that supports the weight-based dosing recommendations of DRV in combination with RTV for the treatment of HIV-1 treatment-experienced pediatric subjects ages 3 to < 6 years and weighing between 10 and 20 kilograms. Twenty-seven subjects were enrolled in the study and were stratified by weight (≥10 - < 15kg, ≥ 15- < 20 kg). The initial dose of DRV was 20 mg/kg in combination with RTV (3 mg/kg) to target DRV exposure between 80% to 130% of the mean adult exposure of 62.3 µg.h/mL achieved with DRV/r

600/100 mg twice daily). The initial dose was adjusted to DRV/RTV 25/3 mg/kg twice daily for children weighing between 10 and < 15 kg, and to a fixed dose of DRV/r 375/50 mg twice daily for children between 15 and < 20 kg based on the sponsor's interim simulation. The sponsor is seeking an approval of the adjusted dosing regimen (b) (4)

3 RESULTS OF SPONSOR'S ANALYSIS

The sponsor conducted a population pharmacokinetic analysis based on the previously developed model in the treatment-experienced adults and pediatric subjects 6 to < 18 years of age to incorporate data from pediatric subjects aged 3 to <6 years from the TMC114-C228 trial. The resulting model was then used to predict the individual pharmacokinetic parameters at Week 24, which were subsequently used for the description of DRV exposures and the evaluation of exposure-response relationships.

The dataset used for the initial model adjustment consisted of 555 plasma DRV concentrations from 95 subjects from the TMC125-C206 and TMC125-C216 trials for adults and TMC114-C212 for pediatric subject aged 6 and above and Week 2 data from the study TMC114-C228 for pediatric subjects aged 3 to <6 years (Table 4). The data from the two studies in adult subjects was chosen to provide a similar richness of pharmacokinetic sampling and a balance between the number of adults and children included in the analysis.

Table 4. Summary of Data Included in Model Adjustment

Item	Trial 1	Trial 2	Trial 3	Trial 4
Trial	TMC114-C228	TMC114-C212	TMC125-C206	TMC125-C216
No. of subjects	24	41	11	19
Administration routes and dose of DRV/rtv	20/3 mg/kg b.i.d.	300-600/50-100 mg b.i.d.	600/100 mg b.i.d.	600/100 mg b.i.d.
Darunavir formulation(s)	100 mg/mL suspension	75-mg tablets (F027) 300-mg tablets (F016)	300-mg tablets (F016)	300-mg tablets (F016)
Ritonavir formulation(s)	80 mg/mL solution	80 mg/mL solution	100-mg capsules	100-mg capsules
Number of samples per subject	5	5	8	8
Assay LOQ	5.00 ng/mL	5.00 ng/mL	5.00 ng/mL	5.00 ng/mL
Time range	0-12 h	0-12 h	0-12 h	0-12 h

Source: Sponsor's tmc114-c228 popPK report, Table 1, page 12

For details and reviews of model development in adults and older kids, please refer to the pharmacometric review of NDA 21-976 by Christine Garnett and NDA 21-976 S009 by Kevin Krudys. Briefly, the model was a two compartment model with the first-order

absorption and apparent clearance dependent on AAG concentrations assuming a linear binding and total daily dose. Clearance was described as:

$$CL/F_i = \frac{CL_{int}/F \cdot \left(\frac{1}{1 + K_{AFF} \cdot AAG_i} \right) \cdot \left(\frac{WT_i}{70} \right)^\theta \cdot e^{\eta_i}}{F_{rel}}$$

Where CL/F_i is the apparent oral clearance of an individual, CL_{int}/F the population estimate of apparent intrinsic clearance, K_{AFF} is the population estimate for the affinity of DRV to α₁-acid glycoprotein (AAG), θ is the influence of the individual weight at baseline (WT_i) on apparent clearance and η_i is the individual random effect. F_{rel} is the population estimate of the relative bioavailability correction for the commercial tablet formulation (F_{rel}=1.18) compared to the clinical trial tablet formulation as determined in the original model in adults.

Final parameter estimates are provided in Table 5. Considerable shrinkage to the mean is apparent in individual estimates of V₂, Q and V₃, but to a smaller extent for CL_{INT} and KA. The goodness of fit plots and visual predictive check provided by the sponsor suggest a sufficient model fit and an adequate predictive ability.

Table 5. Pharmacokinetic Parameter Estimates of the Final Adjusted Model

Parameter	Parameter Estimate	Parameter SEE (CV%)	IIV Estimate (CV%)	IIV SEE (CV%)
CL _{int} /F (L/h)	51.4	5.6	29	19
Influence of WT ^a	0.524	12		
K _{AFF} of AAG (dL/mg)	0.0304	---		
V ₂ /F (L)	131	11	48 ²	103
Influence of WT ^b	0.867	16		
Q/F (L/h)	15.0	---	65	---
V ₃ /F (L)	84.3	---	56	---
KA (1/h)	0.455	---	77 ²	32
F _{rel}	1.18	---		
Residual Error	0.0623	10		

^a Change in parameter based on body weight (WT)

^b Correlation between the variance estimates of apparent central volume and absorption rate constant estimated at 0.67

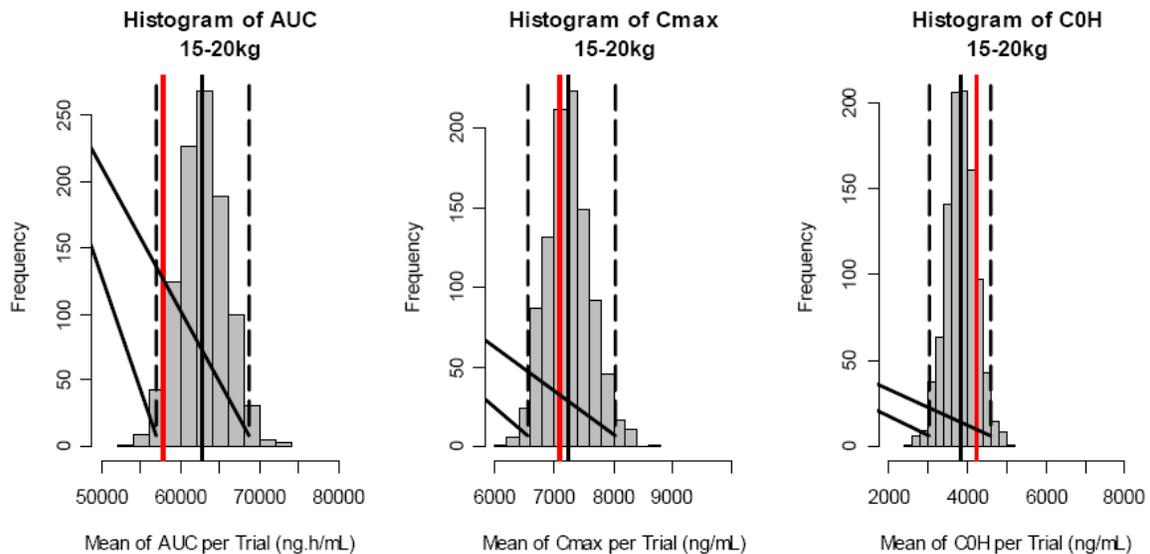
Source: Sponsor's tmc114-c228 popPK report, Table 5, page 18

The dataset used for prediction of DRV pharmacokinetic parameters in pediatric subjects at Week 24 combined richly sampled profiles from 19 subjects at Week 2 and sparse data from 24 subjects. It consisted of a total of 298 plasma DRV measurements from the TMC114-C212 trial. To obtain individual pharmacokinetic parameters, empirical Bayes estimation was performed using NONMEM V with the MAXEVAL=0 option in the \$ESTIMATION record. Simulation records were added to the NONMEM dataset to obtain prediction of C_{0h} at each visit. The area under the model-predicted DRV concentration curve (AUC_{tau}) was calculated as Dose/(CL/F).

Reviewer's Comments: The sponsor's population PK analyses are acceptable and are consistent with previous conclusions in older kids and adults.

The actual observed pharmacokinetics (PK) (AUC_{τ} , C_{\max} and C_{0h}) of darunavir (DRV) after administration of an oral suspension formulation from Study C228 were compared with the expected pharmacokinetics obtained through simulation after administration of the commercial tablet. The population PK model that describes the PK of DRV in children >20 kg and treated twice daily with the commercial tablet (see Dr. Kevin Krudys' previous PM review) was used to simulate concentrations in a selected pediatric population weighing 15 to <20 kg in Study C228. As shown in Figure 6, the observed PK means (AUC_{τ} , C_{\max} and C_{0h}) of the TMC114-C228 study are contained within the 95th prediction interval of the simulated PK means.

Figure 6: Predicted mean distribution of AUC_{τ} , C_{\max} and C_{0h} calculated from the simulations in 15 to <20 kg children treated b.i.d. with the commercial tablet. The solid red line represents the observed trial mean, as obtained in study TMC114-C228, the solid black line represents the mean of the simulated trial means, and the dashed black lines represent the 95th prediction interval of the simulated trial means.



Source: Sponsor's simulation report responding to the teleconference held with the Division on 22 Aug 2011 regarding clinical pharmacology aspects of the oral suspension formulation, Figure 1, page 9.

*Reviewer's Comments: The sponsor's simulation is reasonable and the results suggest that the administration of the DRV oral suspension and the commercial tablet results in similar exposure (AUC_{τ} , C_{\max} and C_{0h}) in HIV-1 infected children weighing 15 to <20 kg. Although the observed mean AUC_{τ} after the DRV oral suspension (~58000 ng*h/mL) is 8% lower than the predicted AUC_{τ} after tablet (~63000 ng*h/mL), this*

difference should not be a clinical concern considering that the exposure-response for both efficacy and safety is shallow. Therefore, the available information supports the use of either the oral suspension or the commercial tablets.

4 LISTING OF ANALYSES DATA SETS, CODES AND OUTPUT FILES

Table 6. Analysis Data Sets

Study Number	Name	Link to EDR
TMC114-C202 and TMC114-C213	xpk.xpt	\\Cdsesub1\evsprod\NDA021976\0006\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\tmc114-c926\datasets\analysis
TMC114-C212	expsaf.xpt	\\Cdsesub1\evsprod\NDA021976\0069\m5\53-clin-stud-rep\535-rep-effic-safety-stud\treatment-of-hiv-1-infection\5352-stud-rep-uncontr\tmc114-c212\datasets\analysis
TMC114-C228	pcad.xpt	\\Cdsesub1\evsprod\NDA202895\0000\m5\datasets\tmc114-c228\analysis\datasets\
TMC114-C228	ppad.xpt	\\Cdsesub1\evsprod\NDA202895\0000\m5\datasets\tmc114-c228\analysis\datasets\ppad.xpt
TMC114-C228	ptad.xpt	\\Cdsesub1\evsprod\NDA202895\0000\m5\datasets\tmc114-c228\analysis\datasets\ptad.xpt
TMC114-C228	vlad.xpt	\\Cdsesub1\evsprod\NDA202895\0000\m5\datasets\tmc114-c228\analysis\datasets\vlad.xpt
TMC114-C228 (WK 2 NONMEM data)	modeldataset-dat.xpt	\\Cdsesub1\evsprod\NDA202895\0006\m5\datasets\tmc114-tidp29-c228\pharmacokinetics\week2-model-app-c
TMC114-C228 (WK 24 NONMEM data)	modeldataset20101021.xpt	\\Cdsesub1\evsprod\NDA202895\0006\m5\datasets\tmc114-tidp29-c228\pharmacokinetics\week24-model-app-d

Table 7. Analysis Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\
eff_analysis_1log.R	IQ – 1 log reduction in viral load exposure-response analysis	Darunavir_NDA202895_JL\ER Analyses
eff_analysis_1log_C0H.R	C _{0h} – 1 log reduction in viral load exposure-response analysis	Darunavir_NDA202895_JL\ER Analyses
eff_analysis_RNA_50.R	IQ – < 50 copies/ml RNA exposure-response analysis	Darunavir_NDA202895_JL\ER Analyses
eff_analysis_RNA_C0H_50.R	C _{0h} – < 50 copies/ml RNA exposure-response analysis	Darunavir_NDA202895_JL\ER Analyses
PKPD_darunavir.sas	Comparing DRV exposure between pediatrics and adults	Darunavir_NDA202895_JL\ER Analyses
week2.ctf	Sponsor’s final model (NONMEM control file)	Darunavir_NDA202895_JL\PPK Analyses\week2-model-app-c
week2.lst	Sponsor’s final model (NONMEM output file)	Darunavir_NDA202895_JL\PPK Analyses\week2-model-app-c
week24.ctf	Sponsor’s model of Week 24 PK parameters (NONMEM control file)	Darunavir_NDA202895_JL\PPK Analyses\week24-model-app-d
week24.lst	Sponsor’s model of Week 24 PK parameters (NONMEM output file)	Darunavir_NDA202895_JL\PPK Analyses\week24-model-app-d

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STANLEY AU
09/06/2011

JIANG LIU
09/06/2011

PRAVIN R JADHAV
09/06/2011
Concur with pharmacometrics review

SARAH M ROBERTSON
09/06/2011

BIOPHARMACEUTICS REVIEW
Office of New Drugs Quality Assessment

Application No.:	NDA 202-895	Reviewer: Mark R. Seggel
Submission Date:	29-MAR-2011	
Division:	DAVP	Team Leader: Angelica Dorantes, Ph.D.
Applicant:	Tibotec, Inc. (J&J)	Supervisor: Patrick J. Marroum, Ph.D.
Trade Name:	Prezista	Date Assigned: -
Generic Name:	Darunavir	Date of Review: 19-AUG-2011
Indication:	HIV infection	GRMP Goal: 06-SEP-2011
Formulation / Strengths	Oral Suspension, 100 mg/mL	PDUFA Goal: 30-SEP-2011
Route of Administration	Oral	Type of Submission: Type 3, Priority submission of a new formulation of darunavir.

SUMMARY: Darunavir is currently available as Prezista Tablets, 75 mg, 150 mg, 400 mg and 600 mg (NDA 21-976). To address the needs of young children (i.e., age 3-6 years) Tibotec has developed an oral suspension formulation containing 100 mg darunavir per mL. Typical pediatric dosing begins at 2.6 mL twice daily.

Darunavir is only very slightly soluble in aqueous systems. It reportedly has intermediate to high absorptive permeability in Caco-2 mono-layers.

The proposed dissolution test employs USP Apparatus 2, paddle, at 75 rpm, and 900 mL of 0.05 M phosphate buffer at pH (b) (4) and containing 0.05% polysorbate 20. The proposed acceptance criterion is Q=(b) (4)% at 30 minutes. (The regulatory dissolution test for darunavir tablets employs USP Apparatus II, paddle, at 75 rpm, and 900 mL of 2% Tween-20 in 0.05 M Sodium Phosphate Buffer, pH 3.0; Q=(b) (4)% at 30 minutes.)

BIOPHARMACEUTIC INFORMATION: Biopharmaceutics information (i.e., dissolution data) submitted in the initial dossier consisted of profiles obtained at release (9 batches) and on three primary stability batches (through 12 months at 25°C/40% RH). Data from a simulated in-use study were also provided. At release, 2 of 9 batches had minimum individual values of (b) (4)% at the 30 minute test point. Minimum values for the remaining 7 batches ranged from (b) (4)%. After storage for 12 months, the minimum individual value observed at 30 minutes was (b) (4)%.

Based on our initial assessment of the available dissolution data, Tibotec was asked to revise the acceptance criterion to Q=(b) (4)% in 30 minutes in order to ensure that a mean of (b) (4)% of darunavir was released from the formulation. In response, Tibotec provided (eCTD 0024) a statistical analysis of available release and 12 month stability data to predict Stage 1, Stage 2, Stage 3 and overall batch failure rates at the time of release and on stability (projected to a 24 month expiration dating period). With a Q=(b) (4)% at 30 minutes an overall batch failure rate of (b) (4)% is predicted at 24 months. It is unclear how much error is built into the model calculations, or what other underlying assumptions were used. Tibotec states that the results of a statistical analysis shows a slight decline (2% per year) in dissolution rates over time and that is projected to continue through 24 months leading batch failure. However, results of a regression analysis of dissolution rate and extrapolated results at 24 months were not provided. The validity of the models used to predict failure rates is questionable. A teleconference with Tibotec was held on 30-AUG-2011 to discuss the models and the acceptance criterion. While the available data support Q=(b) (4)% at 30 minutes, the applicant remains convinced that there will be a high failure rate at the proposed 24-month expiry. Therefore, interim acceptance criteria were discussed: Q=(b) (4)% at 30 minutes with (b) (4) expiry or Q=(b) (4)% at 45 minutes with 24-month expiry.

RECOMMENDATION: An interim acceptance criterion of Q=^(b)₍₄₎% at 45 minutes was agreeable to Tibotec and the FDA Biopharmaceutics review team. Dissolution profile data targeting a Q=^(b)₍₄₎% at 30 minutes will be collected (at Stage 1, Stage 2, or 3 as needed) at release and on stability for one (1) year after approval. Tibotec will analyze the overall dissolution results and propose a final regulatory acceptance criterion for FDA consideration. A post-marketing commitment detailing the terms of the agreement will be provided to the NDA and will be documented in the action letter. Based, on the interim acceptance criterion and the agreement, this NDA is recommended for approval from the Biopharmaceutics perspective.

Signature

Mark R. Seggel

Reviewer

Office of New Drugs Quality Assessment

cc: PMarroum, J.David, L.Onaga, S.Miller, R.Madurawe, S.Au, J.Duan

Signature

Angelica Dorantes, Ph.D.

Biopharmaceutics Team Leader

Office of New Drugs Quality Assessment

Review Notes



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/s/

STANLEY AU
04/29/2011

SARAH M ROBERTSON
04/29/2011