ADDENDUM TO THE OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 202895 NDA: 21976 (SDN 201, S-20)	Submission Date: March 30, 2011 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: 10 kg to less than 15 kg: Darunavir 20 mg/kg coadministered with ritonavir 3 mg/kg **(revised dosage regimen)** using darunavir suspension 15 kg to less than (b) (4): 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-70ºC instead of -20ºC at the clinical trial sites. The applicant had previously stated that all plasma samples were stored at -20ºC. To date, the long term stability data for darunavir and ritonavir plasma samples has been generated at -20ºC 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-70ºC instead of -20ºC at the trial sites. In response to comments from the Division of Antiviral Products, the applicant stated that -70ºC long term sample stability data would be generated for up to one year with submission of 70ºC 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 -70ºC was 7 days. Overall, the storage of plasma samples at -70ºC 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 ºC 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	5th Percentile	Median	95th Percentile
AUC_{12h} (µg.h/mL)							
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
C_{0h} (ng/mL)							
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	5th Percentile	Median	95th Percentile
AUC_{12h} (µg.h/mL)							
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
C_{0h} (ng/mL)							
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	5th Perc.	25th Perc.	Median	75th Perc.	95th 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}	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
(ng.h/mL)	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}	All	19	4220	3749	477	2081	3285 - 5155	1057	1783	2761	3773	5432	7642	9498
(ng/mL)	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
$C_{ss,ave}$	All	19	5575	5201	499	2175	4597 - 6553	2256	2951	4168	5151	6709	9514	10956
(ng/mL)	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	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
(L/h)	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 µg/mL*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	5th Perc.	25th Perc.	Median	75th Perc.	95th Perc.	Max
	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
AUC_{tau}	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
(µg.h/mL)	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
	All subjects	18	5383	4918	568	2412	4269 - 6497	2733	2753	3217	4926	7028	9351	11300
C_{0h}	10 to <15 kg	6	6433	6142	797	1953	4870 - 7996	3299	3791	5595	6879	7244	8572	9007
(ng/mL)	15 to <20 kg	12	4858	4400	728	2521	3432 - 6284	2733	2746	3051	4469	5141	9341	11300
	All subjects	18	7059	6710	572	2428	5938 - 8181	4374	4488	5027	6910	8195	11226	13225
$C_{ss, ave}$	10 to <15 kg	6	7947	7722	814	1993	6352 - 9542	4845	5416	7259	8015	8701	10357	10873
(ng/mL)	15 to <20 kg	12	6615	6255	745	2580	5155 - 8076	4374	4448	4950	5774	7207	11266	13225
	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
CL/F	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
(L/h)	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_{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

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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 $AUC_{(0\text{-}12h)}$ 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)

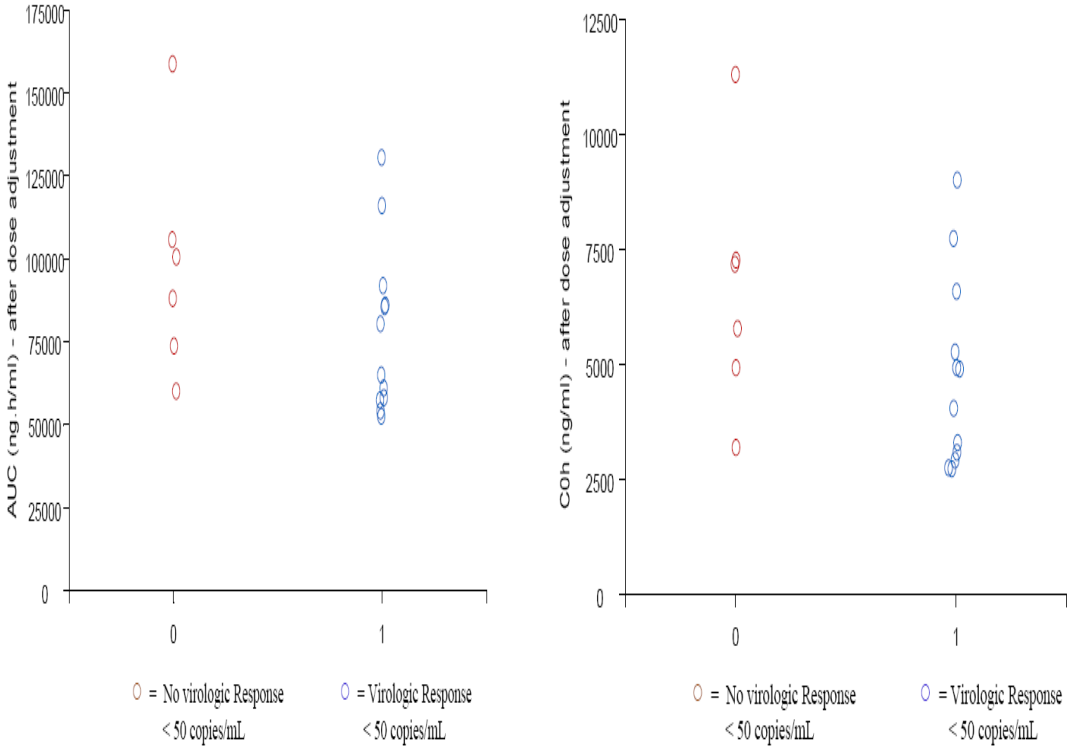
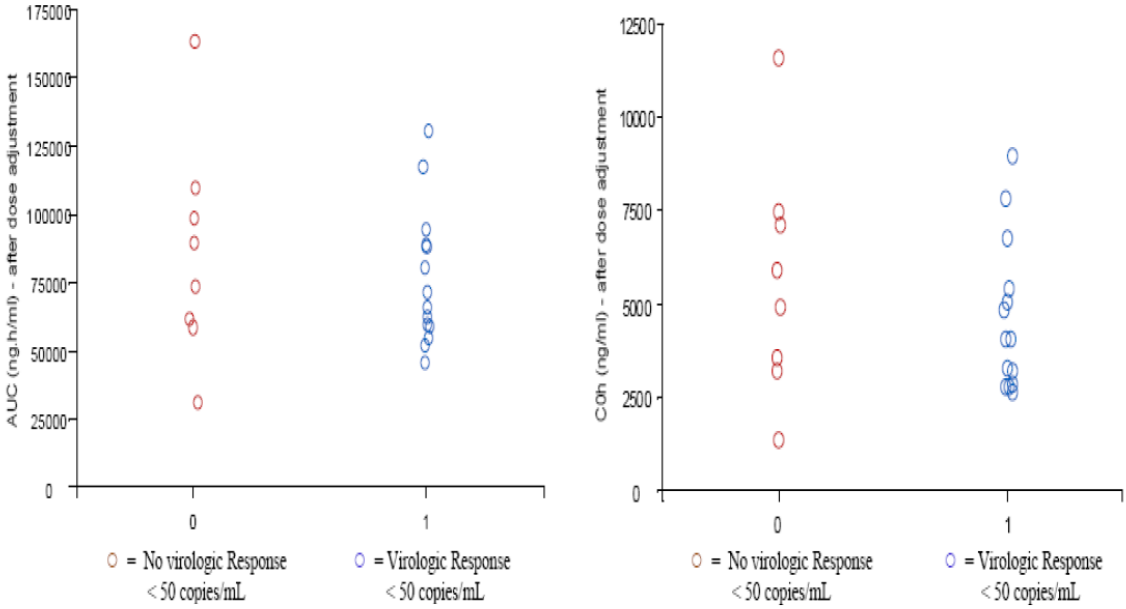


Figure 2-Original darunavir analysis for the comparison of $AUC_{(0\text{-}12h)}$ and C_{0h} (for the adjusted darunavir dosage regimens) for subjects either achieving virologic response or not achieving virologic response (HIV-1 RNA less than 50 copies/mL)



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 $AUC_{(0\text{-}12h)}$ 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 $AUC_{(0\text{-}12h)}$ 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 $AUC_{(0\text{-}12h)}$ values are compared.
3) The higher percentage difference in $AUC_{(0\text{-}12h)}$ 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 $AUC_{(0\text{-}12h)}$ 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 $AUC_{(0\text{-}12h)}$ 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 $AUC_{(0\text{-}12h)}$ 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-Orginal 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 < (b) (4) kg weight group.

(b) (4)	Revised Text
	Subjects may have contributed PK data to both the 10 kg to < 15 kg weight group and the 15 kg to < (b) (4) 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) instead of -20ºC 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