CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-822

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA#:	21-814, 22-292 (SN 005)
DRUG NAME:	Aptivus™ (Tipranavir)
INDICATION:	Treatment of HIV Infection
TYPE OF REVIEW:	Clinical
APPLICANT:	Boehringer-Ingelheim Pharmaceuticals
DATES:	Dec. 21, 2007
REVIEW PRIORITY:	Standard
BIOMETRICS DIVISION:	DB3
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STATISTICAL REVIEW AND EVALUATION

NDA#: 21-814, 22-292

1. Executive Summary

The applicant submitted one randomized, open label, phase IV clinical trial (trial 1182.14) comparing high and low doses of tipranavir oral solution with low dose ritonavir (TPV/r) in 115 HIV-infected children and adolescents aged 2 to 18 years. The study was designed to determine safety and PK profile in children and is the analoque of a phase I-IIa study. As a secondary endpoint, the trial also measured the efficacy endpoint of percent of subjects with viral loads sustained below 50 or below 400 copies/ml.

The applicant has demonstrated in this study that both doses are approximately as effective in children aged 2-18 as boosted tipranavir was in adults in the two pivotal trials. The efficacy appeared to be prolonged out to week 96. There were inconclusive suggestions that the low dose worked better than the high dose in subjects under the age of 6 while the high dose worked better in older subjects but this apparent interaction could easily be nothing but chance.

This trial, combined with the evidence from the pivotal trials in adults, is suggestive of efficacy of boosted tipranavir at the recommended doses to children aged 2-18. Convincing proof of efficacy depends on inference from the PK analysis (q.v. the PK review). The sample size is too small for the more difficult task of establishing or refuting that one of the two doses is superior in efficacy or that the recommended dose should be changed on the basis of some baseline covariate such as age.

2. Introduction

2.1 Overview

The applicant submitted one randomized, open label, phase IV clinical trial (trial 1182.14) comparing high and low doses of tipranavir oral solution with low dose ritonavir (TPV/r) in HIV-infected children and adolescents aged 2 to 18 years. The study was designed to determine safety and PK profile in children and is the analoque of a phase I-IIa study. Because tipranavir is already approved in adults, this review will refer to the study as phase IV. As a secondary endpoint, the trial also measured the efficacy endpoint of percent of subjects with viral loads sustained below 50 or below 400 copies/ml.

2.2 Data Sources

2.2.1 Objectives in Trial

The primary efficacy objective of this trial is percent of subjects with viral load suppressed below the limit of quantitation (LOQ) of either 50 or 400 at week 48. In addition, the applicant followed enough of the subjects to week 96 to permit the evaluation of the secondary efficacy endpoints of viral suppression at week 96.

The patients are expected to be between the ages of 2 and 18 years and HIV infected with viral load > 1500 c/ml. They may be either ART (anit-retroviral therapy) experienced or naive.

All results in section 2 will be those of the applicant. Results generated by the FDA reviewer will be contained in section 3.

2.2.2 Summary of Study Design

Trial 1182.14 is an open-label, randomized, two-arm, parallel, active controlled, multi-center trial. It was conducted at 26 sites, 10 in the United States and 1-3 each in Argentina, Brazil, Mexico, Canada, France, Germany, Spain, and Italy. Subjects were randomly assigned in a 1:1 ratio to TPV at 375mg/m^2 and RTV at 150mg/m^2 or TPV at 290mg/m^2 and RTV at 115mg/m^2. In addition, all subjects received a background regimen of two ARV's, neither of which could be a protease inhibitor (PI). Randomization was stratified by age group: 2-6, 6-12, and 12-18.

2.2.3 Patient Accounting and Baseline Characteristics

115 patients were randomized, 57 to high dose tpv/r and 58 to low dose tpv/r. 17 low dose and 10 high dose discontinued treatment before week 48. Table 2.2.3 A summarizes the primary reasons for discontinuation from the trials (based on the applicant's table 10.1.2.2). The main difference between the two arms is discontinuations

TABLE 2.2.3 A
PATIENT STATUS

	Low dose	High dose
Randomized	58	57
Withdrew by Week 48	17	10
AE	6	7
LTFU**	11	6
Continued to Week 48	41	47
Continued to Week 96	28	25

** LFTU = lost to follow-up

The study population was 57% male with 22% aged 2-6, 32% aged 6-12, and 46% aged 12-18. They were 70% white and 29% black. The median CD4 count at baseline was 380 cells/mm^3; the median HIV RNA level was 10.8 logs. 13% were co-infected with hepatitis B and 3% with hepatitis C. Subjects had on average

been diagnosed with HIV at the age of 2. 57% had had at least 7 previous ARV's; 82% had had at least 3 NRTI's and 50% at least 5; 83% had had a PI, 58% had had at least 2 PI's and 28% had had at least 4. Genotypic sensitivity score was 1 or less for 94% of subjects.

2.2.4 Summary of Methods of Assessment

2.2.4.1 Schedule of Measurements

Patients had HIV RNA and CD4 counts was measured at weeks 0, weeks 2, 4, 6, 8, 12, every 8 weeks to week 48, week 52 and every 12 weeks to week 1**24.** Plasma samples were assessed by [redacted] assay.

2.2.4.2 Assessment of Treatment Effects

The primary efficacy endpoints at week 48 were percent of subjects with sustained viral load below 400 and below 50 c/ml. Subjects were considered to have experience viral rebound to above LOQ if lost to follow-up or switched to another regimen.

2.2.5 Summary of Statistical Analysis

The primary analysis used non-completers as failures. Sensitivity analyses were conducted in which last observation was carried forward for non-completers and in which non-completers were treated as censored. These latter analyses are subject to serious biases and will not be reported here.

2.2.6 Summary of Applicant's Results

The results for the trial are given in table 2.2.6 A. Table 2.2.6 A gives the numbers and percentages of subjects with viral load sustained below 400 or 50 c/ml on the high and low dose arms at 48 and 96 weeks on trial(based on the applicant's section 12.1.4).

TABLE 2.2.6 A

PERCENT BELOW LOQ, WEEKS 48 AND 96

	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW
<400_at_Wk_48	26	31	46%	23	35	40%
Age 2-6			67%			77%
Age 6-12			42%			32%
Age 12-18			39%			27%
GSS 0			37%			42%
GSS .25-1			50%			40%
GSS 1.25-2.25			60%			36%
50_at_Wk_48	18	39	32%	20	38	34%
Age 2-6			50%			54%
Age 6-12			42%			32%
Age 12-18			23%			27%
GSS 0			30%			33%
GSS .25-1			40%			40%
GSS 1.25-2.25			40%			29%

The success rate was highest in the age 2-6 category and worst in the ag3 12-18 category. The high dose appeared to outperform the low dose in the two older age categories but not in the younger age category. Success rates also increased with genotypic sensitivity score (GSS). With respect to this stratum, the greater the sensitivity. The high dose also appears to exceed the low dose by more with higher GSS. Age is confounded with sensitivity: 20% of youngest subjects have GSS>1.5 compared to only 14-15% in the two older groups. Thus, some of the superior performance in the younger age groups is due simply to more effective background regimens.

There is a vaguely contradictory result when one looks at high vs low dose. Low dose is better in the youngest subjects but is inferior to high dose in the subjects with highest sensitivity. Thus, the superior performance of low dose in the youngest group is not simply explicable as a result of the higher sensitivity in this group. The sample sizes are so small that trying to disentangle a three-way intereaction between dose, age, and sensitivity is impossible with this data.

In a multivariate analysis using dose, age, gender, and time since diagnosis, only age was significant. Another multivariate regression with different predictors found only adherence and

sensitivity to be significant. (This latter analysis is statistically invalid since adherence is a response variable, not a baseline covariate, and cannot be used a predictor of response.)

Results stratified by other baseline covariates are given as analyzed by the FDA review in sections 3 and 4 below.

Results with changes in CD4 count also show response being better, the younger the age group, and with high dose apparently better than low dose in the two older categories but not in the youngest category.

TABLE 2.2.6 E
MEAN CHANGE IN CD4 COUNT, WEEK 48

	High Dose	Low Dose
All Subjects	59	100
Age 2-6	140	504
Age 6-12	141	143
Age 12-18	31	25

No confidence intervals are presented here because the small sample size basically insures little or nothing will be statistically significant.

2.2.7. Summary of Applicant's Conclusions

The applicant concluded that the antiviral efficacy of high dose tipranavir/r in the 12-18 age group was comparable to that found for adults in the two pivotal trials. The efficacy was higher in the younger age group, probably as a consequence of the greater sensitivity in that age group. The efficacy was greater by a small amount in the higher dose group but in a multivariate analysis using dose, age, gender, and time since diagnosis, only age was significant. The efficacy was reasonably well preserved beyond out to 96 weeks.

3. Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 Results with Percent BLQ

The FDA reviewer repeated the analyses performed by the applicant with respect to percent of subjects below LOQ both at weeks 48 and 96. The FDA analyses presented in table 3.1.1 A require confirmation of both initial suppression and rebound. In addition, the Mexican site was considered to be in violation of GCP (good clinical practice) so analyses were done with all subjects and excluding the five Mexican patients.

TABLE 2.2.6 A
PERCENT BELOW LOQ, WEEKS 48 AND 96

	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW
All Subjects						
<400_at_Wk_48	26	31	45.6%	24	34	41.4%
			32.7%-58.5%			28.7%-54.1%
<50_at_Wk_48	20	37	35.1%	19	39	32.8%
			22.7%-47.5%			20.7%-44.8%
<400_at_Wk_96	20	37	35.1%	15	43	25.9%
			22.7%-47.5%			14.6%-37.1%
<50_at_Wk_96	17	40	29.8%	9	49	15.5%
			17.9%-41.7%			6.2%-24.8%
No Mexican subjects						
<400_at_Wk_48	25	30	45.5%	22	33	40.0%
<50_at_Wk_48	19	36	34.5%	17	38	30.9%
<400_at_Wk_96	20	35	36.4%	15	40	27.3%
<50_at_Wk_96	17	38	30.9%	9	46	16.4%
Applicant's Results						
<400_at_Wk_48	26	31	46%	23	35	40%
50_at_Wk_48	18	39	32%	20	38	34%

For the first analysis, the table also gives the 95% confidence intervals for the success rate in each dose. These are wide enough that it is clear that finding confidence intervals for the differences between the doses would widely strattle zero. The small differences between the FDA and the applicant's analyses are due to the difference between looking

just at week 48 or requiring confirmation of suppression and rebound (and not counting suppression after confirmed rebound as a success). One can see that, compared to the wide uncertainty due to small sample size, that subtleties in the methods are of little impact.

3.1.2 Effect on CD4 Count

Table 3.1.2 A shows the mean change from baseline in CD4 count and the number of subjects on which that mean was based. There are two analyses presented. In the first, only subjects who have not yet experienced a viral failure (using LOQ=400 as the boundary for failure) are included in each mean; in the second analysis all subjects with observed CD4 count are included. No effort is made to impute data for subjects lost to follow-up.

TABLE 3.1.2 A
CHANGE FROM BASELINE IN CD4 COUNT

Week	N	CD4 Change	N	CD4 Change
	No Viral Rebound		All Subjects	
0	106	0	106	0
12	62	127	94	104
24	51	147	90	125
40	49	168	87	126
48	46	150	79	123
52	40	212	68	161
64	46	170	71	154
76	37	146	57	120
88	37	158	58	113
100	35	185	58	158
112	33	119	52	102

One will notice that the improvements are greater when only subjects without prior viral rebound are included. This suggests that were data available for the subjects lost to follow up and those subjects had not begun a new, effective ARV regimen, the CD4 means would be lower than the observed data. Any inferences drawn from the CD4 counts should thus be considered conditional upon continuing viral success.

3.2 Evaluation of Safety

There are no statistical analyses needed for safety issues in this review.

4. Results in Special Populations

Treatment efficacy was correlated with several baseline covariates: efficacy is higher among younger subjects, among subjects with lower baseline viral load, among subjects with higher baseline CD4 count (the latter two variables are correlated), among subjects with higher GSS, and among subjects with fewer previous anti-retrovirals. Dose-covariate interactions (cases where the better regimen changes between high and low dose systematically with stratum) are less convincing. This can be seen in table 4 A, which gives the mean difference between success rate at high dose and success rate at low dose within each stratum of five of the baseline covariates: age category, quartile of log baseline HIV RNA, quartile of baseline CD4 count, GSS (rounded off to the nearest integer), and quartile of baseline GIQ. Success here is defined as suppression below 400 copies/ml at week 48.

TABLE 4 A
HIGH DOSE - LOW DOSE RATES <400 AT WK 48
BY FIVE BASELINE COVARIATES

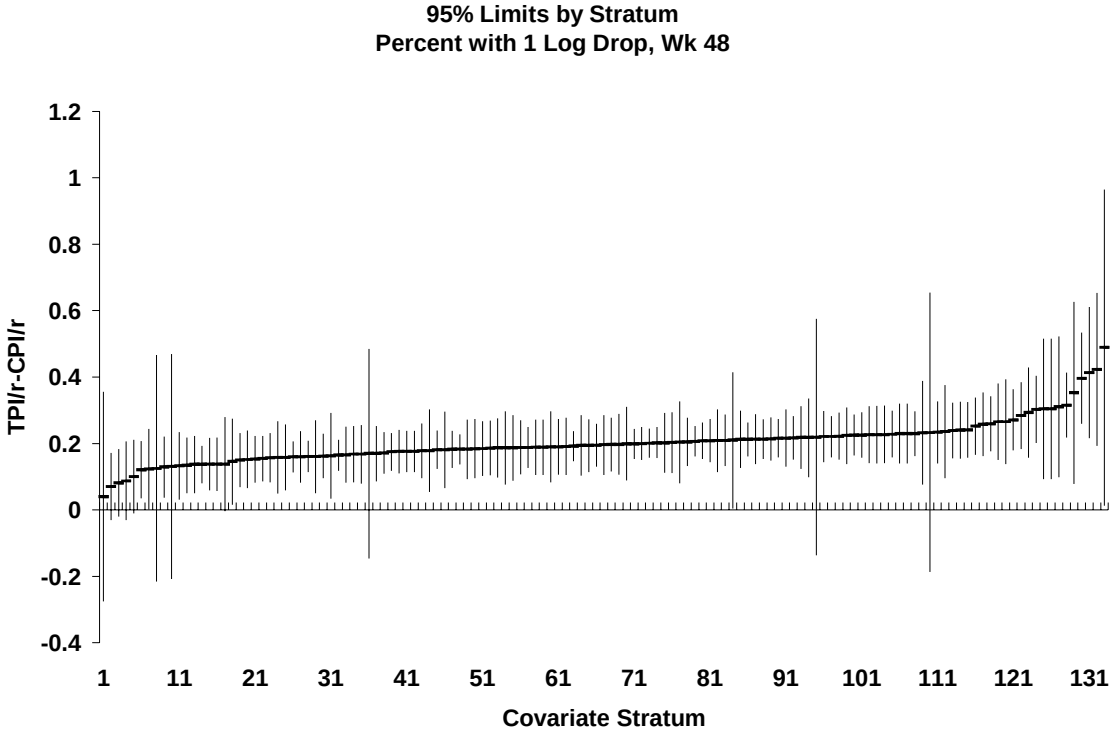
AGECAT	MEANDIFF	LOGBASE_Q	MEANDIFF	CD4BL_Q	MEANDIFF
2-6	0.0%	<9.75	13.2%	<190	19.0%
6-12	13.2%	9.75-10.8	0.5%	190-380	4.6%
12-18	2.6%	10.8-12.1	-20.0%	380-650	-13.6%
		>=12.1	8.5%	>=650	12.5%

GSS	MEANDIFF	GIQ_Q	MEANDIFF
0	2.4%	<4.9	-8.4%
1	-5.0%	4.9-13.8	31.5%
2	32.5%	13.8-30.9	-14.7%
		>=30.9	-12.5%

One will notice that in no case is the difference monotone. There is a suggestion that high dose is better at older ages, at lower baseline HIV and at higher GSS. Given the small sample sizes and the lack of monotone pattern, one should hesitate to read too much into these conclusions.

The FDA reviewer also performed logistic regressions on these data with several predictor variables. The applicant performed two such regressions but both of those were flawed in their choice of covariates. One used time since diagnosis and age. Since all these subjects were infected at birth, age = time

since infection and the extent to which time since diagnosis differs from age is just a measure of the irrelevance of the latter variable. The other applicant analysis used adherence, which is a response variable, not a baseline covariate, so this analysis is statistically invalid. The FDA analysis used age, GSS, and log baseline HIV RNA as continuous predictors, and dose as a categorical predictor. Age and log baseline HIV RNA were highly significant predictors of response; GSS was close to significant (p=.07), and dose was insignificant. Three other logistic regressions; using Age + Age-dose interaction, log baseline HIV + log base-dose interaction, and GSS + GSS-dose interaction; all failed to find any statistically significant interactions.



4.1 *Gender, Race, and Age*

Tables 4.1 A, B, C, and D show success rates for both doses stratified by sex, race, and age. Table 4.1 A shows success defined by sustained decrease in HIV RNA to <400 c/ml at week 48; 4.1 B shows success defined by sustained suppression to <50 at week 48; 4.1 C shows success defined by sustained suppression to <400 at week 96; 4.1 D shows success defined by sustained suppression to <400 at week 96. The tables also include the p-value for the chi-square test for homogeneity of dose differences across strata of the covariate.

TABLE 4.1 A
PERCENT <400 AT WEEK 48 BY SEX, RACE, AGE

<400_at_Wk_48_by_Arm

SEX	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
Female	10	12	45.5%	14	11	56.0%	0.11647
Male	15	18	45.5%	8	22	26.7%	.
RACE	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
Asian	1	1	50.0%	0	0	.	0.50591
Black	7	13	35.0%	6	7	46.2%	.
White	17	16	51.5%	16	26	38.1%	.
AGECAT	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
2-6	7	3	70.0%	7	3	70.0%	0.85992
6-12	9	9	50.0%	7	12	36.8%	.
12-18	9	18	33.3%	8	18	30.8%	.

TABLE 4.1 B
PERCENT <50 AT WEEK 48 BY SEX, RACE, AGE

<50_at_Wk_48_by_Arm

SEX	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
Female	10	14	41.7%	11	15	42.3%	0.71512
Male	10	23	30.3%	8	24	25.0%	.
RACE	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
Asian	1	1	50.0%	0	0	.	0.76717
Black	6	14	30.0%	5	8	38.5%	.
White	13	22	37.1%	14	31	31.1%	.
AGECAT	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
2-6	5	7	41.7%	7	6	53.8%	0.67647
6-12	7	11	38.9%	6	13	31.6%	.
12-18	8	19	29.6%	6	20	23.1%	.

TABLE 4.1 C
PERCENT <400 AT WEEK 96 BY SEX, RACE, AGE

<400_at_Wk_96_by_Arm

SEX	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
Female	7	15	31.8%	9	16	36.0%	0.18032
Male	13	20	39.4%	6	24	20.0%	.
RACE	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
Asian	1	1	50.0%	0	0	.	0.32953
Black	4	16	20.0%	4	9	30.8%	.
White	15	18	45.5%	11	31	26.2%	.
AGECAT	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
2-6	5	5	50.0%	6	4	60.0%	0.29013
6-12	9	9	50.0%	4	15	21.1%	.
12-18	6	21	22.2%	5	21	19.2%	.

TABLE 4.1 D
PERCENT <50 AT WEEK 96 BY SEX, RACE, AGE

P<50_at_Wk_96_by_Arm

SEX	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
Female	6	18	25.0%	6	20	23.1%	0.14321
Male	11	22	33.3%	3	29	9.4%	.
RACE	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
Asian	1	1	50.0%	0	0	.	0.40104
Black	4	16	20.0%	3	10	23.1%	.
White	12	23	34.3%	6	39	13.3%	.
AGECAT	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
2-6	5	7	41.7%	4	9	30.8%	0.81926
6-12	7	11	38.9%	3	16	15.8%	.
12-18	5	22	18.5%	2	24	7.7%	.

4.2 *Other Baseline Covariates*

Tables 4.2 A-D show the same results as tables 4.1 A-D except that the baseline covariates have been changed to quartile of log baseline HIV RNA, quartile of baseline CD4 count, GSS score (rounded off to the nearest integer, quartile of GIQ (Cmin/# mutations), quartile of number of previous antiretrovirals, Pediatric HIV category, naive to ARV's or not, and hepatitis B co-infected or not.

TABLE 4.2 A

PERCENT <400 AT WEEK 96 BY BASELINE COVARIATES

<400_at_Wk_48_by_Arm

LOGBASE_Q	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
<9.75	12	7	63.2%	6	6	50.0%	0.62979
9.75-10.8	7	8	46.7%	6	7	46.2%	.
10.8-12.1	3	7	30.0%	7	7	50.0%	.
>=12.1	3	8	27.3%	3	13	18.8%	.
CD4BL_Q	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
<190	4	9	30.8%	2	15	11.8%	0.53943
190-380	8	11	42.1%	3	5	37.5%	.
380-650	4	7	36.4%	7	7	50.0%	.
>=650	9	3	75.0%	10	6	62.5%	.
GSS	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
0	8	17	32.0%	8	19	29.6%	0.40880
1	10	10	50.0%	11	9	55.0%	.
2	7	3	70.0%	3	5	37.5%	.
GIQ_Q	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
<4.9	1	16	5.9%	3	18	14.3%	0.23770
4.9-13.8	6	5	54.5%	3	10	23.1%	.
13.8-30.9	6	5	54.5%	9	4	69.2%	.
>=30.9	12	4	75.0%	7	1	87.5%	.
NPRVARV_Q	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
<5	8	2	80.0%	6	5	54.5%	0.14318
5-7	7	6	53.8%	7	3	70.0%	.
7-11	6	9	40.0%	9	11	45.0%	.
>=11	4	13	23.5%	0	14	0.0%	.
PEDHIV	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
.	6	17	26.1%	6	15	28.6%	0.095463
Mildly_symp	3	1	75.0%	1	6	14.3%	.
Moderat._symp	4	5	44.4%	7	2	77.8%	.
Not_symp	1	1	50.0%	2	1	66.7%	.
Symptomatic	11	6	64.7%	6	9	40.0%	.
ARVNAIVE	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
No	24	29	45.3%	21	33	38.9%	0.33896
Yes	1	1	50.0%	1	0	100.0%	.
HEPB	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
.	0	1	0.0%	0	0	.	0.99994
No	23	22	51.1%	21	28	42.9%	.
Yes	2	7	22.2%	1	5	16.7%	.

TABLE 4.1 B
PERCENT <50 AT WEEK 48 BY BASELINE COVARIATES

<50_at_Wk_48_by_Arm

LOGBASE_Q	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
<9.75	10	9	52.6%	3	9	25.0%	0.31741
9.75-10.8	6	9	40.0%	7	6	53.8%	.
10.8-12.1	3	8	27.3%	7	10	41.2%	.
>=12.1	1	11	8.3%	2	14	12.5%	.

CD4BL_Q	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
<190	4	11	26.7%	1	16	5.9%	0.40042
190-380	6	13	31.6%	4	5	44.4%	.
380-650	4	7	36.4%	6	10	37.5%	.
>=650	6	6	50.0%	8	8	50.0%	.

GSS	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
0	8	19	29.6%	8	21	27.6%	0.17867
1	7	13	35.0%	10	11	47.6%	.
2	5	5	50.0%	1	7	12.5%	.

GIQ_Q	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
<4.9	1	16	5.9%	3	18	14.3%	0.15357
4.9-13.8	4	8	33.3%	1	13	7.1%	.
13.8-30.9	5	6	45.5%	10	4	71.4%	.
>=30.9	10	7	58.8%	5	4	55.6%	.

NPRVARV_Q	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
<5	4	7	36.4%	6	8	42.9%	0.38974
5-7	8	6	57.1%	5	5	50.0%	.
7-11	5	10	33.3%	8	12	40.0%	.
>=11	3	14	17.6%	0	14	0.0%	.

PEDHIV	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
.	5	18	21.7%	5	16	23.8%	0.086990
Mildly_symp	2	2	50.0%	0	7	0.0%	.
Moderat._symp	4	6	40.0%	7	5	58.3%	.
Not_symp	0	2	0.0%	2	1	66.7%	.
Symptomatic	9	9	50.0%	5	10	33.3%	.

ARVNAIVE	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
No	20	35	36.4%	18	39	31.6%	0.072948
Yes	0	2	0.0%	1	0	100.0%	.

HEPB	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
.	0	1	0.0%	0	0	.	0.99079
No	18	29	38.3%	18	34	34.6%	.
Yes	2	7	22.2%	1	5	16.7%	.

TABLE 4.1 C

PERCENT <400 AT WEEK 96 BY BASELINE COVARIATES

<400_at_Wk_96_by_Arm

LOGBASE_Q	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
<9.75	11	8	57.9%	5	7	41.7%	0.74960
9.75-10.8	5	10	33.3%	4	9	30.8%	.
10.8-12.1	3	7	30.0%	3	11	21.4%	.
>=12.1	1	10	9.1%	3	13	18.8%	.

CD4BL_Q	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
<190	3	10	23.1%	0	17	0.0%	0.35909
190-380	6	13	31.6%	2	6	25.0%	.
380-650	4	7	36.4%	5	9	35.7%	.
>=650	7	5	58.3%	8	8	50.0%	.

GSS	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
0	6	19	24.0%	4	23	14.8%	0.69228
1	8	12	40.0%	8	12	40.0%	.
2	6	4	60.0%	3	5	37.5%	.

GIQ_Q	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
<4.9	1	16	5.9%	1	20	4.8%	0.36984
4.9-13.8	5	6	45.5%	2	11	15.4%	.
13.8-30.9	4	7	36.4%	6	7	46.2%	.
>=30.9	10	6	62.5%	6	2	75.0%	.

NPRVARV_Q	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
<5	7	3	70.0%	6	5	54.5%	0.53161
5-7	6	7	46.2%	5	5	50.0%	.
7-11	4	11	26.7%	4	16	20.0%	.
>=11	3	14	17.6%	0	14	0.0%	.

PEDHIV	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
.	4	19	17.4%	3	18	14.3%	0.075444
Mildly_symp	3	1	75.0%	1	6	14.3%	.
Moderat._symp	3	6	33.3%	6	3	66.7%	.
Not_symp	1	1	50.0%	2	1	66.7%	.
Symptomatic	9	8	52.9%	3	12	20.0%	.

ARVNAIVE	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
No	19	34	35.8%	14	40	25.9%	0.30217
Yes	1	1	50.0%	1	0	100.0%	.

HEPB	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
.	0	1	0.0%	0	0	.	0.83778
No	19	26	42.2%	15	34	30.6%	.
Yes	1	8	11.1%	0	6	0.0%	.

TABLE 4.1 D
PERCENT <50 AT WEEK 96 BY BASELINE COVARIATES

<50_at_Wk_96_by_Arm

LOGBASE_Q	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
<9.75	9	10	47.4%	1	11	8.3%	0.080828
9.75-10.8	4	11	26.7%	4	9	30.8%	.
10.8-12.1	4	7	36.4%	2	15	11.8%	.
>=12.1	0	12	0.0%	2	14	12.5%	.

CD4BL_Q	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
<190	3	12	20.0%	0	17	0.0%	0.28448
190-380	4	15	21.1%	2	7	22.2%	.
380-650	4	7	36.4%	1	15	6.3%	.
>=650	6	6	50.0%	6	10	37.5%	.

GSS	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
0	5	22	18.5%	3	26	10.3%	0.76800
1	6	14	30.0%	4	17	19.0%	.
2	6	4	60.0%	2	6	25.0%	.

GIQ_Q	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
<4.9	1	16	5.9%	0	21	0.0%	0.10133
4.9-13.8	4	8	33.3%	0	14	0.0%	.
13.8-30.9	3	8	27.3%	6	8	42.9%	.
>=30.9	9	8	52.9%	3	6	33.3%	.

NPRVARV_Q	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
<5	5	6	45.5%	4	10	28.6%	0.77452
5-7	7	7	50.0%	2	8	20.0%	.
7-11	3	12	20.0%	3	17	15.0%	.
>=11	2	15	11.8%	0	14	0.0%	.

PEDHIV	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
.	3	20	13.0%	2	19	9.5%	0.070999
Mildly_symp	2	2	50.0%	0	7	0.0%	.
Moderat._symp	4	6	40.0%	4	8	33.3%	.
Not_symp	0	2	0.0%	2	1	66.7%	.
Symptomatic	8	10	44.4%	1	14	6.7%	.

ARVNAIVE	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
No	17	38	30.9%	8	49	14.0%	0.037968
Yes	0	2	0.0%	1	0	100.0%	.

HEPB	S_HIGH	F_HIGH	P_HIGH	S_LOW	F_LOW	P_LOW	PHOMOG
.	0	1	0.0%	0	0	.	0.91724
No	16	31	34.0%	9	43	17.3%	.
Yes	1	8	11.1%	0	6	0.0%	.

6. Statistical Reviewer's Conclusions

The applicant has demonstrated in one study with 115 patients, randomized 1:1 to high and low dose ritonavir-boosted tipranavir that both doses are approximately as effective in children aged 2-18 as boosted tipranavir was in adults in the two pivotal trials. The efficacy appeared to be prolonged out to week 96. There were inconclusive suggestions that the low dose worked better than the high dose in subjects under the age of 6 while the high dose worked better in older subjects but this apparent interaction could easily be nothing but chance.

This trial, combined with the evidence from the pivotal trials in adults, is suggestive of efficacy of boosted tipranavir at the recommended doses to children aged 2-18. Convincing proof of efficacy depends on inference from the PK analysis (q.v. the PK review). The efficacy could also have been established by inclusion of a placebo arm in the efficacy analysis. The sample size is too small for the more difficult task of establishing or refuting that one of the two doses is superior in efficacy or that the recommended dose should be changed on the basis of some baseline covariate such as age.

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