Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Aptivus®		**EudraCT No.:** 2006-005256-33	
Name of active ingredient: Tipranavir		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Disclosure Synopsis date: 10 JUL 2014	**Trial No. / U No.:** 1182.107/U09-1441-01	**Date of trial:** 10 Oct 2007 – 16 May 2008	**Date of revision :** Not applicable

Title of trial:	A multicenter, randomized, open label, clinical trial to evaluate three doses of tipranavir boosted with ritonavir (500 mg/200 mg qd, 250 mg/100 mg bid and 500 mg/100 mg bid) by assessing the steady-state pharmacokinetics and short-term efficacy and safety in HIV-1 positive treatment naïve patients
Principal/Coordinating Investigator:	[redacted]
Trial sites:	Multicenter, International
Publication (reference):	Data of this study has not been published
Clinical phase:	IIb
Objectives:	To identify an optimal dose combination(s) of tipranavir (TPV) and ritonavir (RTV) for antiretroviral treatment naïve HIV-1 positive patients that can be used in pivotal trial by assessing the steady-state pharmacokinetics and short-term efficacy and safety
Methodology:	After successful screening, patients were randomised in a 1:1:1 allocation to one of three treatment groups: tipranavir-boosted with ritonavir (TPV/r) 500 mg/200 mg QD, TPV/r 250 mg/100 mg BID and TPV/r 500 mg/100 mg BID
No. of subjects:	
planned:	entered: 75
actual:	enrolled: 123 Treatment TPV/r 500/200 QD: entered: 30 treated: 30 analysed (for primary endpoint) Treatment TPV/r 250/100 BID: entered: 27 treated: 25 analysed (for primary endpoint) Treatment TPV/r 500/100 BID: entered: 28 treated: 28 analysed (for primary endpoint)
Diagnosis and main criteria for inclusion:	Patients meeting the following criteria were eligible for participation in this study: • Signed informed consent in accordance with GCP and local regulatory

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requirements prior to trial participation

- HIV-1 infected men and non-pregnant women who are treatment naïve, with positive serology (EIA) confirmed by Western blot.
- Age ≥ 18 and ≤ 65 years
- HIV-1 mRNA viral load > 5,000 copies/mL
- CD4 cell count > 200 cells/mm^3
- Ability to swallow multiple large capsules without difficulty.
- Acceptable laboratory values that indicate adequate baseline organ function at screening visit.
- Laboratory values are considered to be acceptable if the severity of any parameter is ≤ Grade 2, based on the DAIDS/ACTG Grading Scale (see Appendix 11.1).
- Acceptable medical history, physical examination, and 12-lead ECG at screening.
- Willingness to abstain from the following starting 2 weeks prior to administration of any study medication and up until the end of the study:
  - Grapefruit or grapefruit juice, Seville oranges, St. John's Wort, and Milk Thistle.
  - Willingness to abstain from alcohol starting 3 days prior to administration of any study medication up to the end of the study.
- Willingness to abstain from the following starting 3 days prior to PK sampling:
  - Garlic supplements and Methylxanthine containing foods or drinks (including coffee, tea, cola, energy drinks, chocolate, etc.).
- Willingness to abstain from over-the-counter herbal medications for the duration of the study.

Willingness to abstain from any over the counter medication 7 days prior to administration of any study medication (including vitamins, minerals, dietary supplements and antacids) during the study until completion of the post study assessments

Test product:	Tipranavir
dose:	Tipranavir 500 mg or 250mg boosted with ritonavir 200 mg or 100 mg QD or BID

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mode of admin.:	Oral Administration
batch no.:	
Reference therapy:	NA
dose:	
mode of admin.:	
batch no.:	
Duration of treatment:	14 (fourteen) days
Criteria for evaluation:	
Efficacy / clinical pharmacology:	The following primary endpoints were evaluated. TPV pharmacokinetics: o AUC_{0-24h} for QD dosing, o AUC_{0-12h} for BID dosing o C_{min} o Cp_{24h} for QD dosing, o Cp_{12h} for BID dosing o C_{max} Efficacy: o Change from baseline in HIV-RNA viral load (log_{10})
Safety:	Determination of safety: 1. Adverse events (treatment related and unrelated) 2. Serious adverse events 3. Laboratory test changes
Statistical methods:	Pharmacokinetics*:*

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The geometric means and 95% confidence intervals will derived and evaluated for the primary TPV pharmacokinetic parameters for each treatment group:

A: TPV/r 500 mg/200 mg QD
B: TPV/r 250 mg/100 mg BID
C: TPV/r 500 mg/100 mg BID

In addition, the proportion of patients whose trough levels (i.e., TPV C_{min}) are <6.5 μM was estimated for each treatment group. The mean and 95% empirical confidence intervals for each estimate was constructed using bootstrap methods.

Efficacy*:*

For the primary analysis, the hypothesis that TPV/r will reduce the median viral load by ≥1.2 RNA $\log_{10}$ copies from baseline was tested for each TPV/r dose combination. Theses hypotheses were tested using a one-sided Wilcoxon signed-rank tests at the 0.05 alpha level.

Safety:

For the safety analyses, descriptive statistics were used to summarize and evaluate adverse events and clinically relevant laboratories

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Median $\log_{10}$ VL reductions (last observation carried forward) and the percentage of patients achieving a 1.2 $\log_{10}$ VL reduction or greater was 1.43 (79.3%), 1.55 (84.0%) and 1.47 (72.7%) for the TPV/r 500/200 QD (N=30), 250/100 BID (N=25) and 500/100 BID (N=28) groups, respectively. Geometric mean [median, min – max] TPV Cmin (μM) for patients with VL and PK measurements was 2.8 [2.7, 0.5 – 12.7] (N=29), 12.7 [11.8, 4.9 – 41.3] (N=25) and 21.3 [18.3, 6.9 – 139.2] (N=22) for the TPV/r 500/200 QD (N=30), 250/100 BID (N=25) and 500/100 BID (N=28) groups, respectively. Pharmacokinetic parameters of TPV and decrease in viral load from baseline are listed as geometric means in Table 1.

Table 1 TPV pharmacokinetics and decrease in viral load from baseline

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TPV/r 500/200 QD

	Cptrough (µM)	Cp24h (µM)	Cmax (µM)	AUC0-24h (h·µM)	Decrease in VL (log10) from baseline
N	29	29	29	29	29
Mean	4 01	4 48	55 73	592 8	1 43
SD	3 56	4 21	11 52	177 9	0 34
Min	0 47	0 93	39 76	364 8	0 79
Median	2 68	2 68	53 91	544 2	1 46
Max	12 70	21 01	81 36	1206 9	2 13
CV%	88 8	94 0	20 7	30 0	23 9
Geo Mean	2 80	3 26	54 64	571 3	1 39
CV% Geo Mean	106 8	92 4	20 2	27 3	26 3

TPV/r 250/100 BID

	Cptrough (µM)	Cp12h (µM)	Cmax (µM)	AUC0-12h (h·µM)	Decrease in VL (log10) from baseline
N	25	25	25	25	25
Mean	14 42	11 49	37 71	299 9	1 51
SD	7 99	6 16	8 03	89 7	0 31
Min	4 94	5 12	24 16	204 8	0 76
Median	11 81	10 00	35 03	273 9	1 55
Max	41 33	32 60	64 91	606 0	2 05
CV%	55 4	53 6	21 3	29 9	20 9
Geo Mean	12 73	10 27	36 98	289 3	1 47
CV% Geo Mean	53 1	49 4	19 9	26 8	23 8

TPV/r 500/100 BID

	Cptrough (µM)	Cp12h (µM)	Cmax (µM)	AUC0-12h (h·µM)	Decrease in VL (log10) from baseline
N	22	22	22	22	22
Mean	29 09	22 21	72 07	574 8	1 45
SD	30 38	18 04	20 52	241 4	0 30
Min	6 92	7 08	41 36	336 3	0 93
Median	18 28	14 28	66 19	515 4	1 51
Max	139 22	82 78	134 57	1361 1	1 97
CV%	104 4	81 2	28 5	42 0	20 4
Geo Mean	21 26	17 75	69 66	538 2	1 42
CV% Geo Mean	86 8	71 7	26 5	36 4	21 9

Safety results: Regarding safety, there were two SAEs reported: one case due to ALT/AST elevations and one case due to drug abuse during the trial, which led to hospitalization. No fatalities were reported.

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Conclusions: All TPV/r dose groups were potent and effective, and each achieved VL reductions >1.2 $\log_{10}$ in both the LOCF and PK+VL groups.

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BI trial number 1182.107
Trial Synopsis - Appendix

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement patient disposition, adverse event results and results for secondary endpoints of the trial.

Results for	presented in
Patient Disposition	Table 15.1.1: 1
Summary of compartmental steady-state pharmacokinetics for TPV for patients receiving TPV/r 500/200 mg QD	Table 15.6.2.2: 1
Summary of compartmental steady-state pharmacokinetics for TPV for patients receiving TPV/r 250/100 mg BID	Table 15.6.2.2: 2
Summary of compartmental steady-state pharmacokinetics for TPV for patients receiving TPV/r 500/100 mg BID	Table 15.6.2.2: 3
Summary of compartmental steady-state pharmacokinetics for RTV for patients receiving TPV/r 500/200 mg QD	Table 15.6.2.3: 1
Summary of compartmental steady-state pharmacokinetics for RTV for patients receiving TPV/r 250/100 mg BID	Table 15.6.2.3: 2
Summary of compartmental steady-state pharmacokinetics for RTV for patients receiving TPV/r 500/100 mg BID	Table 15.6.2.3: 3
AE summary	Table 15.3.2: 1

Table 15.1.1: 1 Disposition of patients

	TPV/r 500/200 QD N(%)	TPV/r 250/100 BID N(%)	TPV/r 500/100 BID N(%)	Total
Enrolled				121
Entered/randomized	30 (100.0)	27 (100.0)	28 (100.0)	85 (100.0)
Treated	30 (100.0)	25 (92.6)	28 (100.0)	83 (97.6)
Not treated	0 (0.0)	2 (7.4)	0 (0.0)	2 (2.4)
Not prematurely discontinued from trial medication	30 (100.0)	25 (92.6)	24 (85.7)	79 (92.9)
Prematurely discontinued from trial medication	0 (0.0)	0 (0.0)	4 (14.3)	4 (4.7)
Adverse event	0 (0.0)	0 (0.0)	3 (10.7)	3 (3.5)
AE study dis. worse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AE-oth.dis. worse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AE-other	0 (0.0)	0 (0.0)	3 (10.7)	3 (3.5)
Lack of efficacy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non compl prot.	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Consent withdrawn	0 (0.0)	0 (0.0)	1 (3.6)	1 (1.2)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 15.6.2.2: 1 Summary of compartmental steady-state pharmacokinetics for TPV for patients receiving TPV/r 500/200 mg QD (Page 2 of 2)

	Ka (h^{-1})	Cl/F (L/h)	V/F (L)	$t_{1/2}$ (h)	Tmax (h)	Cmax (µM)	Cp_{24h} (µM)	AUC_{0-24h} (hyµM)
N	30	30	30	30	30	30	30	30
Mean	0.600	1.50	10.12	4.96	3.10	55.79	4.46	593.0
SD	0.133	0.36	1.41	1.40	0.43	11.33	4.14	174.8
Min	0.382	0.69	7.33	3.35	2.02	39.76	0.93	364.8
Median	0.585	1.52	9.94	4.64	3.10	54.02	2.95	546.9
Max	0.974	2.27	12.66	9.41	4.04	81.36	21.01	1206.9
CV%	22.1	24.37	13.92	28.2	13.9	20.3	92.8	29.5
Geometric Mean	0.586	1.45	10.02	4.79	3.07	54.74	3.28	572.2
CV% Geometric Mean	21.6	26.79	14.33	26.3	14.7	19.9	90.3	26.8
95% CI Lower Mean	-	-	-	-	-	51.57	2.91	527.8
95% CI Upper Mean	-	-	-	-	-	60.02	6.00	658.3

Source: /u02/projects_apm/TIPRANAVIR/1182_0107/PK/TIPRANAVIR/FINAL_MODELS/FINAL/TABLES/TPV_PK_30012.prn

Table 15.6.2.2: 2 Summary of compartmental steady-state pharmacokinetics for TPV for patients receiving TPV/r 250/100 mg BID (Page 2 of 2)

	Ka (h^{-1})	Cl/F (L/h)	V/F (L)	$t_{1/2}$ (h)	Tmax (h)	Cmax (µM)	Cp_{12h} (µM)	AUC_{0-12h} (hyµM)
N	25	25	25	25	25	25	25	25
Mean	0.775	1.48	9.36	4.62	2.37	37.71	11.49	299.9
SD	0.181	0.35	0.86	1.11	0.36	8.03	6.16	89.7
Min	0.416	0.68	8.08	3.29	1.69	24.16	5.12	204.8
Median	0.788	1.51	9.05	4.32	2.30	35.03	10.00	273.9
Max	1.237	2.03	11.05	8.18	3.06	64.91	32.60	606.0
CV%	23.3	23.73	9.20	24.1	15.1	21.3	53.6	29.9
Geometric Mean	0.754	1.43	9.33	4.51	2.34	36.98	10.27	289.3
CV% Geometric Mean	25.2	26.77	9.17	22.4	15.2	19.9	49.4	26.8
95% CI Lower Mean	-	-	-	-	-	34.39	8.94	262.8
95% CI Upper Mean	-	-	-	-	-	41.02	14.03	336.9

Source: /u02/projects_apm/TIPRANAVIR/1182_0107/PK/TIPRANAVIR/FINAL_MODELS/FINAL/TABLES/TPV_PK_30012.prn

Table 15.6.2.2: 3 Summary of compartmental steady-state pharmacokinetics for TPV for patients receiving TPV/r 500/100 mg BID (Page 2 of 2)

	Ka (h^{-1})	Cl/F (L/h)	V/F (L)	$t_{1/2}$ (h)	Tmax (h)	Cmax (µM)	Cp_{12h} (µM)	AUC_{0-12h} (hyµM)
N	24	24	24	24	24	24	24	24
Mean	0.722	1.65	9.46	4.39	2.41	71.43	21.22	562.3
SD	0.181	0.48	1.16	1.73	0.39	19.76	17.56	234.6
Min	0.451	0.61	7.31	2.86	1.67	41.36	7.08	336.3
Median	0.698	1.68	9.40	3.57	2.39	66.19	13.87	493.5
Max	1.235	2.47	12.55	9.74	3.17	134.57	82.78	1361.1
CV%	25.1	29.20	12.28	39.4	16.2	27.7	82.7	41.7
Geometric Mean	0.703	1.57	9.39	4.14	2.38	69.19	16.97	527.6
CV% Geometric Mean	23.9	35.40	12.34	33.6	16.6	25.5	70.3	35.4
95% CI Lower Mean	-	-	-	-	-	63.08	13.81	463.2
95% CI Upper Mean	-	-	-	-	-	79.77	28.64	661.3

Source: /u02/projects_apm/TIPRANAVIR/1182_0107/PK/TIPRANAVIR/FINAL_MODELS/FINAL/TABLES/TPV_PK_30012.prn

Table 15.6.2.3: 1 Summary of compartmental steady-state pharmacokinetics for RTV for patients receiving TPV/r 500/200 mg QD (Page 2 of 2)

	Ka (h^{-1})	Cl/F (L/h)	V/F (L)	$t_{1/2}$ (h)	tmax (h)	Cmax (µg/mL)	Cp_{24h} (µg/mL)	$AUC_{0\text{-}24h}$ (hyµg/mL)
N	30	30	30	30	30	30	30	30
Mean	0.296	42.6	100.8	1.87	2.92	0.667	0.014	5.62
SD	0.035	15.7	26.4	0.86	0.67	0.266	0.037	3.67
Min	0.203	8.5	57.6	0.75	1.66	0.373	0.000	2.38
Median	0.304	39.4	98.9	1.76	3.01	0.637	0.006	5.08
Max	0.367	83.9	168.4	4.87	4.40	1.845	0.203	23.46
CV%	12.0	36.9	26.2	46.2	22.8	39.9	266.5	65.2
Geometric Mean	0.294	39.6	97.5	1.71	2.84	0.632	0.005	5.05
CV% Geometric Mean	12.7	44.0	26.8	45.5	23.9	32.5	206.2	44.0

Source: /u02/projects_apm/TIPRANAVIR/1182_0107/PK/RITONAVIR/FINAL_MODELS/FINAL/TABLES/RTV_PK_final.prn

Table 15.6.2.3: 2 Summary of compartmental steady-state pharmacokinetics for RTV for patients receiving TPV/r 250/100 mg BID (Page 2 of 2)

	Ka (h^{-1})	Cl/F (L/h)	V/F (L)	$t_{1/2}$ (h)	tmax (h)	Cmax (µg/mL)	Cp_{12h} (µg/mL)	AUC_{0-12h} (hyµg/mL)
N	25	25	25	25	25	25	25	25
Mean	0.318	48.5	93.5	1.70	2.40	0.360	0.067	2.50
SD	0.048	19.8	23.7	1.35	0.63	0.106	0.089	1.25
Min	0.262	15.5	57.7	0.72	1.45	0.191	0.005	1.08
Median	0.309	46.8	85.9	1.22	2.18	0.349	0.031	2.14
Max	0.468	92.9	150.5	6.74	3.96	0.624	0.397	6.46
CV%	15.1	40.9	25.4	79.2	26.4	29.5	132.9	50.3
Geometric Mean	0.315	44.4	90.8	1.42	2.33	0.346	0.039	2.25
CV% Geometric Mean	14.3	47.0	24.7	59.5	24.9	30.7	134.0	47.0

Source: /u02/projects_apm/TIPRANAVIR/1182_0107/PK/RITONAVIR/FINAL_MODELS/FINAL/TABLES/RTV_PK_final.prn

Table 15.6.2.3: 3 Summary of compartmental steady-state pharmacokinetics for RTV for patients receiving TPV/r 500/100 mg BID (Page 2 of 2)

	Ka (h^{-1})	Cl/F (L/h)	V/F (L)	$t_{1/2}$ (h)	tmax (h)	Cmax (µg/mL)	Cp_{12h} (µg/mL)	$AUC_{0\text{-}12h}$ (hyµg/mL)
N	24	24	24	24	24	24	24	24
Mean	0.317	62.9	92.2	1.24	2.13	0.308	0.043	1.96
SD	0.050	25.0	24.6	0.76	0.63	0.117	0.061	1.14
Min	0.253	16.6	47.4	0.51	1.39	0.138	0.006	0.79
Median	0.314	63.9	90.8	0.92	1.89	0.279	0.023	1.57
Max	0.407	126.0	135.5	3.44	3.52	0.656	0.277	6.03
CV%	15.6	39.7	26.7	61.6	29.8	38.0	140.0	58.3
Geometric Mean	0.313	57.4	88.9	1.07	2.05	0.291	0.025	1.74
CV% Geometric Mean	15.6	48.9	28.7	56.1	28.8	34.7	129.9	48.9

Source: /u02/projects_apm/TIPRANAVIR/1182_0107/PK/RITONAVIR/FINAL_MODELS/FINAL/TABLES/RTV_PK_final.prn

Table 15.3.2: 1 Adverse event overall summary – treated set

	TPV500/r200 N (%)	TPV250/r100 N (%)	TPV500/r100 N (%)	Total N (%)
Number of patients	30 (100.0)	25 (100.0)	28 (100.0)	83 (100.0)
Patients with any AE	18 (60.0)	12 (48.0)	18 (64.3)	48 (57.8)
Patients with investigator defined drug-related AEs	17 (56.7)	7 (28.0)	18 (64.3)	42 (50.6)
Patients with AEs leading to discontinuation of trial drug	0 (0.0)	0 (0.0)	2 (7.1)	2 (2.4)
Patients with serious AEs	0 (0.0)	0 (0.0)	1 (3.6)	1 (1.2)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Imm life-threatening	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Disability/incap.	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Req.hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Prol.hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Congenital anomaly	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	1 (3.6)	1 (1.2)
DAIDS grade severity (intensity)				
Grade 1 mild	15 (50.0)	8 (32.0)	11 (39.3)	34 (41.0)
Grade 2 moderate	2 (6.7)	4 (16.0)	4 (14.3)	10 (12.0)
Grade 3 severe	1 (3.3)	0 (0.0)	2 (7.1)	3 (3.6)
G4 potent. lifethret	0 (0.0)	0 (0.0)	1 (3.6)	1 (1.2)

A patient may be counted in more than one seriousness criterion.
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 11.1
Dosing: TPV500/r200 = QD, TPV250/r100 = BID, TPV500/r100 = BID