Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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..

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Tipranavir Soft Gel Capsule		**EudraCT No.:** 2005-005264-86	
Name of active ingredient: Tipranavir		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 21 May 2009	**Trial No. / U No.:** 1182-98 / U09-3280-01	**Date of trial:** 01 Mar 2007 – 20 Oct 2008	**Date of revision:** Not applicable

Title of trial:	**S**afety, efficacy and **P**harmacokinetics of tip**R**anavir boosted with low-dose ritonavir (TPV/r) 500 mg/200 mg BID **IN** a racially and **G**ender diverse HIV-positive treatment experienced population with a pilot evaluation of therapeutic drug monitoring (TDM). The **SPRING** study is an open-label, multicenter, multinational trial with randomisation to standard of care (SOC) or TDM TPV/r therapy
Coordinating Investigator:	[redacted]
Trial sites:	Multicenter study, cf. Appendix 16.1.4
Publication (reference):	Data from this study have not been published
Clinical phase:	IIIb
Objectives:	The objective of the trial was to compare the safety and efficacy of TPV/r in a diverse male and female population who were anti-retroviral (ARV) three-class treatment experienced with resistance to more than one PI. The trial was also designed to investigate whether therapeutic drug monitoring (TDM) could further benefit patients receiving TPV/r. Trial Termination: The 1182.98 SPRING study was terminated early due to low patient enrollment. This inability to recruit an adequate number of patients prevents analyzing and reporting data as planned in the protocol.
Methodology:	The 1182.98 SPRING study was an open-label, multicenter, multinational trial with randomization to TPV/r therapeutic drug monitoring (TDM) or TPV/r standard of care (SOC) in each of four race-gender (white/non-white; male/female) strata. Patients meeting screening criteria at Visit 1 had a baseline genotype determination at Visit 2. Baseline genotypic resistance testing and historical ARV medication usage was used by the investigator to construct an optimized background regimen (OBR) to be administered with open-label TPV/r 500 mg/200 mg BID. The OBR contained two to four ARVs. Patients that met criteria at screening Visit 1 and 2 were randomized to the TDM or SOC group at Visit 3 and began their TPV/r with the OBR. Patients were to be treated and followed for 48 weeks, plus a 30-day (after Week 48) study completion visit. Patient strata were set-up to include 200 women (100 non-white and 100 white) and 200 men (100 non-white and 100 white). At

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least 25% of male and female patients were to have a baseline CD4+ count ≥200 cells/mm^3. Using an interactive voice information and request system (IVRS) and/or an interactive web based system (IWBS) patients were randomised at Visit 3 to either the SOC TPV/r group or the TDM TPV/r group.

A patient voluntary post-dose pharmacokinetic (PK) sampling (SOC and TDM patients) was to be performed at Week 4 (Visit 5) at sites equipped to do so. A minimum of 30 non-white male and 30 white male patients, as well as 30 non-white female and 30 white female patients were required for this PK substudy.

TPV and RTV trough samples for SOC and TDM patients were collected at Week 2, 4, 8, 12, 24, 36 and 48.

The methodology used for TDM patients in the study are detailed below.

TDM Methodology:

For TDM management, TPV and ritonavir (RTV) dose adjustments (increase or decrease) were allowed at Week 4, 6, 10, 14, 18, 22, 26 and 30 based on an algorithm in the protocol that took into account the patient viral response, TPV inhibitory quotient (IQ) and TPV trough concentration. An adjustment, if needed, was included in the central TDM bioanalytical report sent to the site.

Virologic response was defined as: ≥1 $\log_{10}$ viral load (VL) reduction from baseline at Week 2, 4, 8 and 12, (and 16 and 20 if needed), and a VL <400 copies/mL from Week 24 on.

The IQ for TPV was calculated by the formula IQ = TPV C_{trough} / (3.75 x Z x fold change of the patients virus), where Z = wild type control IC_{50} IIIB. A dose escalation algorithm was used that did not permit TPV amounts to exceed 750 mg BID.

For patients with a virologic response, trough concentrations and TPV IQ dictated dose change recommendations as follows:

- A dose increase was recommended if the TPV trough concentration was <80 µM and the TPV IQ was ≤60;
- A dose decrease was recommended if the TPV trough concentration was >120 µM and the TPV IQ was >60;

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- A recommendation to consider changing therapy was made if the TPV trough concentration was >120 μM and the TPV IQ was ≤60;
- A recommendation to continue the current TPV/r dose was made if the TPV trough concentration was 80-120 μM and the TPV IQ was either ≤60 or >60, or if the TPV trough concentration was <80 μM and the TPV IQ was >60.

For patients with NO virologic response, the only case a dose change was permitted was when the TPV IQ was 40-60 and the TPV trough concentration was <80 μM. In all other instances the recommendation was to consider changing therapy if the patient had been on more than 4 weeks of TPV/r therapy.

Investigators were permitted to maintain a current dose and not follow a dose change recommendation of the central bioanalytical laboratory based on patient or clinical information that was not part of the algorithm. The investigator was encouraged to discuss such cases with the clinical monitor.

No. of subjects:

planned: Entered: 400 (200 female: 100 white / 100 non-white; 200 male: 100 white / 100 non-white)

actual: Enrolled / Screened: 125

Treatment TPV/r Standard of Care (SOC):
entered: 15 treated (3 female / 12 male; 12 white / 3 black): descriptive statistics

Treatment TPV/r Therapeutic Drug Monitoring (TDM):
entered: 18 treated (6 female / 12 male; 13 white / 5 black): descriptive statistics

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Diagnosis and main criteria for inclusion:	The trial was conducted in HIV-1 positive, multiple ARV-experienced male and female patients who were ≥18 years old. Main criteria for inclusion were: • Three class ARV-experience consisting of nucleoside and/or nucleotide reverse transcriptase inhibitors (N(t)RTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI) with a minimum of 3-months duration for each class. • No previous TPV usage and no patients indicating resistance to TPV. • CD4 +T lymphocyte count of ≥50 cells/µL. • HIV-1 Viral Load (VL) of ≥1000 copies/mL. • Patients were to have an ARV study treatment regimen consisting of at least 3 agents (TPV/r and at least two OBRs). Enfuvirtide, maraviroc and raltegravir, where available, were permitted as part of the OBRs as long as they were "new" to the patient's medication regimen at screening. • Acceptable screening laboratory values that indicated adequate baseline function, and acceptable medical history, as assessed by the investigator, were required. Women who were unwilling to comply with issues surrounding pregnancy were not permitted in the study.

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Test product: Tipranavir (TPV) capsules co-administered with ritonavir (RTV) capsules

dose:

SOC Group: Started and maintained at TPV/r 500 mg/200 mg BID

- TPV: 2 x 250 mg capsule = 500 mg dose
- RTV: 2 x 100 mg capsule = 200 mg dose

TDM Group: Started at TPV/r 500 mg/200 mg BID

- TPV: 2 x 250 mg capsule = 500 mg dose
- RTV: 2 x 100 mg capsule = 200 mg dose

When a patient in the TDM Group required a dose escalation, the algorithm below was used.

Current TPV/r Dose:	Increase TPV/r dose to:
750 mg/200 mg BID	No further increase
500 mg/200 mg BID	750 mg/200 mg BID
500 mg/100 mg BID	500 mg/200 mg BID
250 mg/200 mg BID	500 mg/100 mg BID

When a patient in the TDM Group required a dose reduction, the algorithm below was used.

Current TPV/r Dose:	Decrease TPV/r dose to:
750 mg/200 mg BID	500 mg/200 mg BID
500 mg/200 mg BID	500 mg/100 mg BID
500 mg/100 mg BID	250 mg/200 mg BID
250 mg/200 mg BID	No further decrease

mode of admin.: Oral

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batch no.:	TPV: B063000257, B063000462 RTV: B063000482, B063000564, B073000311
Reference therapy:	Not applicable
dose:	Not applicable
mode of admin.:	Not applicable
batch no.:	Not applicable
Duration of treatment:	48 weeks of treatment with a 30-day post-treatment follow-up visit
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Because of the premature termination of the study due to low patient enrollment, planned efficacy/clinical pharmacology comparisons with the TDM and SOC groups, gender, and race were not performed. However, individual changes from baseline in viral load and CD4+ cell counts are provided.
Safety:	All patients who took at least one dose of tipranavir in the trial were included in the safety analyses. However, because of the premature termination of the study due to low patient enrollment, planned safety comparisons with the TDM and SOC groups, gender, and race were not performed. Instead, treatment emergent adverse events (AEs), which included serious AEs and AIDS-defining and AIDS-related events; and premature discontinuations due to AEs were summarized. In addition, DAIDS Grade 3 or 4 laboratory abnormalities were also summarized to assess safety. A Data Safety Monitoring Board (DSMB) periodically evaluated the progress of the trial including AEs, serious AEs and laboratory information.
Statistical methods:	Descriptive statistics.

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results: The planned efficacy and pharmacokinetic analyses of the trial could not be performed because of early termination of the clinical study. There were too few patients and too few observations to have any useful evaluation of efficacy, pharmacokinetics or therapeutic drug monitoring. Therefore no conclusions can be drawn.

Safety results: There were no deaths and no on-treatment SAEs reported during the trial. There was one patient who discontinued study medication due to severe adverse events of nausea, vomiting, dizziness and nightmares, all considered drug-related, and all that resolved upon discontinuing therapy. This patient had also started efavirenz at the same time they were randomized to TPV/r. The dizziness and nightmares began on the second day of efavirenz treatment. There were no patients with hepatic events or DAIDS Grade 3 or 4 ALT, AST or total bilirubin elevations. There were no patients reported to have had an AIDS-defining event after beginning treatment.

Conclusions: No efficacy, pharmacokinetics, therapeutic drug monitoring, or safety conclusions can be drawn due to the early termination of the clinical study. There were too few patients and too few observations to have any useful evaluation of the primary or secondary efficacy endpoints, evaluation of pharmacokinetics or therapeutic drug monitoring, or comparison of randomized groups, gender or race for safety.

The limited safety information from this study did not alter the safety profile of tipranavir/ritonavir (TPV/r) in adult treatment-experienced patients.

Trial Synopsis - Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement disposition results and results for baseline data and safety endpoints of the trial.

Results for	**presented in**
Patient disposition	Table 15.1.1: 1
Demographic data	Table 15.1.4: 1
Adverse event overall summary	Table 15.3.2: 1

Table 15.1.1: 1 Disposition of subjects - Treated set

	SOC	TDM	Total
Enrolled			125
Not entered/randomised			92
Entered/randomised			33
Not treated			0
Treated [N (%)]	15 (100.0)	18 (100.0)	33 (100.0)
Not prematurely disc. from trial med [N (%)]	3 (20.0)	3 (16.7)	6 (18.2)
Prematurely disc. from trial med [N (%)]			
N	12 (80.0)	15 (83.3)	27 (81.8)
Worsening of disease under study	0 (0.0)	0 (0.0)	0 (0.0)
Worsening of other pre-existing disease	0 (0.0)	0 (0.0)	0 (0.0)
Other adverse event	0 (0.0)	1 (5.6)	1 (3.0)
Non compliant with protocol	1 (6.7)	1 (5.6)	2 (6.1)
Lost to follow-up	1 (6.7)	0 (0.0)	1 (3.0)
Consent withdrawn	0 (0.0)	2 (11.1)	2 (6.1)
Other *	10 (66.7)	10 (55.6)	20 (60.6)
Lack of efficacy	0 (0.0)	1 (5.6)	1 (3.0)
Patient completed [N (%)]	3 (20.0)	3 (16.7)	6 (18.2)
Prematurely discontinued from trial [N (%)]			
N	12 (80.0)	15 (83.3)	27 (81.8)
AE study disease worse	0 (0.0)	0 (0.0)	0 (0.0)
AE other disease worse	0 (0.0)	0 (0.0)	0 (0.0)
AE other	0 (0.0)	1 (5.6)	1 (3.0)
Non compliant protocol	1 (6.7)	1 (5.6)	2 (6.1)
Lost to follow-up	1 (6.7)	0 (0.0)	1 (3.0)
Consent withdrawn	0 (0.0)	2 (11.1)	2 (6.1)
Other *	10 (66.7)	11 (61.1)	21 (63.6)

* Other: categories include 18 patients who discontinued due to closure of trial (10 in TDM and 8 in SOC)

Source data: Appendix 16.2, Listing 1.1 xt_disp.sas 04MAY2009

Table 15.1.4: 1 Demographic data - Treated set

	SOC	TDM	Total
Total treated	15 (100.0)	18 (100.0)	33 (100.0)
Gender [N (%)]			
Male	12 (80.0)	12 (66.7)	24 (72.7)
Female	3 (20.0)	6 (33.3)	9 (27.3)
Race [N (%)]			
White	12 (80.0)	13 (72.2)	25 (75.8)
Black	3 (20.0)	5 (27.8)	8 (24.2)
Ethnicity [N (%)]			
Hispanic or Latino	7 (46.7)	7 (38.9)	14 (42.4)
Not Hispanic or Latino	8 (53.3)	11 (61.1)	19 (57.6)
Age category(years) [N (%)]			
<18	0 (0.0)	0 (0.0)	0 (0.0)
18-40	1 (6.7)	7 (38.9)	8 (24.2)
41-55	12 (80.0)	8 (44.4)	20 (60.6)
56-64	1 (6.7)	2 (11.1)	3 (9.1)
>=65	1 (6.7)	1 (5.6)	2 (6.1)
Age [years]			
N	15	18	33
Mean	46.1	43.2	44.5
SD	8.2	10.6	9.6
Median	45.0	42.0	44.0
Min	31.0	18.0	18.0
Max	65.0	65.0	65.0
Height(cm)			
N	14	18	32
Mean	169.9	174.1	172.3
SD	8.4	6.9	7.8
Median	168.0	174.0	170.5
Min	158.0	157.0	157.0
Max	185.0	185.0	185.0

Table 15.1.4: 1 Demographic data - Treated set

	SOC	TDM	Total
Weight(kg)			
N	15	18	33
Mean	78.4	74.8	76.4
SD	15.1	12.4	13.6
Median	72.5	72.5	72.5
Min	54.3	55.5	54.3
Max	111.9	100.7	111.9
Body mass index			
N	14	18	32
Mean	27.2	24.8	25.9
SD	4.4	5.0	4.8
Median	27.3	24.2	25.2
Min	20.2	17.5	17.5
Max	35.3	36.4	36.4

Table 15.3.2: 1 Adverse event overall summary - treated set

	SOC N (%)	TDM N (%)
Number of patients	15 (100.0)	18 (100.0)
Patients with any AE	12 (80.0)	15 (83.3)
DAIDS grade severity (intensity)		
Grade 1 mild	7 (46.7)	11 (61.1)
Grade 2 moderate	5 (33.3)	3 (16.7)
Grade 3 severe	0 (0.0)	1 (5.6)
G4 potent. lifethret	0 (0.0)	0 (0.0)
Patients with investigator defined drug-related AEs	5 (33.3)	6 (33.3)
Patients with other significant AEs (according to ICH E3)	0 (0.0)	1 (5.6)
Patients with AEs leading to discontinuation of trial drug	0 (0.0)	1 (5.6)
Patients with significant AEs (pre-specified events)	0 (0.0)	0 (0.0)
Patients with serious AEs	0 (0.0)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)
Imm life-threatening	0 (0.0)	0 (0.0)
Disability/incap.	0 (0.0)	0 (0.0)
Req.hospitalisation	0 (0.0)	0 (0.0)
Prol.hospitalisation	0 (0.0)	0 (0.0)
Congenital anomaly	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)

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
Includes AEs with onset date up to 30 days post study drug discontinuation