Clinical Study Synopsis for Public Disclosure

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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 Study Report**		
Name of finished product: Tipranavir				
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Title of study:	An open-label, randomized, single-dose, two-way crossover bioequivalence study assessing subjects receiving tipranavir 500 mg stored at controlled temperature (test product 30°C/70% RH) compared with tipranavir 500 mg stored at controlled refrigerated conditions (reference product 2-8°C), orally co-administered with ritonavir 200 mg under fasting conditions to healthy male and female volunteers
Investigator:	[redacted]
Study center:	[redacted]
Publication (reference):	N/A
Clinical phase:	Phase I
Objectives:	The objective of this trial was to establish the bioequivalence of TPV 250 mg self emulsifying drug delivery system (SEDDS) capsules that had been stored at a controlled temperature of 30°C and controlled relative humidity (RH) of 70% in comparison with TPV 250 mg SEDDS capsules stored at controlled refrigerated conditions between 2°C and 8°C.
Methodology:	This study was an open-label, randomized, single-dose, two-way crossover trial in healthy male and female HIV-negative adult volunteers. This bioequivalence study was designed to determine whether TPV Test SEDDS capsules [TPV (Test)] that had been stored at 30°C and 70% relative humidity (RH) for 24 months were bioequivalent to TPV Reference SEDDS capsules [TPV (Ref)] that had been stored at controlled refrigerated conditions from 2°C to 8°C for 13 months. The initial storage period of 24 months represented the end of the shelf life of this product at controlled room conditions of 20°C to 25°C and <70% RH. The mean tromethamine (TRIS) fill capsule content prior to the medication being sent to the study site was 0.63% for the TPV (Test) capsules and 1.22% for the TPV (Ref) capsules. Both TPV treatments were co-administered with ritonavir (RTV) 200 mg. At the research site, TPV (Test) capsules, TPV (Ref) capsules and RTV capsules were refrigerated at temperatures from 2°C to 8°C.

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Methodology (continued):	The subjects were admitted to the clinic in the evening before administration of study drugs, and stayed overnight while fasting for at least 8 hours before administration of study drugs. Immediately after pre-dose laboratory and pharmacokinetic (PK) sampling at approximately 08:00, subjects were administered a single dose of either TPV/r (Test) 500 mg/200 mg or TPV/r (Ref) 500 mg/200 mg. After administration of study drugs, a 24-hour period of intensive PK sampling (0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 15, 18 and 24 hours) was conducted. Additional PK samples were drawn at 30, 36, 48 and 72 hours. Each dose of TPV/r was separated by a washout period of at least 7 days, so that each subject received both TPV/r (Test) and TPV/r (Ref) doses, separated by the washout period.
No. of subjects:	
planned:	entered: 30
actual:	enrolled: 42 treated: 30 test product of TPV 500 mg + RTV 200 mg [TPV/r (Test)]: 28 subjects reference product of TPV 500 mg + RTV 200 mg [TPV/r (Ref)]: 30 subjects
Diagnosis and main criteria for inclusion:	Healthy male and female volunteers, age ≥18 and ≤60 years, BMI range: ≥18.5 and ≤35.0 kg/m^2
Test product:	Tipranavir capsules stored at 30°C and 70% RH while at BIPI. Stored refrigerated at 2°C to 8°C while at the research site.
dose:	500 mg (2 x 250 mg capsules) of TPV and 200 mg (2 x 100 mg capsules) of RTV
mode of admin.:	Oral administration after an overnight fast with approximately 240 mL of water
batch no.:	Tipranavir Test Product PD-2604. Ritonavir 166902E21
Duration of treatment:	One day for each treatment for a total of 2 days
Reference therapy:	Tipranavir capsules were refrigerated at 2°C to 8°C (36°F and 46°F) at BIPI for 13 months, and then stored at 2°C to 8°C at the research site. Ritonavir soft gelatin capsules stored at 2°C and 8°C at the research site.
dose:	500 mg (2 x 250 mg capsules) of TPV and 200 mg (2 x 100 mg capsules) of RTV
mode of admin.:	Oral administration after an overnight fast, with approximately 240 mL of water
batch no.:	Tipranavir Reference Product PD-2472. Ritonavir 166902E21
Criteria for evaluation:	
Efficacy:	There were no efficacy endpoints in this trial.

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Pharmacokinetics:

Primary endpoints

Bioequivalence was determined on the basis of the following PK parameters:

- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)
- C_{max} (maximum measured concentration of the analyte in plasma)

Secondary endpoints

Pharmacokinetics:

- AUC_{0-tz} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the time of the last quantifiable data point)
- AUC_{0-72} (area under the concentration-time curve of the analyte in plasma over the time interval t_{0h} to t_{72h})
- t_{max} (time from dosing to the maximum concentration of the analyte in plasma)
- λ_z (terminal rate constant in plasma)
- $t_{1/2}$ (terminal half-life of the analyte in plasma)
- MRT_{po} (mean residence time of the analyte in the body after p.o. administration)
- CL/F (apparent clearance of the analyte in the plasma after extravascular administration)
- V_z/F (apparent volume of distribution during the terminal phase λ_z following an extravascular dose)

Safety:

- Clinical laboratory results (haematology, clinical chemistry and urinalysis)
- Adverse events

Safety: Physical examinations, vital signs and ECG, laboratory test and adverse events.

Statistical methods: Point estimators (geometric means) of the median intra-subject ratios of the $AUC_{0-\infty}$ and C_{max} and two-sided 90% confidence intervals (CI) were derived. Safety endpoints were assessed with descriptive statistical methods.

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SUMMARY – CONCLUSIONS:

Pharmacokinetic results: Comparing the PK results of the TPV/r (Test) group with those of the TPV/r (Ref) group, the relative bioequivalence was estimated as 107% (90% CI: 0.97-1.18) in extent of absorption (AUC) and 112% (90% CI: 0.99-1.27) in rate and extent of absorption (C_{max}).

These results indicated that TPV 250 mg SEDDS capsules stored at conditions of 30°C and 70% RH for 24 months (test product), which represented the end of the shelf-life of this product when stored at controlled room conditions of 20°C to 25°C and less than 70% RH, and TPV 250 mg SEDDS capsules that had been stored at controlled refrigerated conditions of 2°C to 8°C (reference product) for 13 months were bioequivalent for extent of absorption (AUC), but not bioequivalent for rate and extent (C_{max}) of absorption.

Safety results: Adverse events, regardless of causality, were experienced by 43.3% (13/28) of subjects who received TPV/r (Ref) and 32.1% (9/30) of subjects who received TPV/r (Test). There were no deaths or other SAEs that occurred during the study. No AEs of a severe intensity were reported. There was one subject from the TPV/r (Ref) group that discontinued the trial because of an AE (viral gastroenteritis) that was of moderate intensity.

Other major safety findings from this single-dose, cross-over trial include:

- The highest frequency of subjects with AEs was in the gastrointestinal disorders SOC 33.3% (10/30), followed by nervous system disorders 16.7% (5/30). The test and reference groups did not differ notably for AEs by SOC.
- The most frequent AEs was nausea, seen in 23.3% (7/30) of subjects followed by headache 13.3% (4/30), diarrhea 10.0% (3/30), pharyngolaryngeal pain 10% (3/30) and nasal congestion 6.7% (2/30). The largest difference between treatment groups was for pharyngolaryngeal pain experienced by 10.0% (3/30) subjects in the TPV/r (Ref) group but no subjects in the TPV/r (Test) group.
- There was a difference in overall AEs frequency between genders: 33.3% (5/15) in males compared with 73.3% (11/15) in females.
- The overall frequency of AEs in males did not differ appreciably between the males in the TPV/r (Ref) group and males in the TPV/r (Test) group. For females, 66.7% (10/15) of females in the TPV/r (Ref) group experienced at least one AE compared with 42.9% (6/14) of females in the TPV/r (Test) group.

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Safety results (continued):	In conclusion, both the TPV/r (Ref) and TPV/r (Test) were well tolerated in this single-dose, two way cross-over trial of 30 subjects. There were no deaths or other SAEs reported and all but one AE was mild in intensity. The one moderate AE of viral gastroenteritis in the TPV/r (Ref) group did result in the subject prematurely discontinuing the trial after administration of the initial treatment. The type and intensity of the AEs experienced in the study suggest similar safety profiles for the TPV/r (Test) capsules with mean TRIS levels of 0.63% and TPV/r (Ref) capsules with mean TRIS levels of 1.22%.
Conclusions:	The PK results obtained from this study revealed that when comparing the TPV capsules that had been stored at the controlled conditions of 30° C and 70% RH for 24 months (representing the end of shelf-life of the TPV product) with TPV capsules that had been refrigerated for 13 months the extent of absorption (AUC) was bioequivalent. However, the rate of absorption (C_{max}) was not bioequivalent. The C_{max} for the TPV/r (Test) group was 12% higher than in the TPV/r (Ref) group. Because the AUC was equivalent and the C_{max} for the TPV/r (Test) group was higher despite lower TRIS levels than the TPV/r (Ref) group, it appears that decreased TRIS concentration levels did not negatively affect the performance of the capsule in the TPV (Test) group. The safety results indicated both treatments were well tolerated and having a lower TRIS concentration level in the TPV Test capsule did not adversely affect the safety profile. The overall results from this two-way, cross-over trial determined that the extent of absorption (AUC) was bioequivalent for both the TPV (Test) and TPV (Ref) capsules, that C_{max} for the TPV (Test) group was 12% higher than the TPV (Ref) group (not equivalent), and decreased TRIS concentration levels did not negatively affect the performance of the capsule in the TPV (Test) group. There was no evidence that the TPV (Test) SEDDS capsules with mean TRIS levels of 0.63% increased the safety risk for the subjects when compared to the same subjects receiving the TPV (Ref) SEDDS capsules with mean TRIS levels of 1.22%. Therefore, the safety results indicate that drug stored at room temperature at the end of the shelf-life with mean TRIS levels of 0.63% was comparable to drug stored under current recommended refrigerated conditions.