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.:** 2005-001-866-15 | |
| **Name of active ingredient:** Tipranavir | | **Page:** 1 of 7 | **Synopsis No.:** |
| **Module:** | | **Volume:** {hyperlink } | |
| **Report date:** 14 SEP 2009 | **Trial No. / U No.:** 1182.71 / U09-3681-01 | **Date of trial:** 25 September 2007 – 20 September 2008 | **Date of revision:** Not applicable |



| | |
|---|---|
| **Title of trial:** | A prospective randomized, open-labelled, multi-centre trial comparing the safety and efficacy of Ritonavir-boosted Aptivus (Tipranavir, TPV/r) to that of Prezista® (Darunavir, DRV/r) in three-class (NRTI, NNRTI, and PI) treatment-experienced patients with resistance to more than one PI.<br>**POTENT**: **Pr**ospec**T**ive **E**valuatio**N** of **T**ipranavir vs. Darunavir in Treatment Experienced Patients |
| **Coordinating Investigator:** | [redacted] |
| **Trial sites:** | Multicentre Study, cf, Appendix 16.1.4 |
| **Publication (reference):** | Data of this study has not been published |
| **Clinical phase:** | IIIb |
| **Objectives:** | To evaluate the efficacy and safety of TPV/r versus DRV/r in three-class (NRTI, NNRTI, and PI) treatment-experienced patients with resistance to more than one PI. |
| **Methodology:** | Qualifying, consenting patients that met all study screening criteria were randomized to receive either TPV/r (500mg/200mg) BID or DRV/r (600mg/100mg) BID in addition to an investigator selected optimized background regimen. Assessment of safety and efficacy were conducted at each clinic visit up to the end of the study. |
| **No. of subjects:** | |
| **planned:** | entered: 800 |
| **actual:** | enrolled: 147 |
| | entered: 40 |
| | Treatment A: 500 mg Tipranavir / 200 mg Ritonavir twice daily<br>entered: 20 treated: 19 analysed (efficacy):<br>Treatment B: 600 mg Darunavir / 100 mg Ritonavir twice daily<br>entered: 20 treated: 20 analysed (efficacy): |

| | | | |
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**Diagnosis and main criteria for inclusion:**

**Inclusion criteria**

1. Signed informed consent prior to trial participation.
2. HIV-1 infected male or female ≥18 years of age.
3. Three-class (NRTI, NNRTI, and PI) treatment-experienced patients (a minimum of 3-months duration for each class or documented hypersensitivity / intolerance) with resistance (minimal or reduced response) to more than one PI on the screening virtual phenotype resistance testing. In the case of NNRTIs, NNRTI resistance in the absence of exposure was equivalent to being NNRTI treatment experienced.
4. Patient's optimized background regimen must have contained one of the following ARV options:
   - A minimum of two genotypically active nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) reported as *"maximal response"* or *"sensitive"* on the screening virtual phenotype report
   - A minimum of one genotypically active NRTI reported as *"maximal response"* or *"sensitive"* on the screening virtual phenotype report plus an Enfuvirtide if not used previously.
   - A minimum of one genotypically active NRTI reported as *"maximal response"* or *"sensitive"* on the screening virtual phenotype report plus an integrase inhibitor if not used previously and if available through an expanded access program and allowed by local regulatory authorities.
   - A minimum of one genotypically active NRTI reported as "*maximal response" or "sensitive"* on the screening virtual phenotype report plus the CCR5 chemokine receptor antagonist Maraviroc if available through an expanded access program, not used previously and allowed by local regulatory authorities.
   - Zero or one genotypically active NRTI reported as *"maximal response"* or *"sensitive"* on the screening virtual phenotype report plus two of the following drugs, Enfuvirtide, integrase inhibitor and Maraviroc, if available, not used previously and allowed by local regulatory authorities.

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**Diagnosis and main criteria for inclusion: (continued)**

- Two genotypically partially active NRTIs (provided that they are not part of the current failing regimen) reported as *"reduced response"* on the virtual phenotype report plus one of the following drugs, Enfuvirtide, an integrase inhibitor or Maraviroc if available, not used previously and allowed by local regulatory authorities.
- For patients who had previously taken 3TC (lamivudine) or FTC (emtricitabine), these drugs are not considered as sensitive regardless of the virtual phenotype report.

5. Patient had been on their current (failing) PI-containing regiment for at least 8 weeks prior to randomization.
6. Patient had on-going viral replication (defined as an HIV-1 viral load of ≥500 copies/ml) and a successful virtual phenotype obtained at screening.
7. Any baseline CD4 cell count was allowed.
8. Karnofsky performance score of ≥70.
9. Acceptable screening laboratory values that indicate adequate baseline organ function. Laboratory values were considered acceptable if the following apply:
   - ALT ≤2.5xULN and AST ≤2.5xULN (≤DAIDS Grade 1, Appendix 10.1).
   - Any DAIDS grade cholesterol, triglycerides, GGT, CPK, or LDH is acceptable.
   - All other laboratory test values had to be ≤DAIDS Grade 2.
10. Willingness to initiate CD4+cell count-guided chemoprophylaxis to prevent opportunistic infections as defined in Protocol Appendix 10.3.2.
    - Willingness to abstain from ingesting substances which may alter plasma study drug levels by interaction with the cytochrome P450 system (listed in Section 4.2.2 and Appendix 10.5 of protocol) during the study.

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**Diagnosis and main criteria for inclusion: (continued)**

**Exclusion criteria**

1. Previous use of TPV or DRV.
2. Full genotypic resistance (reported as "*minimal response*") to TPV or DRV on screening virtual phenotype:
   - *"Minimal response"* was defined by the fold change above the Virco upper clinical cut-off value.
3. Female patient of child-bearing potential who:
   - had a positive serum pregnancy test at screening,
   - was breast feeding,
   - was planning to become pregnant,
   - was not willing to use barrier method protection or requires ethinyl estradiol administration. Barrier methods of contraception include diaphragm with spermicidal substance, condom for females, cervical caps and condoms.
4. History of Progressive Multifocal Leukoencephalopathy (PML) or Visceral Kaposi's Sarcoma (KS).
5. Any AIDS defining illness (Appendix 10.3.1) that was unresolved, symptomatic or not stable on treatment for at least 12 weeks at screening visit.
6. Use of immunomodulatory drugs (such as interferon, cyclosporin, hydroxyurea and interleukin-2) within 30 days prior to randomization.
7. Current use of systemic cytotoxic chemotherapy.
8. Inability to adhere to the requirements of the protocol, including active substance abuse as assessed by the investigator.
9. All contraindications listed in the product monographs of Aptivus, Prezista and Norvir.

| | |
|---|---|
| **Test products:** | Tipranavir (TPV) 250 mg soft gelatin capsules, batch no. B063000647 |
| | Ritonavir (RTV) 100 mg soft gelatin capsules, batch no. B07300614 |
| **dose:** | 500 mg TPV/200 mg RTV, twice daily |
| **mode of admin.:** | Oral |

| | | | |
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| | |
|---|---|
| **Reference therapy:** | Prezista® (DRV) 300 mg tablets, batch no. B073000586<br>Ritonavir (RTV) 100 mg soft gelatin capsules, B073000586 |
| **dose:** | 600 mg DRV/100 mg RTV, twice daily |
| **mode of admin.:** | Oral |
| **Duration of treatment:** | 50 weeks |

**Criteria for evaluation:**

**Efficacy / clinical pharmacology:**

PRIMARY ENDPOINT

The primary endpoint of this study was time to virologic failure, using VL <50 to define virologic response. The data from patients who do not complete the study was to be sent to an independent adjudication committee for a blinded decision if discontinuation from the study was related to virologic failure. This would have allowed a determination if the patient should be censored for the primary analysis .

SECONDARY ENDPOINTS

- Key secondary endpoint was treatment response at Week 48, using VL <50 as the response criterion and the FDA definition for handling drug discontinuations (Non-Completers = Failure)
- A pure Intent-To-Treat analysis of virologic response at Week 48 using VL <50 as the response criterion was also be included, where patients were to be followed until Week 48 for VL regardless of whether or not they remain on study drug
- The primary endpoint was to be analyzed using VL <400 as the response criterion
- Response at each visit using VL <50 copies/mL, VL <400 copies/mL and 1 $\log_{10}$ copies/mL drop from baseline in VL as the response criteria using all 3 methods for handling drug discontinuations (censored [primary], NCF [key secondary], and Intent-To-Treat [secondary])
- Daily average in CD4+ cell count and viral load change from baseline at Weeks 8, 24 and 48

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| | |
|---|---|
| **Efficacy / clinical pharmacology: (continued)** | • Change from baseline in CD4+ cell count and viral load at each visit<br>• Occurrence of new AIDS progression events or death.<br>Note: For all efficacy analyses involving response to <50 and <400, VL ≥500 were to be used to determine a virologic rebounder (see Protocol Section 7 for more details) |
| **Safety:** | • Occurrence of adverse events.<br>• Occurrence of serious adverse events (including AIDS-defining events).<br>• Occurrence of laboratory measurement abnormalities.<br>• Occurrence of DAIDS Grade 3 and 4 elevations in laboratory measurements at each visit.<br>• Change in laboratory test value from baseline.<br>• Occurrence of AEs, by severity and by action taken with regard to trial drug.<br>• Occurrence of discontinuations due to AEs.<br>• Time to first serious adverse event<br>• Time to first occurrence of a rash<br>• Time to first occurrence of DAIDS Grade 3 and 4 triglycerides or cholesterol abnormality<br>• Time to first occurrence of DAIDS Grade 3 and 4 ALT and / or AST elevation<br>• Time to first occurrence of DAIDS Grade 3 and 4 PT and / or PTT elevation<br>• Time to first occurrence of DAIDS Grade 3 and 4 Lipase elevation |
| **Statistical methods:** | The primary endpoint was to be analyzed by Cox regressions, adjusted for the stratification variables and baseline CD4+ cell count. If the upper limit of the 95% confidence interval for the hazard ratio of experiencing virologic failure on TPV/r compared to DRV/r does not exceed the pre-specified non-inferiority margin of 1.38, then non-inferiority of TPV/r and DRV/r in potency will be concluded. If non-inferiority were concluded, it was to be further tested if TPV/r was superior to DRV/r.<br>Response variables, including the key secondary endpoint, were to be analyzed using two-sided 95% confidence intervals for a stratified binary endpoint. Logistic regressions was also to be run where indicated in Protocol Section 7.<br>Time to event endpoints, including the primary endpoint, were to be analyzed by Cox regressions and log rank tests and presented graphically as Kaplan-Meier curves.<br>Continuous endpoints were to be analyzed by ANCOVA models where indicated |

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in Protocol Section 7.

Treatment emergent adverse events and DAIDS Grade 3 and 4 lab elevations were to be analyzed descriptively.

**SUMMARY – CONCLUSIONS:**

**Efficacy / clinical pharmacology results:** The trial was prematurely terminated due to poor enrollment with only 40 patients randomized over a recruitment period of more than eight months (first patient enrolled Sept. 20 2007- trial closure Jul. 1 2008). As such, the planned efficacy analyses of the trial could not be performed. There were too few patients and too few observations to have any useful evaluation of the primary or secondary efficacy endpoints. Of the 39 patients receiving at least one dose of study medication, thirty-five had viral loads lower during their last visit compared with their baseline value. The viral load of 25 patients was <50 copies/mL at their last visit, including five of the six patients that completed thirty-two weeks of treatment.

**Safety results:** As with efficacy, the limited amount of safety data collected did not allow for any safety conclusions to be drawn. Overall, however, the limited safety information described above did not alter the safety profile or the benefit/risk ratio of TPV/r or DRV/r treatment in treatment experienced patients.

**Conclusions:** No safety or efficacy conclusions could be drawn due to the premature termination of the trial. The limited safety data available did not alter the safety profile or the benefit/risk ratio of TPV/r or DRV/r treatment in treatment experienced patients.

## Trial Synopsis - Appendix

The trial was prematurely terminated due to poor enrollment with only 40 patients randomized over a recruitment period of more than eight months. As such, the planned efficacy analyses of the trial could not be performed. The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement the results for the patient disposition, patient baseline characteristics and adverse events.

| **Results for** | **presented in** |
|---|---|
| Patient Disposition | Table 15.1.1: 1 |
| Patient Baseline Characteristics | Table 15.1.4: 1 |
| AE summary | Table 15.3.2: 1 |

Table 15.1.1: 1 Disposition of patients

| | TPV/r | DRV/r | Total |
|---|---|---|---|
| Enrolled | | | 147 |
| Not entered/randomised | | | 107 |
| Entered/randomised | | | 40 |
| Not treated ^ | | | 1 |
| Treated [N (%)] | 19 (100.0) | 20 (100.0) | 39 (100.0) |
| Not prematurely disc. from trial med [N (%)] | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| Prematurely disc. from trial med [N (%)] | | | |
| N | 19 (100.0) | 20 (100.0) | 39 (100.0) |
| 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 | 1 ( 5.3) | 1 ( 5.0) | 2 ( 5.1) |
| Non compliant with protocol | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| Lost to follow-up | 1 ( 5.3) | 0 ( 0.0) | 1 ( 2.6) |
| Consent withdrawn | 1 ( 5.3) | 0 ( 0.0) | 1 ( 2.6) |
| Other * | 13 ( 68.4) | 19 ( 95.0) | 32 ( 82.1) |
| Lack of efficacy | 3 ( 15.8) | 0 ( 0.0) | 3 ( 7.7) |
| Patient completed [N (%)] | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| Prematurely discontinued from trial [N (%)] | | | |
| N | 19 (100.0) | 20 (100.0) | 39 (100.0) |
| 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 | 1 ( 5.3) | 1 ( 5.0) | 2 ( 5.1) |
| Non compliant protocol | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| Lost to follow-up | 1 ( 5.3) | 1 ( 5.0) | 2 ( 5.1) |
| Consent withdrawn | 1 ( 5.3) | 0 ( 0.0) | 1 ( 2.6) |
| Other * | 16 ( 84.2) | 18 ( 90.0) | 34 ( 87.2) |

* Other: patients discontinued due to the early trial termination
^ One patient was randomized but never received drug.

Source data: Appendix 16.2, Listing 1.1

Table 15.1.4: 1 Baseline demographic data and hepatitis status - Treated Set

| | TPV/r | DRV/r | Total |
|---|---|---|---|
| Total treated | 19 (100.0) | 20 (100.0) | 39 (100.0) |
| Gender [N (%)] | | | |
| Male | 15 ( 78.9) | 17 ( 85.0) | 32 ( 82.1) |
| Female | 4 ( 21.1) | 3 ( 15.0) | 7 ( 17.9) |
| Race [N (%)] | | | |
| White | 14 ( 73.7) | 16 ( 80.0) | 30 ( 76.9) |
| Black | 5 ( 26.3) | 1 ( 5.0) | 6 ( 15.4) |
| Asian | 0 ( 0.0) | 3 ( 15.0) | 3 ( 7.7) |
| Amer.Ind./Alaska Nat. | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| Hawaiian/Pacif. Isle | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| Age category(years) [N (%)] | | | |
| <18 | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| 18-40 | 5 ( 26.3) | 8 ( 40.0) | 13 ( 33.3) |
| 41-55 | 14 ( 73.7) | 11 ( 55.0) | 25 ( 64.1) |
| 56-64 | 0 ( 0.0) | 1 ( 5.0) | 1 ( 2.6) |
| >=65 | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| Age [years] | | | |
| N | 19 | 20 | 39 |
| Mean | 44.3 | 43.1 | 43.6 |
| SD | 6.1 | 6.2 | 6.1 |
| Median | 44.0 | 42.0 | 43.0 |
| Min | 33.0 | 34.0 | 33.0 |
| Max | 53.0 | 63.0 | 63.0 |
| Body mass index(kg/m^2) | | | |
| N | 18 | 20 | 38 |
| Mean | 24.9 | 23.3 | 24.0 |
| SD | 4.3 | 3.0 | 3.7 |
| Median | 24.8 | 23.3 | 23.8 |
| Min | 18.7 | 18.7 | 18.7 |
| Max | 33.2 | 33.0 | 33.2 |
| Height(cm) | | | |
| N | 18 | 20 | 38 |
| Mean | 174.7 | 173.6 | 174.1 |

Table 15.1.4: 1 Baseline demographic data and hepatitis status - Treated Set

| | TPV/r | DRV/r | Total |
|---|---|---|---|
| SD | 8.0 | 8.7 | 8.3 |
| Median | 172.0 | 174.5 | 173.0 |
| Min | 161.0 | 157.0 | 157.0 |
| Max | 192.0 | 191.0 | 192.0 |
| Weight(kg) | | | |
| N | 19 | 20 | 39 |
| Mean | 76.0 | 70.2 | 73.0 |
| SD | 14.1 | 11.3 | 12.9 |
| Median | 75.8 | 69.0 | 72.6 |
| Min | 51.0 | 52.5 | 51.0 |
| Max | 111.1 | 101.0 | 111.1 |
| Country [N (%)] | | | |
| Canada | 2 ( 10.5) | 0 ( 0.0) | 2 ( 5.1) |
| Germany | 0 ( 0.0) | 3 ( 15.0) | 3 ( 7.7) |
| Spain | 1 ( 5.3) | 1 ( 5.0) | 2 ( 5.1) |
| France | 5 ( 26.3) | 5 ( 25.0) | 10 ( 25.6) |
| Greece | 0 ( 0.0) | 1 ( 5.0) | 1 ( 2.6) |
| Italy | 2 ( 10.5) | 1 ( 5.0) | 3 ( 7.7) |
| Portugal | 3 ( 15.8) | 1 ( 5.0) | 4 ( 10.3) |
| Thailand | 0 ( 0.0) | 2 ( 10.0) | 2 ( 5.1) |
| USA | 6 ( 31.6) | 6 ( 30.0) | 12 ( 30.8) |
| Hepatitis B Surface Antigen [N (%)] | | | |
| Negative | 19 (100.0) | 19 ( 95.0) | 38 ( 97.4) |
| Positive | 0 ( 0.0) | 1 ( 5.0) | 1 ( 2.6) |
| Hepatitis B Core Antibody [N (%)] | | | |
| Negative | 7 ( 36.8) | 8 ( 40.0) | 15 ( 38.5) |
| Positive | 12 ( 63.2) | 12 ( 60.0) | 24 ( 61.5) |
| Hepatitis C Antibody [N (%)] | | | |
| Negative | 16 ( 84.2) | 18 ( 90.0) | 34 ( 87.2) |
| Positive | 3 ( 15.8) | 2 ( 10.0) | 5 ( 12.8) |

Table 15.3.2: 1 Adverse event overall summary - treated set

| | TPV/r N (%) | DRV/r N (%) | Total N (%) |
|---|---|---|---|
| Number of patients | 19 (100.0) | 20 (100.0) | 39 (100.0) |
| Patients with any AE | 12 ( 63.2) | 15 ( 75.0) | 27 ( 69.2) |
| DAIDS grade severity (intensity) | | | |
| Grade 1 mild | 5 ( 26.3) | 8 ( 40.0) | 13 ( 33.3) |
| Grade 2 moderate | 6 ( 31.6) | 4 ( 20.0) | 10 ( 25.6) |
| Grade 3 severe | 1 ( 5.3) | 2 ( 10.0) | 3 ( 7.7) |
| G4 potent. lifethret | 0 ( 0.0) | 1 ( 5.0) | 1 ( 2.6) |
| Patients with investigator defined drug-related AEs | 4 ( 21.1) | 5 ( 25.0) | 9 ( 23.1) |
| Patients with other significant AEs (according to ICH E3) | 1 ( 5.3) | 1 ( 5.0) | 2 ( 5.1) |
| Patients with AEs leading to discontinuation of trial drug | 1 ( 5.3) | 1 ( 5.0) | 2 ( 5.1) |
| Patients with significant AEs (pre-specified events) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| Patients with serious AEs | 0 ( 0.0) | 2 ( 10.0) | 2 ( 5.1) |
| Fatal | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| Imm life-threatening | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| Disability/incap. | 0 ( 0.0) | 1 ( 5.0) | 1 ( 2.6) |
| Req.hospitalisation | 0 ( 0.0) | 2 ( 10.0) | 2 ( 5.1) |
| Prol.hospitalisation | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| Congenital anomaly | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| Other | 0 ( 0.0) | 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: 12.0