

The Aptivus[®] Compassionate Use Program (CUP): safety and efficacy data from 3,920 patients in the clinic

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Abstract

The Aptivus[®] Compassionate Use Program (CUP) was an open label, non-randomised programme providing early access to tipranavir (TPV) for highly treatment experienced (HTE) patients ineligible for TPV studies. CUP safety data supplemented trial data and clarified TPV's clinical safety profile.

The CUP consisted of an Emergency Use Program (EUP) and Expanded Access Program (EAP). The EUP started in May 2003, three months after RESIST initiation. The EAP began in May 2004 with less restrictive criteria. Provision was for ≤10,000 patients worldwide.

EUP key entry criteria: triple ARV class experienced; failed ≥2 PIs; CD4 <50 cells/mm³; viral load (VL) >10,000 copies/mL. CD4 and VL criteria were removed in EAP. Hepatic impairment was an exclusion criterion. BI advised visits at baseline, week 2, 1st, 2nd, 3rd month, q3rd month; full blood count and standard safety monitoring at each visit.

By October 2005, 3,920 patients had received ≥1 dose of Aptivus[®]; 946 (24.1%) had completed the study; 887 (22.6%) prematurely discontinued; and 2087 (53.2%) were still in CUP. 87% male; 70% Caucasian; median prior ARVs: 12. Median BL: VL 4.83 log₁₀ copies/mL; CD4 96 cells/mm³.

At Day 360, median CD4 increase was 112 cells/mm³ and the median reduction from baseline was 1.8 log₁₀ copies/mL.

<20% of patients reported SAE or AE leading to discontinuation. Main AEs were infections and GI events.

The Aptivus[®] CUP provided access to TPV for HTE patients. No unexpected safety issues were seen. Virologic and immunologic findings were consistent with RESIST data.

Introduction

Tipranavir (TPV, Aptivus[®]) is a new generation protease inhibitor (PI) that has potent activity against multiple PI-resistant HIV-1. TPV co-administered with low dose ritonavir (TPV/r; 500/200 mg BID) is being evaluated in the RESIST 1 and 2 studies, which are randomised, ongoing, open label, comparative Phase III trials [1,2]. TPV/r exhibited potent activity and superiority to CPI/r in highly treatment-experienced patients at Weeks 24, 48 and 96 of the RESIST studies. TPV/r is effective and well tolerated in patients who have taken ≥2 PI-based regimens [1–4].

The Aptivus[®] Compassionate Use Program (CUP) was an open label, non-randomised programme providing early access to TPV/r for highly treatment-experienced patients who were unable to participate in the clinical development studies of TPV/r. CUP safety data supplemented trial data and clarified the clinical safety profile of TPV/r.

The CUP consisted of two parts: an Emergency Use Program (EUP) and an Expanded Access Program (EAP). The EUP started in May 2003, three months after the initiation of the Phase III RESIST studies. The EAP began in May 2004 with less restrictive criteria.

We report safety and efficacy data from 3,920 patients who took part in the Aptivus[®] CUP.

Patients and key entry criteria

Initial key entry criteria for the EUP were:

- Triple antiretroviral (ARV) class-experienced
- Failed ≥2 PI regimens
- CD4 cell count <50 cells/mm³
- Viral load (VL) >10,000 copies/mL
- Age >13 years (if <18 years, total body weight had to be >50 kg)

CD4 cell count and VL restrictions were removed in the EAP.

Hepatic impairment (defined as AST or ALT >5× ULN or total bilirubin >3.5× ULN; or AST or ALT >2.5× ULN and total bilirubin >2× ULN) was an exclusion criterion because, at the time of the CUP, the safety of TPV/r in this patient population had not yet been established.

Boehringer Ingelheim advised that patients visited the clinic at baseline, Week 2; and then monthly for the 1st, 2nd, 3rd month; subsequently, every 3rd month. Performing a full blood count and monitoring standard serum chemistries (including AST, ALT, total bilirubin) were advised at each visit.

Routine efficacy data were not collected during the CUP. Safety data collection within the CUP focused predominantly on the collection and reporting of serious adverse events (SAEs). Wherever possible, information on patients who discontinued TPV/r due to a non-serious AE was collected.

Results

Patient disposition and baseline characteristics

By October 2005, 3,920 patients had received ≥1 dose of Aptivus[®]. At this time, 946 (24.1%) patients had completed the study; 887 (22.6%) patients had prematurely discontinued TPV/r for a variety of reasons; and 2,087 (53.2%) were still participating in the CUP. The estimated patient exposure to TPV/r during the CUP was approximately 2,124 patient years of treatment.

Table 1: Patient disposition in CUP

	EUP	EAP	EUP + EAP
Total number of patients	1,091	2,829	3,920
Number of patients who had completed study by October 2005	198 (18.1%)	748 (26.4%)	946 (24.1%)
Number of patients who were taking study drug on 28 October 2005	479 (43.9%)	1608 (56.8%)	2087 (53.2%)
Number of patients who had prematurely discontinued TPV/r by October 2005	414 (38.0%)	473 (16.7%)	887 (22.6%)
Reason for premature discontinuation			
Death	69 (16.7%)	60 (12.7%)	129 (14.5%)
Other serious adverse event	35 (8.5%)	46 (9.7%)	81 (9.1%)
Non-serious adverse event	61 (14.7%)	123 (26.0%)	184 (20.7%)
Non-compliance with protocol	23 (5.6%)	17 (3.6%)	40 (4.5%)
Lost to follow-up	33 (8.0%)	58 (12.3%)	91 (10.3%)
Consent withdrawn	38 (9.2%)	76 (16.1%)	114 (12.9%)
Other: not specified	155 (37.4%)	93 (19.7%)	248 (28.0%)

The majority of patients (87%) were male and 70% were Caucasian. The median number of prior ARVs was 12 (5 PIs, 6 NRTIs and 1 NNRTI), reflecting the extensive treatment experience of this patient population.

At baseline, the median VL was 4.83 log₁₀ copies/mL and the median CD4 cell count was 96 cells/mm³. The majority of patients in the EUP (69.3%) had baseline CD4 cell counts <50 cells/mm³. The removal of the CD4 cell count restriction in the EAP meant that 26.8% of EAP patients had baseline CD4 cell counts <50 cells/mm³ and 36.4% had baseline CD4 cell counts of 50–200 cells/mm³. In the EUP, approximately half of the patients (50.9%) had baseline VLs 100,000–1,000,000 copies/mL; whereas 29.4% of patients in the EAP had this level of VL.

At Day 360, the median CD4 increase was 112 cells/mm³ (n=217 patients) and the median reduction in VL from baseline was 1.8 log₁₀ copies/mL (n=212 patients). Efficacy data were not available for all patients in the CUP, as explained above.

Clinical safety analysis

A total of 865 case reports of AEs were received up to October 2005; 90% (780/865) of these were classified as serious and 10% (85/865) as non-serious. The disproportionate number of serious events was due to the safety reporting requirements of this study as outlined above. The 865 reports referred to 676 individual patients (range: 1–8 reports per patient; average: 1.3 reports per patient). Figure 1 shows the case distribution by study.

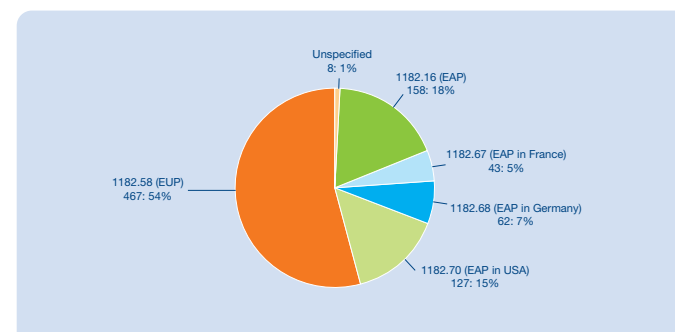


Figure 1: Case distribution by study

Seventeen percent of CUP patients contributed at least one AE case report. The overall number of AEs reported was 1,703; 84% (1,424/1,703) of which were serious AEs. It is noteworthy that most (83%) patients in the CUP did not report a serious AE or an AE leading to discontinuation.

Figure 2 shows the number and distribution of the reported cases by their primary system organ class (SOC). Every reported case was assigned to one SOC, even though several events were reported for some cases. The most common reports described infections (480/1,703; 28%) and gastrointestinal AEs (222/1,703, 13%).

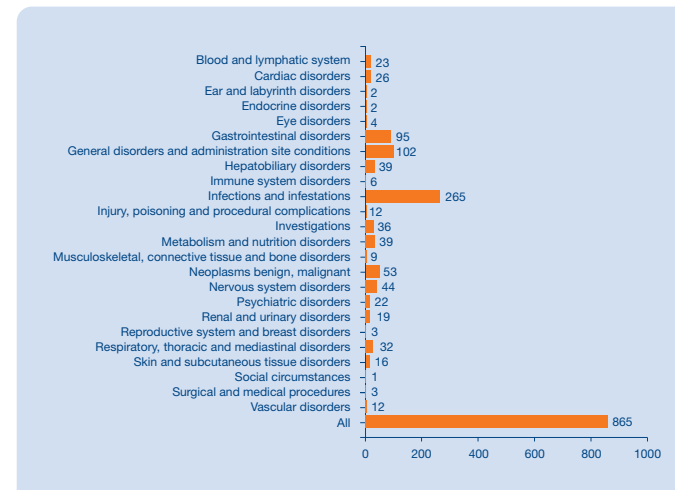


Figure 2: Number and distribution of reported cases

There were no substantial differences in the case reports for the EUP and the EAP, suggesting that the safety profile of TPV/r was similar in both patient populations.

The ten most frequently reported AEs were pyrexia (84/1,703, 4.9%), diarrhoea (59/1,703, 3.5%), pneumonia (50/1,703, 2.9%), vomiting (38/1,703, 2.2%), nausea (34/1,703, 2.0%), anaemia (33/1,703, 1.9%), general physical health deterioration (23/1,703, 1.4%), oesophageal candidiasis (21/1,703; 1.2%), dehydration (19/1,703, 1.1%), cachexia (18/1,703, 1.1%), and *Pneumocystis jirovecii* pneumonia (17/1,703, 1.0%).

There were 39 reports of hepatobiliary AEs during the CUP. Three fatal cases involved a hepatic event. The baseline CD4 cell counts and VLs ranged between 20 and 58 cells/mm³ and 18,000 to >750,000 copies/mL respectively. Two patients were HCV co-infected. In two patients, the cause of death was reported as 'worsening of hepatic function in the context of multi-organ failure and hepatic failure'. The third case was a patient who developed non-serious hyperbilirubinaemia with jaundice and who died one month after all drugs were discontinued due to progressive multifocal leukoencephalopathy. The two most frequently reported events were 'cytolytic hepatitis' (16 reports) and 'jaundice' (7 reports).

Two cases of intracranial haemorrhage (ICH) in two different patients were reported; one event had a fatal outcome. The annual incidence of ICH during the CUP was calculated to be 0.09%.

There were 162 fatalities during the CUP; an estimated incidence of 7.6 fatal cases per 100 patient-years of treatment. Given the advanced nature of HIV disease in the CUP patients and their limited treatment options, this fatality rate was not unexpected. In the PLATO cohort of HTE patients with low CD4 cell counts (<50 cells/mm³), a rate of 22 deaths per 100 patient-years of treatment was reported [5]. The majority (91/98, 93%) of patients in the CUP who died and for whom data were available had entered the programme with CD4 cell counts <50 cells/mm³ and their CD4 cell counts had failed to increase during the CUP. Similarly, 62/72 (86.1%) patients (for whom data were available) had entered the CUP with VLs >100,000–1,000,000 copies/mL and died with VLs at this level.

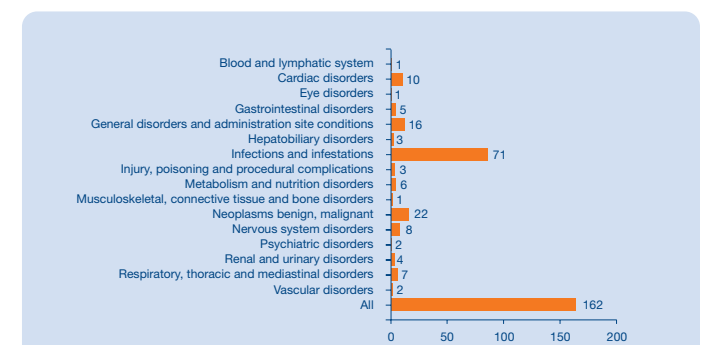


Figure 3: Distribution of fatal cases by SOC

The distribution of fatal cases by SOC is shown in Figure 3. Given the advanced nature of this patient population, it is not surprising that the most frequent classification of cases was 'infections and infestations' (71/162; 44%). HIV infection/AIDS or end stage AIDS was reported for 30 fatal cases. There were 22 reports of neoplasms: various forms of lymphomas for 13 cases and three cases of Kaposi's sarcoma.

Laboratory safety analysis

The majority (96.3%) of patients who entered the CUP with normal AST levels maintained AST levels within normal limits or experienced a Grade 1 elevation during treatment. Only 1.5% of patients experienced an AST increase to Grade 3 or 4. The corresponding figures for ALT levels were 94.1% and 2.0%, respectively.

No patients entered the CUP with a Grade 3/4 AST or ALT level. Of the patients who entered the programme with normal ALT levels, 94% (713/757) maintained normal ALT levels or experienced Grade 1 elevations. Only 1.8% (14/757) developed Grade 3 or 4 ALT elevations. Data were available for 37 patients who entered the programme with Grade 2 ALT levels. For 54.1% (20/37) of these patients, ALT levels fell to Grade 1 or normal levels, 41% (15/37) went to Grade 2 and 5.4% (2/37) went to Grade 3; none of these patients developed a Grade 4 ALT elevation. Data on 32 patients who entered the programme with Grade 2 AST levels were available: levels returned to Grade 1 or normal levels in 63% (20/32) of these patients. ALT data were available for 965 patients, of whom 27 (2.8%) developed a Grade 3 or 4 ALT elevation. Overall, 90% of these patients maintained normal ALT levels or developed a maximum of a Grade 1 elevation.

Of the patients who entered the CUP with normal total cholesterol levels, 93.4% (506/543) had normal levels or a Grade 1 elevation. In approximately 2.7% (15/543) of these patients, total cholesterol levels increased to a Grade 3 or 4 level. Of patients entering the CUP with a Grade 1 total cholesterol level, 81% (77/95) returned to normal levels or remained at Grade 1, while only 4.2% (4/95) developed a Grade 3 or 4 elevation.

Two-thirds (66.5%; 341/513) of patients who entered the programme with normal triglyceride values stayed within normal limits. In approximately 8.6% (44/513) of these patients, the total triglyceride levels increased to a Grade 3 or 4 level. For patients entering the CUP with a Grade 2 hypertriglyceridaemia, 16.1% (15/93) returned to normal values, 38.7% (36/93) stayed at Grade 2; and 45.1% (42/93) increased to Grade 3 or 4. Data on 27 patients who entered the studies with a Grade 3 or 4 hypertriglyceridaemia were available. Of these, 26% (7/27) decreased to Grade 2, and 74% (20/27) stayed at Grade 3 or 4 levels.

Drug discontinuations due to non-fatal reasons

Overall, 22.6% (887/3,920) of the patients who entered the CUP discontinued TPV/r due to various reasons. Reasons for non-fatal discontinuation included: other SAEs (i.e. non-fatal SAEs), non-serious AEs, lack of compliance, lost to follow-up, withdrawal of consent and other reasons. The majority of patients who discontinued for 'other reasons' (156/232, 67%) did so because of virological failure. This was expected since the CUP patients had advanced HIV disease and very few options to construct a fully suppressive ARV regimen. The second most frequent reason for a premature non-fatal drug discontinuation was non-serious AEs (n=184). Overall, 34.2% (63/184) of the patients discontinued due to cutaneous AEs, hepatic laboratory abnormalities (transaminase and bilirubin elevations) and hyperlipidaemia.

Conclusions

- The Aptivus[®] CUP provided 3,920 highly treatment-experienced patients with access to TPV/r, prior to its marketing approval.
- The safety profile of TPV/r in the EUP and EAP was similar to that observed in the pivotal RESIST studies. However, fewer cases of Grade 3/4 ALT or AST elevations were seen in the CUP.
- No unexpected safety issues were seen during the Aptivus[®] CUP.
- The majority of patients who entered the CUP with normal laboratory values stayed within normal limits or only experienced Grade 1 elevations.
- 83% of patients in the CUP did not report a serious AE or an AE leading to discontinuation.
- In those patients for whom virologic and immunologic data were available, findings from the Aptivus[®] CUP were consistent with RESIST data.

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