



## ASX Release

### Avexa Releases ATC Phase IIb Clinical Trial Update

26 July, 2007

Australian biotechnology company Avexa (ASX:AVX) announced today further information relating to its Phase IIb clinical trial on apricitabine (ATC) as presented by Dr Pedro Cahn to the International AIDS Society (IAS) meeting in Sydney yesterday afternoon. Dr Cahn is not only one of Avexa's lead investigators for ATC but is also the President of the International AIDS Society. Dr Cahn's talk was titled "Superior Activity of Apricitabine in treatment experienced HIV-1 infected patients with M184V and NRTI resistance."

Dr Cahn presented information in his lecture over and above that outlined in the Avexa press release dated the 20<sup>th</sup> of March, 2007. Avexa's ATC was also mentioned in several other keynote and plenary presentations during the conference, covering new treatments for HIV.

The highlights from Dr Cahn about the Phase IIb study were:

- ATC demonstrates significant clinical activity against a wide range of drug-resistant HIV, including HIV strains harbouring the lamivudine resistance mutation (M184). In addition, ATC is active against virus which has both the M184V mutation and encodes the AZT- and other drug-resistance mutations known as TAMS.
- ATC is a very well tolerated drug. The adverse effect (AE) profile of ATC demonstrates that this drug is very well tolerated with very few side effects noted in the trial. In fact there were no drug-related withdrawals from the trial or drug-related serious adverse events (SAEs). Overall there were fewer adverse effects (AE's) in either ATC arm than in the 3TC control group.
- No mutations that conferred resistance to ATC and none of the in-vitro selected mutations were observed in patients treated over the clinical trial period reported. The high genetic barrier, (that is, the slow rate at which resistance to ATC develops in-vitro) appears to be mirrored in the clinic.
- It is also significant that the M184V mutation was maintained in all 38 patients whose virus could be genotyped. Virus containing this M184V mutation is generally accepted to be replicatively incompetent compared to wild-type HIV, although still able to replicate in and damage the patient's immune cells. Therefore it is beneficial to maintain this weakened virus at a lower level rather than having it replaced by other more replicatively competent and / or drug-resistant viruses. Moreover, the M184V also confers sensitivity to other antiviral treatments although remaining resistant to 3TC. Ideally it would be best if patients could have their viral loads reduced to undetectable levels, as was achieved with ten of the patients in the ATC arms of the Phase IIb trial.



- To date sixteen patients out of a possible seventeen patients have elected to enter the extension study after completing the 48 week study. “The willingness of patients to enter the extension study provides us with strong encouragement that ATC is providing benefit to patients with HIV and helping in the treatment of their disease” stated Avexa’s CEO Dr. Julian Chick.

Dr Pedro Cahn’s IAS conference presentation will be available on the Avexa website at  
[www.avexa.com.au](http://www.avexa.com.au)

### **Clinical trial design and detailed results**

ATC is a cytidine analogue that is a potent inhibitor of HIV reverse transcriptase (RT) which acts by selective chain termination of the virus. ATC is active against all clades of HIV tested, including strains with the 3TC resistance mutation (M184V) and thymidine- (TAMs) and nucleoside-analogue mutations (NAMs). The drug has been demonstrated to have a very low potential for drug-drug interaction issues and can be taken with or without food. Furthermore ATC has been demonstrated in-vitro to have a very low toxicity profile (including mitochondrial- and myelo- toxicity) and there are no significant hepatic metabolism, glucuronidation or P450 interactions.

As described in the Avexa press release dated the 20<sup>th</sup> of March, 2007, the Phase IIb trial on ATC successfully achieved its primary endpoint. The designated endpoint for Phase IIb success was a 0.6 log<sub>10</sub> decrease in viral load after 21 days treatment with ATC. However, ATC exceeded this endpoint, achieving an overall viral load decrease of 0.8 log<sub>10</sub> in that time period. Lamivudine (3TC) was the comparator in this Phase IIb trial.

### **Activity**

The Phase IIb study was a randomized, double-blinded dose-ranging study of ATC versus 3TC in treatment experienced HIV infected patients with the M184V mutation in RT. Key inclusion criteria were that patients had to be failing their current 3TC-containing anti-retroviral treatment (ART) and have HIV RNA levels above 2000 copies per ml. The patients had to have been treatment experienced in at least two classes of ART and their HIV had to contain the M184V mutation and could also harbour up to 6 TAMs. The drug doses used in the trial were 600mg and 800mg of ATC twice a day and 150mg of 3TC twice a day.

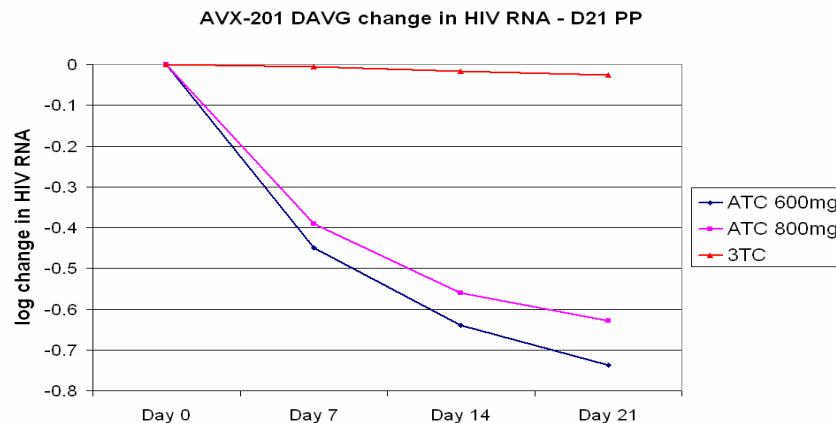
There were two primary endpoints of the trial. These were the mean time-weighted average change from baseline in HIV RNA through 21 days, (which means the rate at which the amount of virus decreases in the blood of the patients) and the change from the baseline in HIV RNA at day 21, (which is the overall viral load decrease in the patients blood after 21 days).



The trial can be seen as having three time components. Over the first 21 days ATC is given as a functional monotherapy (i.e. only the 3TC in the patient's treatment regimen is swapped for ATC; or 3TC is maintained in the control arm). At the end of this first period the primary endpoints were determined (as described above) and show the clinical activity of ATC against drug-resistant virus. After the 21 days of functional monotherapy, the patients' background therapy is optimized, with the study drug or control arm continuing otherwise unchanged. The following 21 week period is therefore designed to determine the longer term antiviral activity and safety profile of the drug in comparison to 3TC in this cohort of drug-resistant patients over a 24 week period as part of regular ART. The final 24 weeks of the trial is an open label study period with all patients being treated with 800mg of ATC twice daily. The primary purpose of this period is to study maintenance of antiviral activity and longer term safety.

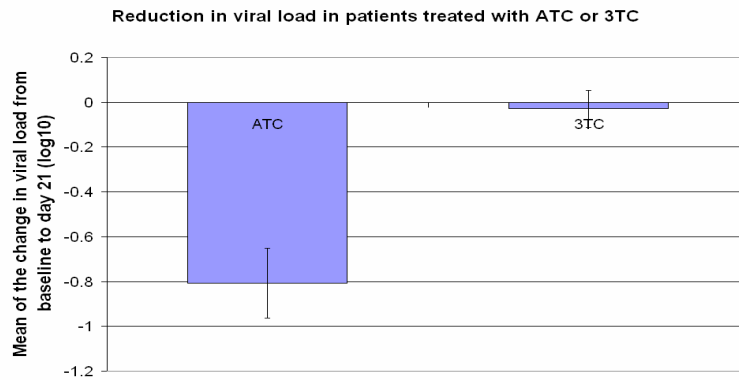
There is also an extension study which allows patients to elect to keep taking ATC if they or their doctors feel that they are receiving benefit from the treatment. Sixteen from a possible seventeen patients have elected to enter the extension study having completed the 48 week study and continue to receive ATC as part of their antiviral therapy. This gives Avexa great hope that patients are benefiting from ATC as part of their daily HIV treatment and moreover that ATC is well tolerated by HIV-infected patients.

The following graph shows the effect over a 21 day period of the two doses of ATC on the mean time-weighted viral change. These data demonstrate that both doses of ATC are extremely active in reducing the viral load in patients, when compared to 3TC. Both doses of ATC were significantly different from 3TC,



however, overall there were no clinically significant differences between the two ATC doses.

The following graph shows the combined mean of the change in viral load from baseline to Day 21 ( $\log_{10}$ ) for both doses of ATC compared to the 3TC arm. These data demonstrate that ATC is extremely active in reducing the viral load in patients, when compared to 3TC.



Bars on the figure above indicate the standard error of the two groups.

The following table shows the viral load reduction at day 21 for the two doses of ATC and for the 3TC comparator arm. These data again demonstrate that ATC is extremely active in reducing the viral load in patients, when compared to 3TC.

Although overall there was no clinically significant difference between the two ATC doses, in patients with the M184V and 3 or more TAMs, the 800mg ATC dose appears to have better activity as shown in the table below.

	<b>150mg 3TC (n=14)</b>	<b>600mg ATC (n=17)</b>	<b>800mg ATC (n=16)</b>
<b>Mean change from baseline in log<sub>10</sub> HIV RNA at D21</b>	-0.029	-0.9 (p=0.006)	-0.71 (p=0.05)
<b>Mean change from baseline in log<sub>10</sub> HIV RNA at D21 in patients with ≥3 TAMs at baseline</b>	0.025	-0.37	-0.75

## Resistance

Analysis of the genotypes of 38 patients' virus prior to and after the 21-day treatment segment of the trial was undertaken. Only 38 genotypes were analysed as the remainder of the patients' virus loads dropped to undetectable. Of those 38 genotypes available at D21, 38/38 of the patients maintained the M184V mutation. Four patients lost 1 TAM at D21, one in the 3TC arm and three in the ATC arm. Five patients gained 1 TAM at D21, two from the 3TC arm and three from the ATC arm (all 3 were taking AZT as well). No patients gained K65R, 74V, 115F, 75T/M/A or other sentinel nucleoside analogue resistance mutations.



## Safety

During the first 21-days of the Phase IIb trial 31 patients reported no adverse events (AEs) at all. Forty treatment-emergent AEs were reported by 20 patients, of which most were either mild or moderate. There were two severe (grade 3) AEs, one being a case of thrombocytopenia (low platelet counts) in the ATC arm and the other a case of elevated triglycerides (3TC arm). Neither of these adverse effects was deemed related to study drug and both of these patients remain in the trial. The most frequent AEs were nausea (4 cases; in both the ATC and 3TC arms); diarrhea (3 cases; in both the ATC and 3TC arms), 2 cases of dyspepsia (upset stomach) in the ATC arm and 2 cases of nasopharyngitis (in both the ATC and 3TC arms).

There were only 3 mild adverse events reported to be associated with ATC, those being nausea, dyspepsia and anorexia / weight loss. There was one moderate adverse event reported to be related to 3TC, that being an exacerbated peripheral neuropathy.

The following table shows the adverse effect profile for the two doses of ATC and for the 3TC comparator arm. These data again demonstrate that ATC is a very well tolerated compound and was not associated with serious side effects that have been observed for some other nucleoside analogues. The safety profile of ATC is comparable to that of 3TC which is considered to be an extremely well tolerated and safe antiretroviral medicine.

AVX-201 AE profile – treatment emergent AEs Day 0 - Day 21	150mg 3TC (n=16)	600mg ATC (n=17)	800mg ATC (n=18)
No. patients with any AE D0-D21	9 (56.3%)	4 (23.5%)	7 (38.9%)
No. patients with mild AE	7 (43.8%)	2 (11.8%)	6 (33.3%)
No. patients with moderate AE	4 (25%)	2 (11.8%)	5 (27.8%)
No. patients with severe AE (grade 3)	1 (6.3%)	0	1 (5.6%)*
No. patients with serious AE (SAE)	0	0	0
No. patients discontinuing due to AE	0	0	0
No. patients with related AE	1 (6.3%)	1 (5.9%)	2 (11.1%)

\* As previously reported this patient experienced an episode of thrombocytopenia. The patient had a history of previous thrombocytopenia. All HIV drugs including ATC were temporarily interrupted for a short period. The event was not considered related to ATC. The patient remains in the clinical trial and has completed 24 weeks dosing.

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Avexa Limited is a Melbourne-based biotechnology company with a focus on research and development of drugs for the treatment of infectious diseases, in particular diseases which have a significant unmet medical need. Avexa has dedicated resources and funding for key projects including its HIV integrase program and an antibiotic program for antibiotic-resistant bacterial infections. The Company's lead program is apricitabine (ATC) which has recently successfully completed the 21 day dosing of its Phase Ib trial. The Company continues to progress ATC towards Phase III trials. Avexa has entered into a collaboration with TargetDrug in China to identify new CCR5 inhibitors for the treatment of HIV infections and has an exclusive option to license TargetDrug's lead CCR5 inhibitor, Nifeviroc.