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CASE STUDY OF A PATIENT WITH SERIOUS HEPATOTOXICITY IN MARAVIROC 2B/3 TRIAL REPORTED AT 'TARGETING HIV ENTRY- 1ST INTERNATIONAL WORKSHOP'

Bethesda, MD- Howard Mayer, MD of Pfizer Global Research and Development presented today on a case of one patient with serious hepatotoxicity in the treatment naïve trial of the maraviroc phase 2b/3 program. Speaking at the 'Targeting HIV Entry- 1st International Workshop', Mayer said the single case was reported to Pfizer in early November through standard safety monitoring procedures. At the time, approximately 1300 patients with HIV had enrolled in this phase 2b/3 clinical program (~ 75% on maraviroc).

Pfizer recently reported that detailed reviews of safety and efficacy by the independent maraviroc Data Safety Monitoring Board (DSMB) conducted in July and September concluded that there were no safety concerns at that time, including no signal of significant liver dysfunction potentially associated with maraviroc. Upon learning of this case, Pfizer requested an ad-hoc DSMB review and informed all investigators, patients and regulatory authorities of this latest information. Key details of the case that Mayer reported today were:

- Patient was HIV and HCV seropositive, HCV RNA negative, with radiographic evidence of underlying hepatic steatosis at time of screening into study.
- Seven weeks prior to study drug initiation, isoniazid (INH) and cotrimoxazole (trimethoprim-sulfamethoxazole) were started for primary prophylaxis of HIV-associated infections. Liver enzymes were reported as normal at this time.
- During the seven week study screening period, the patient's alanine aminotransferase (ALT) increased more than five-fold to three times the upper limit of normal (grade 2) with an elevated aspartate aminotransferase (AST).
- After the seven week study screening period, the patient first began receiving study drugs that included maraviroc 300 mg once daily (blinded study drug) and zidovudine/lamivudine.
- On day 5 of the regimen described, after having received four doses of maraviroc and zidovudine/lamivudine, the patient developed rash and fever. Maraviroc was discontinued after five doses of maraviroc 300 mg QD (1500 mg total).
- On day 6, liver enzymes were documented to be significantly elevated (ALT 32 times upper limit of normal). Lopinavir/ritonavir was started. Parenteral acetaminophen (paracetamol) was also initiated at this time.
- INH, lopinavir/ritonavir, zidovudine/lamivudine, cotrimoxazole, and parenteral acetaminophen were continued for several days after maraviroc was stopped (all discontinued by day 10).
- A liver biopsy was performed on day 9. Preliminary review of the case by an independent expert hepatologist resulted in an assessment of severe drug induced hepatocellular injury with INH, co-trimoxazole, or the study drug possibly involved either singularly or in combination.
- The patient's liver enzymes continued to worsen resulting in placement on the liver transplant list on day 14.
- Patient underwent liver transplantation on study day 16 and is clinically stable post transplant.

Upon review, the DSMB concluded that the other medications administered during this episode appear more likely to be associated with the hepatotoxicity; however, they could not exclude that maraviroc had a role in this patient's illness.

The DSMB recommended amendments to the ongoing phase 2b/3 protocols, all of which Pfizer is implementing, include:

- Exclusion of isoniazid for newly enrolled subjects in all protocols.
- Further confirmation of stable liver function tests during the screening period by additional testing at the randomization visit, prior to start of study drugs.
- Immediate discontinuation of ALL study drugs and all potentially hepatotoxic drugs in treatment naive patients when new grade 3/4 liver enzyme abnormalities (> 5 times the upper limit of normal) are observed until the cause is determined or the abnormalities resolve.

The DSMB recommends no further changes to the maraviroc program at this time and will meet again as scheduled in January 2006.