Data Review of aplaviroc trials

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Background information

- Aplaviroc development stopped due to evidence of idiosyncratic hepatoxicity
- 640 subjects dosed, >350 with multiple doses in phase IIb and III
- Review of SAEs, AEs and HIV associated conditions
  - 3 reports found
    - Squamous cell carcinoma
    - Burkitt's Lymphoma
    - "Possible Lymphoma"
- None reported as "drug related"

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Squamous Cell Carcinoma

- 41 y female randomized to COM+APL (600mg BID)
  - 01APR05: vaginal discharge with blood
  - 18APR05: enrolled into the APL trial
  - 28APR05: invasive epidernoid carcinoma of vagina diagnosed by biopsy
  - 17MAY05: hospitalized: further biopsy “invasive adenocarcinoma”
  - 14/15JUN05: Chemotherapy with cis-platinum and radiotherapy initiated
  - 27JUN05: patient withdrawn from study
  - SAE reported as “no reasonable possibility that vaginal carcinoma was related to investigational product”.

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Burkitt's Lymphoma

- 33 y male randomized to COM+APL (800mg BID)
  - 21FEB05: enrolled in APL trial
    - BL WBC was 6500, Hb was 8.8
  - 12MAR05: developed anemia/leukopenia (WBC:1700, Hb: 7.0) with 2^{o} pneumonia, fatigue, SOB and tachycardia.
  - 12MAR05: subject hospitalized and transfused
  - 14MAR05: study drug discontinued
  - 17MAR05: events resolved and considered anemia/leucopenia linked to COM

Burkitt's Lymphoma contd.

- 19MAY06: new follow-up information provided to GSK.
  - 12MAR05: heme+ stools noted while in hospital
    - Patient found to have large retroperitoneal mass
  - Biopsy showed Burkitt's Type Lymphoma
  - SAE now reported as BL instead of anemia/leucopenia
  - 29MAR05: subject refused treatment, was discharged
  - 09APR05: subject died, no autopsy performed
  - SAE considered related to underlying HIV infection

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“Possible Lymphoma”

- 58 y male randomized to COM+APL (800mg BID)
  - Hx of advanced HIV and 2-3 mths of R-sided arm pain
  - 04APR05: enrolled in APL trial
  - 13MAY05: worsening R upper extremity pain plus new R lower extremity pain and new foot drag. Subject hospitalized
  - Brain MRI: L parietal punctated lesion and a lesion in cervical cord
  - SPECT –ve, serologies for crypto and toxo –ve
  - Initial SAE report “viral reconstitution syndrome, likely infectious or lymphoma” likely assoc with HIV disease

“Possible Lymphoma” contd.

- 30JUN05: SAE report changed to “possible Cerebral Tuberculosis”. R-sided weakness improved with dexamethasone.
- Started on 12 month course of INH, PZA, ethambutol, ofloxacin and Vitamin B6
- 27AUG05: follow-up MRI showed no mass, CSF cultures –ve.
- Patient had residual limited dexterity in R hand, no signif motor weakness
- Gained weight 3 months on TB meds, maintained appetite , weight and energy.
- To remain on TB meds til May06.
- SAE not felt to be associated with study meds; remained on trial til sept 05