Hypothetical Case Description: Enrolling Adolescents in an HIV Vaccine Clinical Study

The following case description uses published information to construct a generic description of a typical clinical investigation that is not unique or specific to any particular product.

Proposed Clinical Trial

- A phase 2 “proof of concept” trial of a new vaccination strategy against HIV infection is being considered.
- The strategy combines three initial priming vaccinations with a DNA vaccine that incorporates selected HIV genes including envelope, followed at six months by a modified poxvirus vectored vaccine containing the same HIV genes.

Pre-clinical Testing

- Pre-clinical testing of this prime/boost regimen demonstrated relative protection against homologous simian immunodeficiency virus challenges in non-human primate models involving mucosal exposure.
- Although the vaccine did not prevent HIV infection, immunized animals had a reduced per-exposure probability of becoming infected as compared with controls.

Early phase adult human experience

- Several phase 1 clinical trials involving healthy adult volunteers demonstrated T cell responses lasting in the majority of subjects out to 12 months.
- In these adult studies, no serious adverse events were identified.
- The most common local reactions were pain and erythema at the injection site, experienced by the majority of subjects. Mild and moderate fatigue and myalgia, lasting up to four days, occurred in a minority of subjects.

Early phase adult human experience

- Of note, the majority of subjects also developed false-positive results from commercial HIV screening tests at the dose selected for phase 2 testing.
- Additional testing can discern false versus true positive tests for HIV infection; however, the duration that commercial screening tests for HIV remain positive is unknown.
- To date, there is no immunological surrogate that can serve as a short term marker of potential clinical benefit in reducing the incidence or mitigating the severity of HIV infection.

Proposed Endpoints

- The phase 2 clinical trial plans to enroll a sufficient number of high risk adult subjects 18 to 30 years of age to be able to evaluate
  1) whether the vaccination regimen reduces the acquisition of HIV infection (as the primary endpoint) and/or
  2) decreases the viral load at three months post-diagnosis in those subjects who become HIV infected.

Study Conduct

- The study will be conducted at multiple sites selected based on a high prevalence of HIV infection. After informed consent, subjects will be randomized equally to either active or placebo vaccination administered in a blinded fashion to minimize bias. The study duration has been estimated based on a sufficient number of HIV infections occurring in the enrolled subjects to assess the primary endpoint. Risk reduction counseling, use of post-exposure prophylaxis, and standard anti-retroviral treatments for those subjects who become HIV infected during the trial are all included in the protocol. Interim analyses are planned for safety and efficacy after half of the necessary HIV infected cases have occurred.

Question

- Please discuss the ethical considerations that should go into a decision about whether (and, if yes, when) to enroll adolescents in the above phase 2 clinical investigation.
- As part of your discussion, please address the threshold of evidence necessary to establish that the study intervention offers a sufficient prospect of direct benefit to justify the risks of vaccine administration.
  - For example, are interim or final results from adult phase 2 or 3 studies needed prior to studies in adolescents?
  - How does the lack of an immunological surrogate for clinically meaningful benefit affect the prospect of direct benefit?
- Issues you may want to consider include:
  a) the distinction between evidence sufficient to establish the prospect of direct benefit versus evidence sufficient to establish efficacy;
  b) the choice of adolescent populations (i.e., at risk); and
  c) the use of comparable adolescent immunogenicity and/or safety data as a bridge to extrapolate from adult clinical outcomes data to efficacy in the adolescent population.