Regulatory issues and vaccine licensure at the country level

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Reference:

"*Guidelines for the Clinical Evaluation of Dengue Vaccines in Endemic Areas*"

TBA from WHO Initiative for Vaccine Research (IVR)*

*US FDA is in basic accord with the elements of this document.

Problems Related to Dengue Vaccine Development

- Four Serotypes
  - Need for a tetravalent vaccine
- Complex pathogenesis
  - Enhanced disease d/t secondary infection
- Appropriate population for study
  - Pediatric population
  - Role of maternal antibodies in infants
  - Previous dengue infection
- Definition of a protective immune response

Problems Related to Dengue Vaccine Development (2)

- Effect of prior exposure to other flaviviruses.
- Requirement for solid epidemiology in areas where efficacy studies will be done.
- Serology: Neutralizing Abs
  - CMI testing?
  - Assays need to be standardized and validated
- Requirement for extended safety study post-vaccination
  - Possible enhancing effect of waning vaccine-induced immunity

Clinical Development Pathway

- Phase I: Safety and immunogenicity
  - Adults, non-endemic area
- Phase II:
  - Larger numbers, dose ranging, step-down or step-up to younger or older age groups
  - Phase IIb studies may be conducted in endemic areas
- Phase III: Pivotal efficacy trial in at-risk population
  - Determines ability of vaccine to prevent disease
  - Adds larger numbers of subjects to prove safety

Phase III Considerations

- Go-ahead is based on results of phase I and II trials
  - Does the vaccine elicit a tetravalent response in most subjects?
  - Is the reactogenicity “acceptable”?
- Initial Phase III trials will involve live, attenuated tetravalent vaccines.

Probable design of Phase III trial (see also WHO Guidelines)

- Double-blind, controlled trial
  - Control group could receive a well-established vaccine vs placebo.
- Number of subjects in each arm will depend upon the incidence of “dengue” in the endemic area, if that is the primary endpoint (case definition)
- Probably primary endpoint will be “dengue”, as defined by identification of virus in blood using RT-PCR, culture, and/or anti-NS1 immune response, NS1 antigenemia, in a subject with two or three days of “fever”.
  - Secondary endpoint could include incidence of “serious” dengue and/or DHF/DSS
- A cohort of subjects in both vaccine and control groups will be followed for dengue immune status prior to vaccination and for 3 to 5 years thereafter, by periodic sampling of blood for Abs and PBMCs.

How N is determined

- Case definition = “dengue”
- Epidemiology data to estimate number of cases of “dengue” in vaccinated population per year or per season
- Make estimate for efficacy of vaccine to prevent “dengue”, e.g., 80%
- Power the study to detect 80% efficacy with 95% confidence

Phase III trial, first year

- Safety and immunogenicity follow-up
  - Post-vaccination reporting of all fevers in vaccine and placebo groups
  - F/U all fevers of 2-3 day duration with clinic visit or bedside visit
    - Blood sample - Dengue viremia? (culture, RT-PCR, NS1)
      - Neut Abs and ?NS1 Abs, PBMCs for reference storage
    - Decision: dengue vs not dengue
  - Immunogenicity cohort will donate blood samples at regular intervals throughout first year, TBD.

Phase III trial, longterm f/u

- Follow-up of vaccine and placebo cohorts for 3 to 5 years will be necessary
- *Possible* methods:
  - Active surveillance at regular intervals
    - Evaluate general health by verbal report or questionnaire
  - Passive: study monitors to be contacted for fever, hospital visit or hospitalization for any illness
    - If subjects are seen when febrile, initiate dengue screen
    - Record and tabulate all cases of “severe” dengue, include serotype of infecting virus
    - Record and tabulate all other flavivirus infections

How to declare success during a long term study

- FDA agrees that an “adaptive” or “sequential” design could be built into the study plan and the statistical analysis plan, so that efficacy might be declared prior to study termination without stopping the study or violating the blinded status.

Long term data collection

- Follow-up for immunology cohort
  - Collect blood at “regular” (3-, 4-, or 6-month) intervals for dengue neut Ab titers and for PBMCs
    - At present the consensus is that PBMC samples will be stored for future decisions regarding testing
- Correlate/Surrogate for protection?
  - Possibly a certain level of neut Abs can be shown thru results of this study to correlate w/ protection
    - Based on longterm data after phase III and into phase IV

Phase IV Studies

- Based on the art of the possible and TBD by sponsors, but
  - Should include continued F/U of subjects who participated in phase III, for up to 10 years.
    - Suggest: Monitor mortality and hospitalizations
      - Requires a stable medical infrastructure with study-affiliated doctors, preferably a common health care facility, a pre-determined battery of tests to be performed on acutely ill subjects
- Long term safety: Follow a randomly selected cohort of vaccinees who receive the vacine post-licensure
  - This is typically done for all newly licensed vaccines in the US