A comprehensive overview of the clinical development program of TAK-003

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Background: Dengue has a major public health impact. However, developing a live-attenuated dengue vaccine has been challenging for ~century. Challenges have included balancing safety/immunogenicity through proper attenuation, eliciting a multi-faceted tetravalent immune response, and obtaining enough serotype-level information through prolonged efficacy and safety evaluation in different settings. We present an overview of Takeda's live-attenuated tetravalent dengue vaccine (TAK-003) clinical development program.

Methods: TAK-003 was developed over several decades by extensive pre-clinical characterization and 19 clinical studies (28,175 volunteers, 1.5-60-years-old from 13 countries). Studies evaluated vaccine formulation, safety, and immunogenicity. Formulation and dosing schedule were established in phase I/II trials and used in the DEN-301(NCT02747927) study.

Results: Early studies confirmed genetic stability, optimal attenuation, low reactogenicity, and balanced immunogenicity. The DEN-204 (NCT02302066) study supported the two-dose schedule to maximize multivalent seroconversion in most recipients. In DEN-301, the vaccine efficacy (VE) was 80.2%(95%CI:73.3-85.3) against virologically confirmed dengue (VCD) after 12 months (primary endpoint) and after 18 months 90.4%(95%CI:82.6-94.7) against hospitalization. VE against VCD and hospitalization was comparable among baseline seronegative and seropositive recipients. Cumulative VE through 4.5 years was 61.2%(95%CI:56.0-65.8) against VCD and 84.1%(95%CI:77.8-88.6) against hospitalization, while variable by serotype. Integrated safety analysis found no clinically significant safety risks, irrespective of baseline serostatus/age.

Conclusions: TAK-003, developed through a comprehensive clinical program, displayed low reactogenicity, balanced immunogenicity, and long-term efficacy and safety, addressing an unmet need for a dengue vaccine with no identified important safety risks.

Funding: Takeda