Takeda's Dengue Vaccine Candidate Associated with Reduced Incidence of Dengue in Children and Adolescents; New 18-Month Interim Phase 2 Data Published in The Lancet Infectious Diseases

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- *Trial assesses safety and immunogenicity of different schedules of TAK-003 dengue vaccine candidate in children and adolescents ages 2 through 17 living in dengue-endemic areas*[1]
- *Children and adolescents who received TAK-003 had a relative risk of symptomatic dengue of 0.29 (95% CI: 0.13–0.72) compared to children and adolescents in the placebo control group*[1]
- *TAK-003 induced sustained antibody responses against all four serotypes of dengue virus, regardless of previous dengue exposure and dosing schedule*[1]
- *TAK-003 is currently being evaluated in a two-dose schedule, administered three months apart, in the pivotal Phase 3 TIDES efficacy trial*[2]

Osaka, Japan, Nov. 7, 2017 – Takeda Pharmaceutical Company Limited [TSE: 4502], ("Takeda") today announced that data from an 18-month interim analysis of the ongoing Phase 2 DEN-204 trial of its live, attenuated tetravalent dengue vaccine candidate, TAK-003 (also referred to as TDV), have been published in *The Lancet Infectious Diseases* . The results of this interim analysis, a pre-planned evaluation of data from an ongoing trial, show that TAK-003 is associated with a reduction in the incidence of dengue in children and adolescents.[1] These data were also presented today at the American Society of Tropical Medicine and Hygiene Annual Meeting.[3] Phase 3 data are required to confirm these findings.

The Phase 2 DEN-204 trial is ongoing and evaluating the safety and immunogenicity of TAK-003 in 1,794 children and adolescents ages 2 through 17 living in dengue-endemic areas (the Dominican Republic, Panama and the Philippines). The primary objective of the trial is to assess the vaccine-induced antibody levels to all four types of dengue virus following different vaccine schedules.[4] Trial participants received either one primary dose of TAK-003, two primary doses of TAK-003 administered three months apart, one primary dose of TAK-003 followed by a booster dose one year later, or a placebo.[1] Febrile surveillance and assessment of safety and immunogenicity will continue through the 48-month study period of the trial.[1]

These interim results showed:[1]

- In the safety set (the group of participants who received at least one dose of TAK-003 or placebo), children and adolescents who received TAK-003 had a relative risk of symptomatic dengue of 0.29 (95% CI: 0.13–0.72)

studies.[1]

- The immune response against all four dengue serotypes was durable across all vaccinated groups, with antibody levels persisting out to 18 months regardless of vaccine schedule or previous exposure to the dengue virus.[1]
- There was limited difference in geometric mean titers (GMTs) and seropositivity rates between those who received one primary dose and those who received two primary doses three months apart, regardless of serostatus. However, importantly, in participants who were seronegative at baseline, a second dose given at Month 3 improved the tetravalent seropositivity rate at Month 6 to 86%, compared to 69% in the one-dose group.[1] A booster dose at Month 12 resulted in a 100% tetravalent seropositivity rate at Month 13 in participants who were seronegative at baseline.[1]

These findings support selection of a two-dose regimen, administered three months apart, for Takeda's ongoing global pivotal Phase 3 efficacy trial. This regimen quickly achieves a high rate of response to all four dengue serotypes regardless of previous dengue exposure.[1]

"We are seeing an acceptable safety profile and sustained antibody responses out to 18 months in this trial. These data are an important step in the development of our dengue vaccine candidate," said Derek Wallace, M.B.B.S., Global Dengue Program Lead at Takeda.[1] "The reduced incidence of dengue in children and adolescents receiving TAK-003 is encouraging, however data from our ongoing Phase 3 efficacy trial, TIDES, are required to confirm these findings."[1]

TAK-003 is currently under evaluation in the Tetravalent Immunization against Dengue Efficacy Study (TIDES), a large-scale Phase 3 efficacy trial being conducted in eight dengue-endemic countries.[2] TIDES will build on DEN-204 and other previous studies in continuing to assess the tolerability, safety and immunogenicity of the vaccine against all four dengue serotypes in multiple age groups and to determine whether the vaccine helps prevent symptomatic dengue.[2, 5, 6] Data from TIDES will be available in late 2018.[2]

About the Phase 2 DEN-204 Trial

The Phase 2 DEN-204 trial is a randomized, double-blind, placebo-controlled, multi-center trial designed to assess the safety and immunogenicity of either one- or two-dose schedules of TAK-003 in 1,794 healthy participants living in dengue-endemic areas (the Dominican Republic, Panama and the Philippines).[7]

About TAK-003

Takeda's tetravalent dengue vaccine candidate (TAK-003) is based on a live, attenuated dengue serotype 2 virus (DENV-2), which provides the genetic 'backbone' for all four vaccine viruses.[8] Phase 1 and 2 data have supported progression into Phase 3 study, suggesting that TAK-003 is safe and well-tolerated in children and adolescents (no vaccine-related SAEs occurred and reactogenicity was limited) and induced immunogenicity against all four dengue serotypes, even in seronegative participants. [7, 9, 10, 11]

About Dengue

Dengue is the fastest spreading mosquito-borne viral disease.[12] Dengue is spread by *Aedes aegypti* and *Aedes albopictus* mosquitoes and is caused by any of four dengue virus serotypes, each of which can cause dengue fever or severe dengue.[13, 14] The prevalence of individual serotypes varies across different geographies, countries, regions, seasons and over time.[15, 16]

Dengue outbreaks are observed in tropical and sub-tropical areas and have recently caused outbreaks in parts of the continental U.S. and Europe.[13, 17, 18] Approximately half of the world now lives under the threat of dengue, which is responsible for approximately 390 million infections and 20,000 deaths globally each year.[13, 19]

Dengue virus can infect people of all ages and is a leading cause of serious illness among children in some

years, Takeda has supplied vaccines to protect the health of people in Japan. Today, Takeda's global vaccine business is applying innovation to tackle some of the world's most challenging infectious diseases, such as dengue, Zika, norovirus and polio. Our team brings an outstanding track record and a wealth of knowledge in vaccine development, manufacturing and global access to advance a pipeline of vaccines to address some of the world's most pressing public health needs.

About Takeda Pharmaceutical Company Limited

Takeda Pharmaceutical Company Limited (TSE: 4502) is a global, R&D-driven pharmaceutical company committed to bringing better health and a brighter future to patients by translating science into life-changing medicines. Takeda focuses its research efforts on oncology, gastroenterology and central nervous system therapeutic areas. It also has specific development programs in specialty cardiovascular diseases as well as late-stage candidates for vaccines. Takeda conducts R&D both internally and with partners to stay at the leading edge of innovation. New innovative products, especially in oncology and gastroenterology, as well as its presence in emerging markets, fuel the growth of Takeda. About 30,000 Takeda employees are committed to improving quality of life for patients, working with our partners in health care in more than 70 countries. For more information, visit https://www.takeda.com/newsroom/ .

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