News Release

**Takeda Presents 18-Month Data from Pivotal Phase 3 Trial of Dengue Vaccine Candidate at the American Society of Tropical Medicine and Hygiene (ASTMH) 68th Annual Meeting**

* ***Data presented from the pivotal Phase 3 trial include an update on overall efficacy of the vaccine candidate, as well as formal analyses of secondary efficacy endpoints by serotype, baseline serostatus and disease severity***
* ***18-month results build upon the efficacy and safety data reported in the 12-month analysis; overall vaccine efficacy remained generally consistent and the trial met all secondary endpoints for which there were a sufficient number of cases; safety and efficacy will be assessed over a total of four and a half years***
* ***Takeda presented 11 abstracts across its vaccine pipeline at ASTMH, including oral presentations on its dengue and Zika vaccine candidates***

**Cambridge, Mass., and Osaka, Japan, November 23, 2019 –** Takeda Pharmaceutical Company Limited ([TSE:4502/NYSE:TAK](https://www.takeda.com/investors/)) (“Takeda”) today announced that updated results from the ongoing pivotal

Phase 3 [Tetravalent Immunization against Dengue Efficacy Study (TIDES)](https://clinicaltrials.gov/ct2/show/record/NCT02747927?term=den-301&rank=1) trial of its dengue vaccine candidate (TAK-003) were presented at the American Society of Tropical Medicine and Hygiene (ASTMH) 68th Annual Meeting. The data presented include an update on overall vaccine efficacy (VE) and a formal assessment of secondary efficacy endpoints by serotype, baseline serostatus and disease severity (18 months after the second dose, which was administered three months after the first dose). The TIDES trial met all secondary endpoints for which there were a sufficient number of cases. Overall vaccine efficacy and safety results from the second part of the study were generally consistent with the data reported in the primary endpoint analysis (overall VE was 73.3% [95% confidence interval (CI): 66.5% to 78.8%; p<0.001] in the 18-month analysis, and VE was 80.2% (95% CI: 73.3% to 85.3%) in the primary endpoint analysis [12 months after the second dose]). The primary endpoint analysis of overall VE was recently published in the [New England Journal of Medicine](https://www.nejm.org/doi/full/10.1056/NEJMoa1903869)*,*[[1]](#endnote-1) demonstrating protection against virologically-confirmed dengue (VCD) in children ages four to 16 years, regardless of previous exposure to dengue.

Assessment of secondary endpoints showed that VE against hospitalized dengue was 90.4% (95% CI: 82.6% to 94.7%; p<0.001) and VE against dengue hemorrhagic fever was 85.9% (95% CI: 31.9% to 97.1%); efficacy against severe VCD could not be determined due to an insufficient number of cases (VE: 2.3% [95% CI: -977.5% to 91.1%). Overall efficacy was similar in baseline seropositive and seronegative individuals (VE: 76.1% [95% CI: 68.5% to 81.9%] vs. VE: 66.2% [95% CI: 49.1% to 77.5%], respectively). Efficacy results varied by individual serotype: VE was 69.8% for dengue serotype 1 (95% CI: 54.8% to 79.9%), 95.1% for dengue serotype 2 (95% CI: 89.9% to 97.6%), and 48.9% for dengue serotype 3 (95% CI: 27.2% to 64.1%). There were an insufficient number of dengue serotype 4 cases to adequately assess efficacy at this time (VE: 51.0% [95% CI: -69.4% to 85.8%]). Efficacy endpoints will continue to be assessed over the course of the trial.

Analyses of exploratory endpoints in VCD showed similar VE among seropositive and seronegative individuals for dengue serotype 1 (VE: 72.0% [95% CI: 52.2% to 83.6%] vs. VE: 67.8% [95% CI: 40.3% to 82.6%]) and dengue serotype 2 (VE: 93.7% [95% CI: 86.1% to 97.1%] vs. VE: 98.1% [95% CI: 85.8% to 99.7%]). For dengue serotype 3, VE in seropositive individuals was 61.8% (95% CI: 43.0% to 74.4%), and

-68.2% (95% CI: -318.9% to 32.4%) in seronegative individuals. The VE against dengue serotype 3 in seronegative individuals was statistically inconclusive but suggests a lack of efficacy. Efficacy against dengue serotype 4 could not be determined due to a limited number of cases. Planned follow-up will further characterize the performance of the vaccine candidate in dengue serotypes 3 and 4.

Consistent with previous results, Takeda’s dengue vaccine candidate was generally well tolerated, and there have been no important safety risks observed to date.

“The 18-month data presented at ASTMH further our understanding of the efficacy and safety of Takeda’s dengue vaccine candidate,” said Shibadas Biswal, M.D., Medical Director, Dengue Clinical Development, Takeda, who presented the TIDES data at ASTMH. “These results are encouraging, and we’re particularly pleased to see the consistency in overall efficacy as compared to our 12-month analysis, as well as the overall efficacy in seronegative participants. While additional data is needed to fully understand the profile of TAK-003, particularly against serotype 3 in seronegatives, we see its potential to address key priorities for dengue control, including protection of seronegative populations and prevention of hospitalization.”

The Phase 3 TIDES trial is ongoing and will continue to assess safety and efficacy of the vaccine candidate in study subjects for a total of four and a half years. Takeda’s dengue vaccine candidate is not currently licensed anywhere in the world.

In total, Takeda presented two oral and nine poster presentations at ASTMH, including data for its Zika vaccine candidate from ZIK-101, a randomized, placebo-controlled, double-blind Phase 1 trial designed to evaluate the safety and immunogenicity of the investigational vaccine candidate in 240 male and female subjects between the ages of 18 and 49.[[2]](#endnote-2) The Phase 1 trial also assessed different dose levels to support the progression of the vaccine candidate into future studies.2 Takeda's Zika program is supported by federal funds from Biomedical Advanced Research and Development Authority (BARDA), within the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services.

**About the Phase 3 TIDES (DEN-301) Trial**

The double-blind, randomized, placebo-controlled Phase 3 TIDES trial is evaluating the safety and efficacy of two doses of TAK-003 in the prevention of laboratory-confirmed symptomatic dengue fever of any severity and due to any of the four dengue virus serotypes in children and adolescents.[[3]](#endnote-3) Study participants were randomly assigned to receive either TAK-003 0.5 mL or placebo by subcutaneous injection on Day 1 and Day 90.3 The study is comprised of three parts. The primary endpoint analysis evaluated vaccine efficacy (VE) and safety through 15 months after the first dose (12 months after the second dose).3 The second part of the study continued for an additional six months to complete the assessment of the secondary endpoints of VE by serotype, baseline serostatus and disease severity.3 The final part of the study evaluates VE and long-term safety by following participants for an additional three years.3

The trial is taking place at sites in dengue-endemic areas in Latin America (Brazil, Colombia, Panama, Dominican Republic and Nicaragua) and Asia (Philippines, Thailand and Sri Lanka) where there are unmet needs in dengue prevention and where severe dengue is a leading cause of serious illness and death among children.3 Baseline blood samples were collected from all individuals participating in the trial to allow for evaluation of safety and efficacy based on serostatus. Takeda and an independent Data Monitoring Committee of experts are actively monitoring safety on an ongoing basis.

**About TAK-003**

Takeda's tetravalent dengue vaccine candidate (TAK-003) is based on a live-attenuated dengue serotype 2 virus, which provides the genetic “backbone” for all four vaccine viruses.[[4]](#endnote-4) Clinical Phase 1 and 2 data in children and adolescents showed that TAK-003 induced immune responses against all four dengue serotypes, in both seropositive and seronegative participants, and the vaccine was found to be generally safe and well tolerated.[[5]](#endnote-5),[[6]](#endnote-6),[[7]](#endnote-7),[[8]](#endnote-8)

**About Dengue**

Dengue is the fastest spreading mosquito-borne viral disease and is one of the World Health Organization’s top 10 threats to global health in 2019.[[9]](#endnote-9),[[10]](#endnote-10) Dengue is mainly spread by *Aedes aegypti* mosquitoes and, to a lesser extent, *Aedes albopictus* mosquitoes. It is caused by any of four dengue virus serotypes, each of which can cause dengue fever or severe dengue.9 The prevalence of individual serotypes varies across different geographies, countries, regions, seasons and over time.9,[[11]](#endnote-11) Recovery from infection by one serotype provides lifelong immunity against only that serotype, and later exposure to any of the remaining serotypes is associated with an increased risk of severe disease.9

Dengue is pandemic prone, and outbreaks are observed in tropical and sub-tropical areas and have recently caused outbreaks in parts of the continental U.S. and Europe.9,[[12]](#endnote-12),[[13]](#endnote-13) Approximately half of the world now lives under the threat of dengue, which is estimated to cause 390 million infections and 20,000 deaths globally each year.8,[[14]](#endnote-14) The dengue virus can infect people of all ages and is a leading cause of serious illness among children in some countries in Latin America and Asia.9

**Takeda’s Commitment to Vaccines**

Vaccines prevent 2 to 3 million deaths each year and have transformed global public health.[[15]](#endnote-15) For the past 70 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 and norovirus. 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. For more information, visit [www.TakedaVaccines.com](http://www.TakedaVaccines.com).

**About Takeda Pharmaceutical Company Limited**

Takeda Pharmaceutical Company Limited ([TSE:4502/NYSE:TAK](https://www.takeda.com/investors/)) is a global, values-based, R&D-driven biopharmaceutical leader headquartered in Japan, committed to bringing Better Health and a Brighter Future to patients by translating science into highly-innovative medicines. Takeda focuses its R&D efforts on four therapeutic areas: Oncology, Rare Diseases, Neuroscience, and Gastroenterology (GI). We also make targeted R&D investments in Plasma-Derived Therapies and Vaccines. We are focusing on developing highly innovative medicines that contribute to making a difference in people's lives by advancing the frontier of new treatment options and leveraging our enhanced collaborative R&D engine and capabilities to create a robust, modality-diverse pipeline. Our employees are committed to improving quality of life for patients and to working with our partners in health care in approximately 80 countries.

For more information, visit [https://www.takeda.com](https://www.takeda.com/).

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