Information for the public

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD) executed by Merck Sharp & Dohme (Europe), Inc. Belgian Branch

Protocol: V181-003

1. Background:

MSD is developing a dengue quadrivalent vaccine rDENV Δ 30 (live, attenuated), hereafter referred to as V181, for the prevention of dengue disease in individuals at risk of exposure by living in or traveling to dengue-endemic areas.

Dengue is among the most important mosquito-borne viral disease in terms of human morbidity and mortality in the world. Approximately 3 to 4 billion people living in tropical and subtropical countries are at-risk for infection. Each year, approximately 390 million people are infected with dengue viruses, causing an estimated 96 million symptomatic cases. Of these, 2.1 million cases are severe, resulting in approximately 21,000 deaths. Furthermore, approximately 120 million people travel to dengue-endemic regions annually.
Dengue disease is caused by 4 virus serotypes: DENV1, DENV2, DENV3, and DENV4. Infection by any of the 4 serotypes is believed to result in life-long immunity against that serotype. Infection with one serotype may provide short-term protection (ie, 6 to 24 months) against other serotypes, but does not provide long-term protection. Therefore, there is a large, unmet medical need for safe and effective dengue vaccines. MSD is developing a dengue quadrivalent vaccine, to try to meet the medical need.

TITLE OF THE STUDY:

A Phase 2, Randomized, Double-Blind, Multicenter Study to Evaluate the Safety and Immunogenicity of Three Different Potency Levels of V181 (Dengue Quadrivalent Vaccine rDENVΔ30 ([Live, attenuated]) in healthy Adults

2. SHORT DISCRIPTION OF THE STUDY:

V181 will be assessed in a worldwide randomized/ double-blinded study, comparing the trial vaccine with a placebo (the placebo may look close or exactly like V181, but it has no active ingredients), within healthy adults (male & female) between the age of 18 to 50 years old (inclusive). The study is designed to assess the safety and ability to induce antibodies of 3 potency levels of V181: low, moderate & high potency.

Participants will be assigned randomly in a 2:4:4:1 ratio to the V181 or placebo groups. Each participant will receive V181 or placebo as an injection under the skin, once enrolled in the trial.

MSD estimates that the study will require approximately 20 months from the time the first participant signs the informed consent until the last participant's last study related contact (visit or telephone call). Each participant will be enrolled in the trial for an estimated period of 12 months.

This trial is done to test the safety of V181 across the 3 different strengths compared to placebo; to see how well participants tolerate V181 across the 3 different strengths compared to placebo; to test the V181 antibody response of the middle strength compared to the low strength. In addition, MSD

wants to evaluate the safety and tolerability of 3 different V181 potency levels with respect to the proportion of participants experiencing serious adverse events.

3. DESCRIPTION OF THE GMO:

3.1. Recipient organism:

The parental organisms are the four dengue serotypes, DENV1, DENV2, DENV3, DENV4

3.2. Methods used for genetic modification:

The genetic modification is performed by the deletion of genetic material.

3.3. Resulting genetically modified organism

Composition of the V181 is reached after modifying rDENV1Δ30, rDENV3Δ30/31, and rDENV4Δ30 components of V181. The vaccines strains are modified by deleting a portion of the dengue virus which makes the viruses less potent. For the rDENV2/4 Δ30 (ME) component of V181, the rDENV4 Δ 30 backbone is utilized, genes are deleted from the backbone and the homologous pre-M and E genes from DENV2 are inserted in its place.

4. ASSESSING THE POTENTIAL RISKS TO HUMAN HEALTH AND THE ENVIRONMENT, LINKED TO THE DELIBERATE RELEASE

Dengue virus is only believed to infect humans via direct exposure to blood/ blood products or via mosquito bite. Dengue viruses are transmitted by Aedes sp. Mosquitos which are day-biting mosquitos found commonly in urban environments. Human to human transmission of dengue is mediated primarily by the mosquito transmitter.

Humans are infectious to mosquitoes starting a few days prior to the febrile phase of illness through a few days following fever end. A mosquito acquiring dengue via a blood meal from an infected human typically become infectious to humans within 10-14 days.

The transmissibility described above is applicable for the Dengue virus in the wild format. The transmissibility of the GMO V181 is different because weakened viruses comprising V181 are not transmitted from human to human via mosquitos. Experimental infection and transmission studies using vaccine virus and mosquito vectors have shown that the peak virus titer of all the V181 live attenuated dengue vaccine tested thus far in humans were at least ≥100-fold below the viremia level required for transmission to mosquitoes.

Furthermore, for the vaccine virus to be transmitted from one human to another the following series of events would have to take place: (1) The subject would have to be viremic with a peak virus titer that is much higher than the level induced by the vaccine; (2) The viremic subject would then have to be bitten by a viable mosquito at the peak of viremia; (3) This mosquito would have to live for a 10 – 14 day period following the blood meal to make the mosquito infectious for the vaccine virus; (4) The same mosquito would then have to bite another individual. Given the above requirements and the fact that the mosquitos that are hosts for dengue are not endemic in the countries where the trial will take place the risk that V181 will be transmitted from vaccinated to non-vaccinated individuals is very low.

5. THE PROPOSED MEASUREMENTS TO LIMIT THE POSSIBLE RISKS, TO CONTROL THE DELIBERATE RELEASE AND TO ASSURE THE FOLLOW-UP OF ANY RELEASE

Even though the overall risk of V181 to human health and the environment is considered negligible. The Sponsor will implement certain management strategies in order to prevent the exposure of V181 to people and animals all together.

- The administration of the vaccine will take place under controlled conditions at the site by delegated & trained study staff in order to prevent release into the environment by accident. Shedding from vaccinated people or infection of mosquitoes is anticipated to be very limited which makes it highly unlikely that V181 reaches the environment at large.

- To mitigate against the risk of unintentional release, the GMO will be appropriately contained and labelled during transport. Staff handling the GMO and samples that could potentially contain the GMO should be wearing gloves.
    - In the event of an accidental spill, staff will follow their site standard operating procedure (SOP) for spill response and cleanup. Bleach, quaternary ammonium- and phenolic -based disinfections are proven to reduce viral infection potential after only a few minutes.
- The study subjects will be instructed not to donate blood or fluid product for 6 weeks after vaccination. This further minimizes the possibility that V181 would be transmitted to other humans.
- V181 is to be administered by subcutaneous injection in subjects under a clinical trial setting. Each participant will receive a 1 dose (0.5 mL) of the GMO/Placebo (Day1). To minimize spread of the GMO post vaccination, the injection site will be covered with an adequate bandage (e.g. any adhesive bandage or gauze and tape) that provides a physical barrier to protect against direct contact.

(a) Type and amount of waste generated

Empty vials, medical waste, used personal protective equipment (PPE) & bandages

(b) Treatment of waste

The bandage used as physical barrier after V181 administration will be removed 30-minutes post-vaccination, once no visible fluid leakage ends. The bandages will be disposed of in a standard biomedical waste container.

The used and empty vaccine vials will be disposed of in standard biomedical waste container and used syringes will be discarded as medical waste according to the site SOP for medical waste.

Table 1: measurement in case of unintentional release incidents:

Exposure scenario	**Measure**
Accidental breakage/spillage of V181 during transport or administration	In the event of an accidental spill, staff will follow their site SOP for spill response and cleanup. Bleach, quaternary ammonium- and phenolic-based disinfectants will inactivate the virus.
Accidental needle stick injury by medical personnel	Rare case reports of dengue transmission via needlestick in patient care and laboratory accident, blood transfusion, bone marrow transplant or organ transplant, exist. In case of an accidental needle stick injury, the injected dose of V181 will be much lower than the actual subcutaneous dose that is intended to be injected in study subjects. In the unlikely event that the study personnel receive the full dose of V181 via accidental needle stick, the safety profile is expected to be similar to the study participants, which is expected to be favorable. For any affected study personnel, the injection site should be immediately disinfected and covered with an adequate bandage (e.g. any adhesive bandage or gauze and tape) that provides a physical barrier to protect against direct contact. The bandage may be removed when there is no visible fluid leakage at the end of the 30-minute postvaccination observation period. The used, empty vaccine vials and the bandages will be disposed of in standard biomedical waste container and used syringes will be discarded as medical waste according to the site SOP for medical waste. Affected study personnel should be followed for safety according to local procedures for such events.
Unintended use / Misuse	Doses of V181 to be delivered to the sites for injections are well controlled and are handled as a GMO per local regulations. Only medical personnel trained to handle V181 have access to the drug. If eye contact occurs, eyes will be flushed with tepid tap water for 5 minutes. If skin contact occurs, area will be washed with ordinary soap and tap water. Detailed instructions on accidental breakage/spillage have been developed and will accompany each shipment of V181.

6. INFORMATION ON BELGIAN STUDY SITES AND THE STUDY IN BELGIUM

The study is expected to commence on the 09 August 2022 in Belgium. The study will have an enrollment target of 185 participants on the 4 Belgian sites. The study is planned to be closed on 12 August 2025.

Site	**Site name**	**Site address**	**Planned number of patients**
Site 1	UZ Gent – CEVAC – Center For Vaccinology	10, Corneel Heymanslaan BC001; 9000 Gent; Belgium	60
Site 2	CHU Saint-Pierre	Rue Haute 322, 1000 Brussels, Belgium	25
Site 3	Insituut voor Tropische Geneeskunde – Department Clinial Services	155, Nationalestraat; 2000 Antwerpen, Belgium	60
Site 4	ANIMA Research Center	Alkerstraat 28, 3570 Alken, Belgium	40